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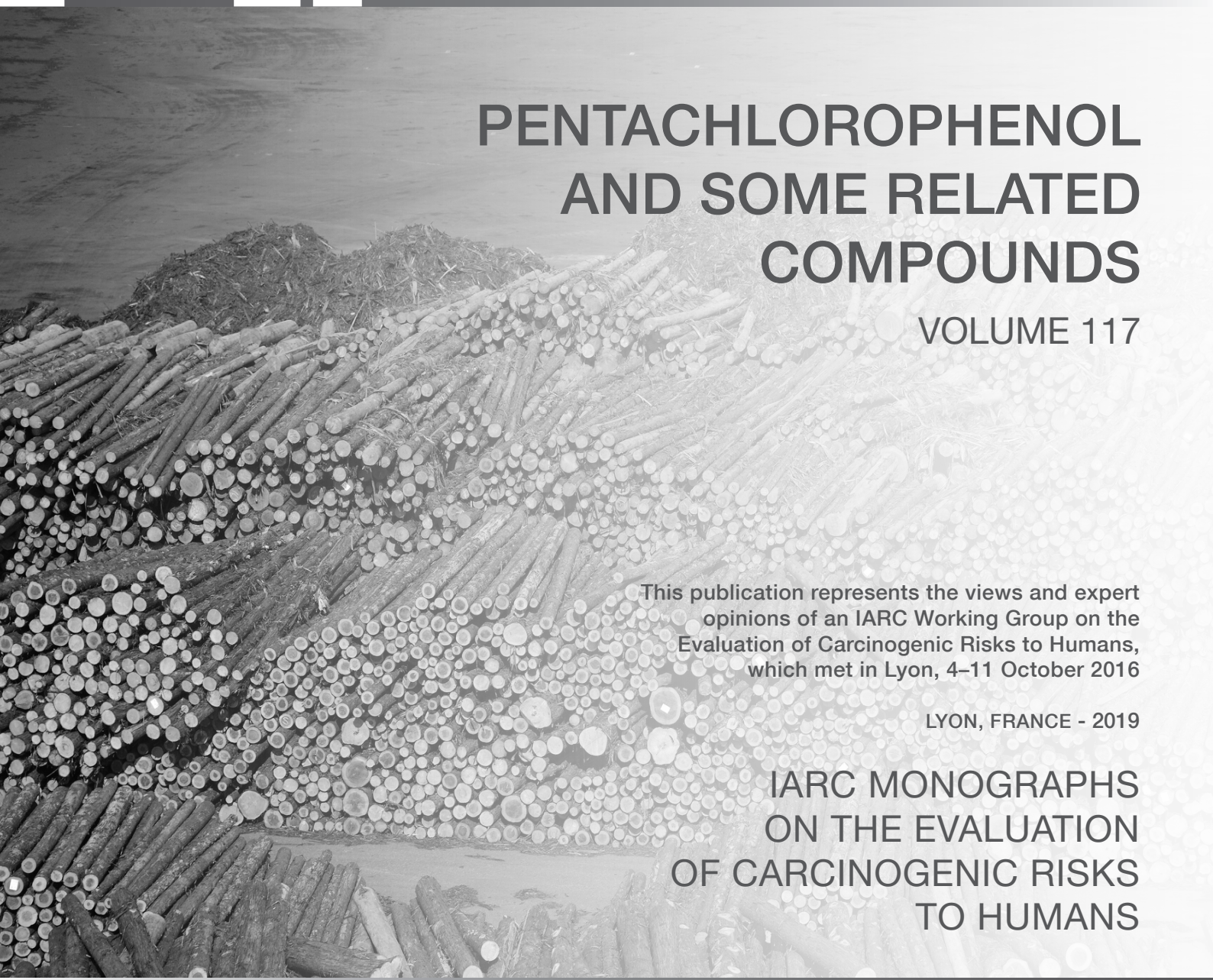

PENTACHLOROPHENOL AND SOME RELATED COMPOUNDS

VOLUME 117

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

ALDRIN AND DIELDRIN

1. Exposure Data

1.1 Identification of the agents

1.1.1 Nomenclature

(a) Aldrin

Chem. Abstr. Serv. Reg. No.: 309-00-2

IUPAC Systematic Name:

(1*R*,4*S*,4a*S*,5*S*,8*R*,8a*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene (HHDN)

Synonyms:1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-*exo*-1,4-*endo*-5,8-dimethanonaphtalene; HHDN (ATSDR, 2002)

"Aldrin" is most commonly used to mean HHDN with a purity of > 95%, except in Denmark and the countries of the former Soviet Union, where it is the name given to pure HHDN (IPCS, 1989, WHO, 2003).

(b) Dieldrin

Chem. Abstr. Serv. Reg. No.: 60-57-1

IUPAC Systematic Name:

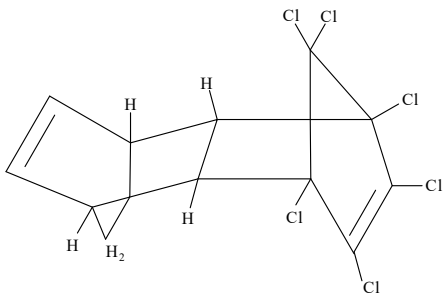
(1*R*,4*S*,4a*S*,5*R*,6*R*,7*S*,8*S*,8a*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene (HEOD)

Synonyms: 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octa-hydro-1,4-*endo*,exo-5,8-dimethanonaphtalene; HEOD

"Dieldrin" is most commonly used to mean HEOD with a purity of > 85%, except in Denmark and the countries of the former Soviet Union, where it is the name given to pure HEOD (IPCS, 1989; WHO, 2003).

1.1.2 Chemical and physical properties of the pure substances

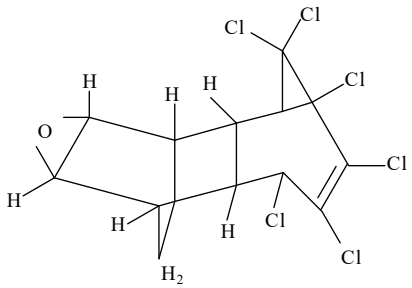
(a) Aldrin



Molecular formula: $C_{12}H_8Cl_6$

Relative molecular mass: 364.91

(b) Dieldrin



Molecular formula: $C_{12}H_8Cl_6O$

Relative molecular mass: 380.91

Table 1.1 summarizes the chemical and physical properties of aldrin and dieldrin.

Chemical reactivity: Aldrin is stable to heat, and in the presence of inorganic and organic bases, hydrated metal chlorides, and mild acids. Epoxidation of aldrin with peracetic or perbenzoic acid forms the 6,7-epoxy derivative, dieldrin. The unchlorinated ring is attacked by oxidizing agents and strong acids (IARC, 1974).

1.1.3 Technical products and impurities

(a) Aldrin

Some trade names: Aldrec; Aldrex; Drinox; Octalene; Seedrin; Compound 118 (ATSDR, 2002)

Impurities: Octachlorocyclopentene, hexachlorobutadiene, toluene, and polymerization products (IPCS, 1989; WHO, 2003)

In 1967, the composition of technical aldrin was reported to be as follows: hexachloro-hexahydro-dimethano-naphthalene, 90.5%; other polychloro-hexahydro-dimethano-naphthalene (isodrin), 3.5%; hexachloro-tetrahydro-methano-indene (chlordane), 0.5%; hexachlorocyclopentadiene, 0.6% hexachlorobutadiene, 0.2%; octachlorocyclopentene, 0.5%; hexachloroethane, < 0.1%; HHDN diadduct, 0.1%; bicycloheptadiene, < 0.1%; toluene, 0.3%; and other compounds (primarily a complex mixture of compounds formed by polymerization of hexachlorocyclopentadiene and bicycloheptadiene during the aldrin reaction), 3.6% (IARC, 1974).

In the 1960s–70s, aldrin was available in the USA as a technical-grade product containing 95% minimum active ingredient (equivalent to 90.3% HHDN and 4.7% other insecticidally active related compounds) (Whetstone, 1964; Frear, 1972a). It was formulated into emulsifiable concentrates, wettable powders, dusts, granules, and mixtures with fertilizers (IARC, 1974).

(b) Dieldrin

Some trade names: Alvit; Dieldrix; Octalox; Quintox; Red Shield (ATSDR, 2002)

Impurities:Otherpolychloroepoxyoctahydro-dimethanonaphthalenes and endrin (IPCS, 1989; WHO, 2003)

In the 1960s–70s, dieldrin was available in the USA as a technical-grade product containing 100% active ingredient (equivalent to 85% HEOD and 15% other insecticidally active related compounds) with a chlorine content of 55–56%, free acid (as hydrochloric acid) at < 0.4%, and water at < 0.1% (Whetstone, 1964; Frear, 1972b). It was formulated into emulsifiable concentrates, solutions, wettable powders, dusts, granules, and mixtures with fertilizers (IARC, 1974).

1.2 Production and use

1.2.1. Production process

Aldrin and dieldrin were first synthesized in the laboratory in about 1948 (Whetstone, 1964) (Galley, 1970); commercial production in the USA was first reported in 1950 (US Tariff Commission, 1951).

Aldrin is produced by the Diels–Alder reaction of hexachlorocyclopentadiene with bicycloheptadiene (Whetstone, 1964).

Dieldrin is made commercially by the epoxidation of aldrin with a peracid (e.g. peracetic or perbenzoic acid), but can also be produced by the condensation of hexachlorocyclopentadiene with the epoxide of bicycloheptadiene (Galley, 1970; IARC, 1974).

Table 1.1 Chemical and physical properties of pure aldrin and dieldrin

Property	Aldrin	Dieldrin
Colour	White (pure); tan to brown (technical grade)	White (pure); light brown (technical grade)
Physical state	Crystalline solid	Crystalline solid
Melting point	104–105.5 °C; 49–60 °C (technical grade)	176–177 °C; 95 °C (technical grade)
Boiling point	Decomposes	Decomposes
Density	1.6 g/L at 20 °C	1.75 g/L at 25 °C
Odour	Mild chemical odour	Mild chemical odour
Odour threshold:		
Water	No data	No data
Air	0.017 mg/kg	0.041 mg/kg
Solubility:		
Water at 20 °C	0.011 mg/L	0.110 mg/L
Organic solvents	Very soluble in most organic solvents	Moderately soluble in common organic solvents except aliphatic petroleum solvents and methyl alcohol
Partition coefficients:		
Octanol/water, Log K_{ow}	6.50	6.2
Organic carbon, Log K_{oc}	7.67	6.67
Vapour pressure:		
at 20 °C	7.5×10^{-5} mmHg	3.1×10^{-5} mmHg
at 25 °C	1.2×10^{-4} mmHg	5.89×10^{-6} mmHg
Henry's law constant:		
at 25 °C	4.9×10^{-5} atm-m³/mol	5.2×10^{-6} atm-m³/mol
Flammability limits	Nonflammable	Nonflammable
Conversion factors	1 ppm = 14.96 mg/m³ at 25 °C, 1 atm	1 ppm = 15.61 mg/m³ at 25 °C, 1 atm
Explosive limits	Stable	Stable

ppm, part per million
From ATSDR (2002)

1.2.2. Production volumes

Global production, which was estimated to be 13 000 tonnes per year in 1972, had decreased to less than 2500 tonnes per year in 1984 (IPCS, 1989).

The following European countries were reported to be producing aldrin and/or dieldrin in 1972 or 1973: Belgium (one supplier), Federal Republic of Germany (one), France (two), Italy (two), the Netherlands (one), and the United Kingdom (one) (Ragno, 1972; Chemical Information Services Ltd, 1973). In 1972, Japan was reported to have eight suppliers of aldrin and/or dieldrin and their formulations (Chemical Information Services Ltd, 1973). Imports into Japan were reported to be 143 000 kg for aldrin and 43 000 kg for dieldrin in 1970 (Hayashi, 1971; IARC, 1974).

The production, import, and use of aldrin and dieldrin in the USA were cancelled or at least considerably reduced by the time aldrin was listed as a Toxic Release Inventory (TRI) chemical in 1986 (EPA, 2003). Nonetheless, the industry trade literature revealed that 11 companies in the USA between 1989 and 1999, and 7 companies in the USA in 2016 reported production of aldrin and/or dieldrin (Jorgenson, 2001; Chem Sources, 2016). It is not known whether these chemicals were primarily exported, or whether they were

used as chemical intermediates for other products, or only for scientific research (Jorgenson, 2001).

In 2016, few facilities reported the production of aldrin and/or dieldrin in Europe and in Asia: Germany (one), United Kingdom (one), Belgium (one), Switzerland (one), China (two), Hong Kong Special Administrative Region (one), and Japan (one) (Chem Sources, 2016). In China, small-scale production for research purposes has been reported (Wong et al., 2005). No information was available concerning production in other countries.

1.2.3 Use

Aldrin and dieldrin are synthetic organochlorine insecticides. Originally, they were used as broad-spectrum soil insecticides for the protection of various food crops, as seed dressings, to control infestations of pests such as ants and termites, and to control several insect vectors of disease (EPA, 2003).

The respective quantities of aldrin and dieldrin used in, or sold for, agricultural purposes in 1970 were reported to be as follows (in tonnes): Myanmar (4.2 and not reported, NR); Canada (18.5 and NR); Colombia (198.5 and 27.8); El Salvador (21.9 and 2.6); Ghana (15.5 and 0.5); Iceland (0.1 and NR); Israel (1 and NR); Italy (2.765 and 9.7); Madagascar (3.5 and 0.1); Ryukyu Islands (9.1 and NR); Sudan (NR and 4.5); and Uruguay (9 and 10) (FAO, 1972). Aldrin and dieldrin use in California, a major agricultural state in the USA, was reportedly 22.7 tonnes for aldrin and nearly 32 tonnes for dieldrin in 1971. For aldrin, almost 90% was used for insect control on wooden structures, whereas for dieldrin, 34% was used for insect control on wooden structures, 14% was used on grapes and 13% was used on pears (California Department of Agriculture, 1972, 1973). In 1972, an estimated 80% of the combined production of aldrin and dieldrin in the USA was used on corn crops, and about 10% was used for termite control (IARC, 1974). Minor uses of dieldrin in the USA and in several other countries were for moth-proofing woollen clothes and carpets (Lipson, 1970; IARC, 1974).

An indication of possible uses of aldrin and dieldrin can be derived from the recommended residue limits for aldrin and dieldrin established by the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) for the following food products: asparagus, broccoli, Brussels sprouts, cabbages, cauliflowers, cucumbers, aubergines, horse radishes, onions, parsnips, peppers, pimentos, radishes, radish tops, fruits (including citrus), rice, potatoes, carrots, lettuces, milk and milk products, raw cereals, and eggs (FAO/WHO, 1973).

Since the early 1970s, use of aldrin and dieldrin, especially in agriculture, has been severely restricted or banned in many countries all over the world (IPCS, 1995). In 1972, the United States Environmental Protection Agency (EPA) cancelled all except three specific uses of these compounds (subsurface termite control, dipping of non-food plant roots and tops, and completely contained moth-proofing in manufacturing processes), which by 1987 were voluntarily cancelled by the manufacturer (EPA, 2003).

In tropical countries, dieldrin was reported to be used as a residual spray in residential dwellings to control vector-borne diseases such as malaria, and also to control termites (CDC, 2009).

1.3 Analytical methods

The analytical methods available for detecting, measuring, and/or monitoring aldrin and dieldrin, their metabolites, and other biomarkers of exposure to and effects of aldrin and dieldrin have been described in detail elsewhere (ATSDR, 2002).

1.4 Occurrence and exposure

Under most environmental conditions, aldrin is readily converted to dieldrin (ATSDR, 2002). The half-lives of aldrin and dieldrin in air are estimated to range from 1 to 10 hours for aldrin and from 3 to 40.5 hours for dieldrin (Kwok & Atkinson, 1995; Jorgenson, 2001). In surface waters, aldrin has a reported biodegradation half-life of 24 days (Eichelberger & Lichtenberg, 1971). In the soil, aldrin is converted to dieldrin by epoxidation, with an estimated half-life of between 1.5 and 5.4 years, depending on the composition of the soil (Jorgenson, 2001). In contrast, the average half-life of dieldrin in soil ranges between 2.6 and 12.5 years and appears to be a function of its concentration (Jorgenson, 2001). Consequently, aldrin is infrequently measured in occupational and environmental samples. Dieldrin originating from the application or manufacture of aldrin cannot be distinguished from applied dieldrin. Measurements of dieldrin in the air, soil, water, or body may represent exposure to dieldrin, or aldrin, or both. Dieldrin from both sources bioaccumulates in body fat and is typically measured in blood or body tissues. Dieldrin is excreted in the bile, faeces, and breast milk, and can cross the placenta (Jorgenson, 2001; ATSDR, 2002).

1.4.1 Occupational exposure

Occupational exposure may occur in workers involved in the manufacture of dieldrin or aldrin and formulations containing dieldrin or aldrin, applicators who spray or mix dieldrin or aldrin, farm workers engaged in re-entry tasks, and vector-control workers.

(a) Air and skin

In the USA in the 1960s, estimates of potential dermal exposure to dieldrin during orchard spraying ranged from 14.2 to 15.5 mg per hour, and estimates of potential respiratory exposure ranged from 0.03 to 0.25 mg per hour (Wolfe et al., 1963, 1967). Dieldrin was found on the hands of two out of five greenhouse workers (4.9 and 8.4 ng/hand), one out of nine veterinarians (1.9 ng/hand), and none out of seven florists monitored in France in 2002; however, no dieldrin was detected in their breathing air (Bouvier et al., 2006). In a limited number of stationary air samples collected between 1958 and 1960 from a pesticide formulation plant located in the Netherlands, aldrin and dieldrin concentrations were generally less than 0.25 mg/m^3, with concentrations of dieldrin of up to 4 mg/m^3 measured during drum filling (de Jong, 1991).

(b) Biological markers and intake

Dieldrin has been measured in the blood of agricultural workers and pesticide-treatment workers (Table 1.2). Blood concentrations of dieldrin have been steadily declining in agricultural workers since dieldrin and aldrin were banned (Hayes & Curley, 1968; see also Section 1.5). A correlation of 0.6 between concentration of dieldrin in plasma and total hours of exposure was observed in pesticide-manufacturing workers (Hayes & Curley, 1968). The highest blood concentrations of dieldrin were observed in the 1960s in aldrin formulators in the USA (Mick et al., 1972) and in insecticide-plant workers in the Netherlands (de Jong, 1991). In the latter study of 343 insecticide-plant workers between 1963 and 1970, 18% had levels of 100 µg/L or higher and 5% had levels of 200 µg/L and higher (de Jong, 1991). Estimated daily intake of dieldrin was highest in people employed in the formulation plant, with the estimated median daily intake of assistant operators and cleaners decreasing from 2122 µg/day in 1963 to 575 µg/day in 1969, and the estimated median daily intake of operators decreasing from 1546 µg/day in 1963 to 291 µg/day in 1969. Aldrin/dieldrin plant workers had the second highest estimated daily intake of dieldrin: assistant operators' and cleaners' estimated median intake decreased from 1163 µg/day

to 427 µg/day between 1963 and 1969; estimated median intake for maintenance workers varied between 116 µg and 186 µg between 1963 and 1969 (highest levels in 1964 and 1965); and operators' estimated median intake varied from 291 to 826 µg (highest levels in 1964 and 1965) (de Jong, 1991). Dieldrin intake by occupationally exposed workers employed in the manufacture of dieldrin, aldrin, endrin, and other insecticides has been estimated to range from 0.72 to 1.10 mg/person per day (Hayes & Curley, 1968) compared with 0.025 mg/person per day for the general population (Hunter & Robinson, 1967).

Aldrin in the blood of occupationally exposed workers has been infrequently measured (Table 1.2). Mean aldrin concentrations in the blood of pesticide manufacturing workers in the 1960s in the USA were highest in aldrin formulators (29.5 µg/L) and much lower in 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) formulators (0.8 µg/L) (Mick et al., 1972).

1.4.2 Community exposure

The general population can be exposed to dieldrin and aldrin directly or from residues on food or from living near areas where dieldrin or aldrin was sprayed. Exposures may occur during personal use of products containing dieldrin or aldrin, such as during pesticide treatments carried out in and around the home to prevent termites (ATSDR, 2002), and as a result of their persistence in the environment: aldrin and dieldrin are classified as persistent organic pollutants (POPs) (Stockholm Convention, 2001). Aldrin was consistently found less frequently than dieldrin and, when quantified, in smaller quantities (see below).

(a) Water

Dieldrin and aldrin are hydrophobic and do not dissolve easily in water (Mackay & Wolkoff, 1973). Water concentrations are usually < 0.01 µg/L, with higher levels attributed to contamination from industrial effluents and soil erosion during agricultural use (WHO, 2003). Detectable concentrations of dieldrin are regularly reported in samples collected 5–15 years after use of dieldrin and aldrin was discontinued. In water samples collected in the early 1970s, an average dieldrin concentration of 0.3 ng/L was found in drinking-water in Hawaii, USA (Bevenue et al., 1972), and 0.19 µg/L in 50% of cistern-water samples taken in one locality in the Virgin Islands (Lenon et al., 1972). Surface, ground, lake, and marine waters generally contained low concentrations of aldrin and dieldrin.

In the 1980s, dieldrin was detected in surface- and groundwater samples from Canada, from Puerto Rico, and from 48 states of the USA (EPA, 1987). In a similar survey in the USA in1992–2001, dieldrin was found in less than 5% of samples of stream water and ground water, but most frequently and at the highest concentrations in areas where corn crops had been treated extensively with aldrin and dieldrin (USGS, 2006). Dieldrin and aldrin were detected in samples collected from the Sarno River, Italy (Montuori et al., 2014), and rivers in Greece (Golfinopoulos et al., 2003; Konstantinou et al., 2006; Litskas et al., 2012), but not in samples from the Nile River and its estuaries, Egypt (Abbassy et al., 1999).

(b) Sediment and soil

Past use of aldrin and dieldrin has resulted in the presence of residues of these compounds in the soil today. Both compounds bind to soil and are absorbed into the food chain (Jorgenson, 2001). Sunlight and bacteria change aldrin to dieldrin. Dieldrin has low volatility and its half-life in soil has been estimated to range from 2.6 to 12.5 years (Jorgenson, 2001; Beyer & Gale, 2013). Dieldrin has been detected in river-bed sediments in the USA (20–45% of samples) (USGS, 2006), in marine sediments in Portugal (Carvalho et al., 2009), in marine sediments directly exposed

Table 1.2 Concentrations of aldrin and dieldrin in blood samples from occupationally exposed workers

Agent	Country, year	Occupation	Work task or type of worker	No. of workers	Exposure level[a]	Exposure range	Reference
Aldrin	Brazil, 1997	Agricultural workers	Mixing, loading, and/or applying pesticides	26	NR	All < 1.4 µg/L	Paumgartten et al. (1998)
Aldrin	Columbia, 2005–2006	Agricultural workers	Tasks involving pesticide use in the past 2 yr	99	0.0037 µg/L	NR–0.209 µg/L, 15% detects	Varona et al. (2010)
Aldrin	USA	Pesticide manufacturing workers	Aldrin formulators	7	29.5 µg/L		Mick et al. (1972)
Aldrin	USA	Pesticide manufacturing workers	Warehouse	4	7.6 µg/L		Mick et al. (1972)
Aldrin	USA	Pesticide manufacturing workers	Maintenance and miscellaneous	3	2.8 µg/L		Mick et al. (1972)
Aldrin	USA	Pesticide manufacturing workers	2,4-D & 2,4,5-T formulators	6	0.8 µg/L		Mick et al. (1972)
Dieldrin	Brazil, 1997	Agricultural workers	Mixing, loading, and/or applying pesticides	26	NR	< 1.4–3.7 µg/L, 4% detects	Paumgartten et al. (1998)
Dieldrin	Columbia, 2005–2006	Agricultural workers	Tasks involving pesticide use in the past 2 yr	99	0.004 µg/L	< 0.020–0.090 µg/L, 11% detects	Varona et al. (2010)
Dieldrin	USA, NR	Farmer	Pre- and post-pesticide application	12	NR	< 0.23–21 µg/L, 33% detects	Brock et al. (1998)
Dieldrin	USA, NR	Pesticide manufacturing workers	Pipefitters, shippers, and helpers	20	23.3 µg/L	1.2–4.6 µg/L	Hayes & Curley (1968)
Dieldrin	USA, NR	Pesticide manufacturing workers	Operators, foremen	26	18.9 µg/L	3.2–108 µg/L	Hayes & Curley (1968)
Dieldrin	USA, NR	Pesticide manufacturing workers	Painters, carpenters, engineers, inspectors, laboratory workers	17	9.8 µg/L	1.3–21.5 µg/L	Hayes & Curley (1968)
Dieldrin	USA, NR	Pesticide manufacturing workers	Clerical workers	8	5.4 µg/L	< 0.7–25.5 µg/L	Hayes & Curley (1968)
Dieldrin	The Netherlands, NR	Pesticide manufacturing workers	Manufacture of dieldrin, aldrin and endrin	12	26 µg/L	0.5–110 µg/L	Hunter et al. (1972)
Dieldrin	USA, NR	Pesticide manufacturing workers	Aldrin formulators	7	182.5 µg/L	NR– ~300 µg/L	Mick et al. (1972)
Dieldrin	USA, NR	Pesticide manufacturing workers	Warehouse	4	77.5 µg/L	NR– ~150 µg/L	Mick et al. (1972)
Dieldrin	USA, NR	Pesticide manufacturing workers	Maintenance and miscellaneous	3	35.2 µg/L	NR– ~80 µg/L	Mick et al. (1972)

Table 1.2 (continued)

Agent	Country, year	Occupation	Work task or type of worker	No. of workers	Exposure level[a]	Exposure range	Reference
Dieldrin	USA, NR	Pesticide manufacturing workers	2,4-D & 2,4,5-T formulators	6	11.0 µg/L	NR – 20 µg/L	Mick et al. (1972)
Dieldrin	Australia, NR	Pesticide treatment workers	Vehicle and plant maintenance or stores	5	Median, 7 µg/L	0.9–14.5 µg/L	Edwards & Priestly (1994)
Dieldrin	Australia, NR	Pesticide treatment workers	Termiticide applicators	10	Median, 5.3 µg/L	2.5–145 µg/L	Edwards & Priestly (1994)
Dieldrin	Australia, NR	Pesticide treatment workers	Pre-building treatment of building sites and foundations	5	Median, 16 µg/L	2.5–250 µg/L	Edwards & Priestly (1994)
Dieldrin	Australia, NR	Pesticide treatment workers	Office and sales	10	Median, 4.8–5.8 µg/L	0.7–26 µg/L;	Edwards & Priestly (1994)
Dieldrin	Sudan, NR	Pesticide treatment workers	Mixing and spraying insecticides	22	NR	< 10–50 µg/L, 27% detects	El Zorgani & Musa (1976)
Dieldrin	Argentina, NR	Pesticide workers	Sprayers, spray truck drivers, supervisors using hexachlorocyclohexane or DDT	20	Catamarca Province: 1.09 ± 0.60 µg/L; Salta Province: 1.16 ± 0.72 µg/L	NR	Radomski et al. (1971)
Dieldrin	Argentina, NR	Pesticide workers	Former sprayers in malaria control programme	10	Catamarca Province: 2.81 ± 3.59 µg/L	NR	Radomski et al. (1971)
Dieldrin	Argentina, NR	Pesticide workers	Administrative personnel	19	Catamarca Province: 2.09 ± 1.25 µg/L; Salta Province: 0.77 ± 0.74 µg/L	NR	Radomski et al. (1971)
Dieldrin	The Netherlands, 1963–1970	Insecticide manufacturing workers	Various	343	NR	< 10 µg/L to > 200 µg/L	de Jong (1991)

[a] Exposure levels expressed in mean unless indicated otherwise

2,4-D, 2,4-dichlorophenoxyacetic acid ; DDT, dichlorodiphenyltrichloroethane; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; NR, not reported; yr, year(s)

to wastewater in Marseille, France (Syakti et al., 2012), in agricultural soil samples in Shanghai, China (Jiang et al., 2009), and in soil samples from the Czech Republic (Shegunova et al., 2007).

(c) Air

Concentrations of dieldrin in air are generally low; however, exposures may be greater for residents living around sites where aldrin or dieldrin has been used. Atmospheric transport has resulted in detectable concentrations of dieldrin in remote areas of Scandinavia and the Arctic, where it is unlikely that aldrin or dieldrin were ever used (USGS, 2006). Dieldrin was detected at only one out of nine localities in the USA, at a maximum level of 29.7 ng/m^3 (Stanley et al., 1971). In London and its suburbs, England, very small quantities of dieldrin (18–21 g/10^{12} g of air) were detected in air (Abbott et al., 1966). In the Bahamas in the early 1970s, concentrations of dieldrin in air ranged from 0.33 ng/m^3 to 0.86 ng/m^3 (Davies et al., 1975). More recently, air measurements collected between 2001 and 2008 in Mali found dieldrin at concentrations of 0.091–1.8 ng/m^3 (mean, 1.1 ± 0.8 ng/m^3; median, 1.7 ng/m^3) (Garrison et al., 2014). Concentrations were more than twice as high in samples from an urban area of Kati, Mali, than in samples from downwind sites. Alegria et al. (2000) reported mean concentrations of dieldrin of 0.044 ng/m^3 in an inland agricultural area of Belize in 1995–1996. Low dieldrin concentrations (maximum, 0.64 ng/m^3; median, 0.00 ng/m^3) were reported at mid-continental sites in the USA in 1994 (Majewski et al., 1998).

In air samples collected in the USA, aldrin was infrequently detected and, when detected, occurred at low concentrations ranging from 0.1 to 4 ng/m^3 (Tabor, 1966; Stanley et al., 1971).

(d) Residential exposure

Detectable concentrations of dieldrin were found at a range of < 0.1 to 0.3 ng/m^3 in 42% of air samples collected in homes of residents with no occupational exposure, in France (Bouvier et al., 2006). Samples collected from the hands of these residents showed dieldrin at detectable concentrations (30% detects; range, < 0.8–5.5 ng/hand). Dieldrin was detected in house dust in eight out of nine homes in the USA sampled in the early 1990s, with a mean of 0.12 µg/m^2 and maximum of 0.38 µg/m^2 (Lewis et al., 1994). Aldrin was detected in five out of nine homes in the USA sampled in the early 1990s, but in only one to three of the six environmental matrices examined in these homes (Lewis et al., 1994). Concentrations of dieldrin in carpet dust were higher than those in samples from the walkway, entryway, or play-area soil. Detectable concentrations of dieldrin in air were found in four out of eight homes (mean, 0.07 µg/m^3). For children, estimated dieldrin intake ranged from < 0.1 to 0.13 µg/day via air, and from < 0.01 to 0.04 µg/day via dust. Average dieldrin concentrations were higher in samples of interior dust (2.84 ppm) than in samples of exterior soil (0.07 ppm) from homes in the Bahamas (Davies et al., 1975).

(e) Residues in food, and dietary intake

Dieldrin is stored in the adipose tissue, liver, brain, and muscle of mammals, fish, birds, and other organisms in the food chain (WHO, 2003). The half-life in whole fish is estimated to be about 30 years (USGS, 2006). In whole fish collected from streams draining from watersheds with mixed land use in the USA from 1969 to 1999, dieldrin concentrations in fish tissue varied substantially during the early 1970s, then continued to decline slowly through the early 1990s (USGS, 2006). In Australia, the maximum concentration in fish tissue was 0.14 and 1.75 µg/g wet weight in the 1970s and 1980s, respectively, for aldrin, and 0.37, 3.1, and 0.23 µg/g wet weight in the 1970s, 1980s, and 1990s, respectively, for dieldrin (Connell et al., 2002).

In Poland, the mean daily intake of aldrin and dieldrin combined from milk for an adult was 4.1 ng/kg body weight (bw) based on mean

concentrations in cows' milk of 0.5–4.8 ng/g wet weight for aldrin and 0.03–0.2 ng/g wet weight for dieldrin (Witczak et al., 2013).

In a study in which the median concentration of dieldrin in mothers' milk was reported to be 6 µg/L, the estimated intake by breast-fed babies was approximately 1 µg/kg bw per day (IPCS, 1989). In Denmark, the average daily intake of dieldrin in infants was estimated to be 0.045 µg/kg per day based on average dieldrin concentrations in breast milk of 9 ng/g fat (Danish National Board of Health, 1999). Measurements taken in samples of children's meals in the Salinas Valley of California, USA, in 2002 found detectable levels of dieldrin in 10% of toddlers' solid food samples, with a maximum concentration of 6.1 ng/g (Bradman et al., 2007).

The total dietary intake of dieldrin in the late 1960s was found to range between 0.05 and 0.08 µg/kg bw per day in the USA (Duggan & Corneliussen, 1972), 0.07 µg/kg bw per day in Japan (Uyeta et al., 1971), and 0.30 and 0.09 µg/kg bw per day in the United Kingdom for 1965 and 1966–67, respectively (McGill & Robinson, 1968; Abbott et al., 1969).

The average daily intake of aldrin from food ranged from 0.04 to 0.0001 µg/kg bw per day for 1965–1970, with an average intake of 0.01 µg/kg bw per day (Duggan & Lipscomb, 1969). The reduction in use of aldrin since the 1970s has decreased food residues in many countries (IPCS, 1989). Intake in 1980–1982 was estimated to be below 0.2 µg/kg bw per day in several countries (IPCS, 1989).

(f) Biological markers

Dieldrin has been measured in the blood of populations of varying ages and in various geographical locations over the past several decades (Table 1.3). Although serum dieldrin concentrations have generally decreased over time, detectable levels continue to be measured decades after use of dieldrin and aldrin was banned. Serum dieldrin levels at the 95th percentile in samples from the National Health and Nutrition Examination Surveys (NHANES) 2001–2002 and 2003–2004 were approximately 10 times lower than in samples from NHANES 1976–1980 (Stehr-Green, 1989; CDC, 2009). Detection rates for aldrin measured in the blood were generally low. An exception was observed for blood samples collected from people living in an agricultural area of southern Spain. Carreño et al. (2007) found detectable levels of aldrin in 79% of blood samples from young men. Aldrin and dieldrin have also been detected in adipose tissue and breast milk (Table 1.3). For example, dieldrin was detected in 59% of adipose tissue samples collected in a Danish population between 1993 and 1997, with a median concentration of 17 and 19 µg/kg for women and men, respectively (Bräuner et al., 2012). Cerrillo et al. (2006) found detectable levels of aldrin in 30% of adipose tissue samples from women aged 33–75 years. Because aldrin rapidly converts to dieldrin, the high rate of detection of dieldrin may indicate recent exposure to aldrin, despite its ban in the mid-1980s (Cerrillo et al., 2006). [The Working Group noted that the pattern of results across different matrices and for aldrin and dieldrin was difficult to explain by exposure or release from adipose tissue.]

Dieldrin has been detected at a mean concentration of 0.01–11 µg/L in breast milk in Europe and the USA (IPCS, 1989). Dieldrin concentrations in breast milk decreased from an average of 1.33 ng/g milk in 1982 to 0.85 ng/g milk in 1986 (WHO, 2003). However, higher concentrations of up to 35 ng/g were found in the 1980s in breast milk from Australian women whose houses were treated annually with aldrin (Stacey & Tatum, 1985).

Dieldrin has also been measured in breast tissue (Djordjevic et al., 1994; Mathur et al., 2002), and bone marrow (Scheele et al., 1992).

Aldrin and dieldrin were detected in 82% and 75%, respectively, of samples of umbilical cord blood collected in 2013–2014 from 999 pregnant

Table 1.3 Concentrations of aldrin and dieldrin in biological samples from the general population

Agent	Sample matrix	Country, year	Age (years)	No. of samples	Exposure level[a]	Exposure range,% detects	Comments	Reference
Aldrin	Adipose tissue	Spain, NR	33–75, mean 56 ± 10.46	458	10.51 ng/g lipid	NR, 30.3% detects	Women living in agricultural areas of southern Spain that have the largest area of intensive greenhouse agriculture in Europe	Cerrillo et al. (2006)
Aldrin	Adipose tissue	Spain, NR	Mean age, 53	200	25.6 ± ng/g lipid	NR–137 ng/g lipid, 40% detects	Women living in intensive greenhouse agriculture area	Botella et al. (2004)
Aldrin	Blood	India, NR	21–70	50	115 µg/L	NR	Similar levels in rural and urban environments (mean, 168 µg/L vs 101 µg/L)	Mathur et al. (2002)
Aldrin	Serum	Spain, NR	Mean age, 53	200	2.17 µg/L	NR – 14.2 µg/L, 56% detects	Women living in intensive greenhouse agriculture area	Botella et al. (2004)
Aldrin	Serum	Spain, NR	18–23	220 (Males)	3.75 µg/L; Median, 2.62 µg/L	< 3.0–33.76 µg/L, 79% detects	Extensive greenhouse agricultural area	Carreño et al. (2007)
Aldrin	Serum	Nicaragua, 2002	11–15	38	NR	0% detects	LOD estimated, < 10 ng/g lipid; Working and living at municipal waste-disposal site and in nonworking children living both nearby and far from site	Cuadra et al. (2006)
Aldrin	Serum	Brazil, 1999	19–63	33	NR	< 1.4 µg/L, 0% detects	Urban area	Delgado et al. (2002)
Aldrin	Serum	India, NR	≥ 18	50	2.08 µg/L	NR	Controls, no occupational exposure	Tomar et al. (2013)
Aldrin	Serum	Norway, 1973–1991	18–60; mean, 41.2	300	NR	< 0.08–NR ng/g, lipid 1% detects		Ward et al. (2000)
Aldrin	Plasma	France, Germany, Spain, NR	Mean, 56.5 ± 15.7	203	Median of detectable, 19.8 µg/L	6.7–NR µg/L, Spain 9% detects; France and Germany 0% detects		Cocco et al. (2008)
Aldrin	Breast milk	Israel, 2011–2012	23–35; mean, 30	52	NR	NR, 0% detect	Pooled sample	Wasser et al. (2015)

Table 1.3 (continued)

Agent	Sample matrix	Country, year	Age (years)	No. of samples	Exposure level[a]	Exposure range,% detects	Comments	Reference
Aldrin	Breast milk	Turkey, NR	NR	75	36.6 ng/g lipid	< 5–230.6 ng/g, 58.7% detects		Yalçın et al. (2015)
Dieldrin	Adipose tissue	Denmark, 1993–1997	Men, 51–64	126	Mean, 22 µg/kg lipid; median, 19 µg/kg lipid	5–95th percentile: 10–42 µg/kg lipid	59% detects overall (includes women)	Bräuner et al. (2012)
Dieldrin	Adipose tissue	Denmark, 1993–1997	Women, 51–64	119	Mean, 24 µg/kg lipid; median, 17 µg/kg lipid	5–95th percentile: 8–49 µg/kg lipid	59% detects overall (includes men)	Bräuner et al. (2012)
Dieldrin	Adipose tissue	USA, NR	37–66	5		All < 10 µg/kg fatty tissue, 0% detects	Study controls	Djordjevic et al. (1994)
Dieldrin	Adipose tissue	Australia, 1990–1991	NR	31	Median, 40 µg/kg extractable fat	10–1100 µg/kg extractable fat, 100% detects	Nursing mothers	Stevens et al. (1993)
Dieldrin	Adipose tissue	Spain, NR	Mean, 53	200	17 ng/g lipid	NR–84 ng/g lipid, 28.5% detects	Postmenopausal women living in intensive greenhouse agriculture area	Botella et al. (2004)
Dieldrin	Blood	USA, 1999–2004	≥ 20	2341	Median detected, 8.74 ng/g lipid-adjusted	< 10.5 ng/g lipid-adjusted, 22% detects	Nationally representative sample (NHANES)	Everett & Matheson (2010)
Dieldrin	Blood	Israel, 1975–1986	NR	15	2.7 ng/g	NR	Females of reproductive age	Pines et al. (1987)
Dieldrin	Blood	USA, NR	NR	26	1.49 ± 1.00 µg/L	NR	Adults	Radomski et al. (1971)
Dieldrin	Blood	Argentina, NR	NR	20	1.43 ± 1.21 µg/L	NR	Adults	Radomski et al. (1971)
Dieldrin	Blood	Argentina, NR	Children, 5–10	18	0.94 ± 0.92 µg/L	NR		Radomski et al. (1971)
Dieldrin	Blood	Argentina, NR	Children, 1–5	19	0.54 ± 0.29 µg/L	NR		Radomski et al. (1971)
Dieldrin	Blood	Argentina, NR	Newborns	13	0.59 ± 0.42 µg/L	NR	Ratio newborn to mother: 0.44 ± 0.16 µg/L	Radomski et al. (1971)

Table 1.3 (continued)

Agent	Sample matrix	Country, year	Age (years)	No. of samples	Exposure level[a]	Exposure range,% detects	Comments	Reference
Dieldrin	Serum	Spain, NR	Mean, 53	200	1.21 µg/L	NR–6.35 µg/L, 47% detects	Postmenopausal women living in intensive greenhouse agriculture area	Botella et al., (2004)
Dieldrin	Serum	Spain, NR	Men, 18–23	220	Mean, 1.85 µg/L; median, 0.50 µg/L,	< 3–29.42 µg/L, 40.7% detects	Extensive greenhouse agricultural area, association with maternal employment in agriculture	Carreño et al. (2007)
Dieldrin	Serum	Nicaragua, 2002	11–15	38	NR	0% detects	LOD estimated < 10 ng/g lipid; working and living at municipal waste-disposal site and in nonworking children living both nearby and far from site	Cuadra et al. (2006)
Dieldrin	Serum	The Bahamas, 1970–1971	≥ 20; mean, 39	148	Mean, 1.1 µg/L	< 1–9.2 µg/L		Davies et al. (1975)
Dieldrin	Serum	Brazil, 1999	19–63	33	NR	All < 1.4 µg/L	Urban area	Delgado et al. (2002)
Dieldrin	Serum	USA, NR	67.6 ± 14.6	144	Geometric mean, 0.38 µg/L	NR	Study controls; concentrations associated with older age, higher education, higher BMI, a few other factors	Louis et al. (2006)
Dieldrin	Serum	Costa Rica, 2012	≥ 65	53	3.40 µg/L			Steenland et al. (2014)
Dieldrin	Serum	United Republic of Tanzania, NR	NR	47	Females, 0.50 ± 0.07 ng/g; males, 0.55 ± 0.09 ng/g	NR	Adults, reproductive age	Weiss et al. (2006)
Dieldrin	Serum	Germany, NR	NR	42	Women, 0.02 ± 0.01 ng/g; men, 0.08 ± 0.01 ng/g	NR	Adults, reproductive age	Weiss et al. (2006)
Dieldrin	Serum	Norway, 1973–1991	18–60; mean, 41.2	300	Median, 16.1 ng/g lipid	< 0.47 ng/g – NR, 67.9% detects		Ward et al. (2000)

Table 1.3 (continued)

Agent	Sample matrix	Country, year	Age (years)	No. of samples	Exposure level[a]	Exposure range,% detects	Comments	Reference
Dieldrin	Plasma	Spain, Germany, France, NR	54.7	203	Median of detectable, 16.2 µg/L	6.2–NR µg/L, Spain 34% detects; France and Germany 0% detects		Cocco et al. (2008)
Dieldrin	Seminal plasma	United Republic of Tanzania, NR	NR	31	Mean, 0.13 ± 0.05 ng/g	NR	Men, reproductive age	Weiss et al. (2006)
Dieldrin	Seminal plasma	Germany, NR	NR	21	Mean, 0.03 ± 0.01 ng/g	NR	Men, reproductive age	Weiss et al. (2006)
Dieldrin	Follicular fluid	United Republic of Tanzania, NR	NR	31	Mean, 0.17 ± 0.02 ng/g	NR	Women, reproductive age	Weiss et al. (2006)
Dieldrin	Follicular fluid	Germany, NR	NR	21	Mean, 0.03 ± 0.01 ng/g	NR	Women, reproductive age	Weiss et al. (2006)
Dieldrin	Breast milk	Denmark, 1997–2001	NR	36	Median 4.66 ng/g	25th–75th percentiles: 3.06–5.98 ng/g	Women had a narrow age distribution and were mainly from higher social class	Krysiak-Baltyn et al. (2010)
Dieldrin	Breast milk	Finland, 1997–2001	NR	32	Median 2.21 ng/g	25^{th}–75^{th} percentiles: 1.86–3.10 ng/g	Women had a narrow age distribution and were mainly from higher social class	Krysiak-Baltyn et al. (2010)
Dieldrin	Breast milk	USA, NR	NR	1436	Mean 164.2 ± 436.2 ppb fat-adjusted	< 1 – > 500 ppb, 80.8% detects		Savage et al. (1981)
Dieldrin	Breast milk	Israel, 2011–2012	23–35 ; mean, 30	52	2.8 ng/g lipid	NR	Pooled sample	Wasser et al. (2015)
Dieldrin	Breast milk	Turkey, NR	NR	75	NR	All < 5 ng/g lipid, 0% detects		Yalçın et al. (2015)
Dieldrin	Breast milk	Denmark, 1993–94	25–29	36	Median, 8 ng/g fat	3–19 ng/g fat	Women, several days after giving birth	Danish National Board of Health (1999)

[a] Exposure levels expressed as the mean, unless otherwise indicated

BMI, body mass index; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; NR, not reported

women in China, with a mean aldrin concentration of 7.29 µg/L and mean dieldrin concentration of 5.27 µg/L (Luo et al., 2016).

1.5. Regulations and guidelines

In the USA, the American Conference of Governmental Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA) have all adopted a time-weighted average (TWA) concentration limit of 0.25 mg/m^3 in air for aldrin and dieldrin, also noting dangers from cutaneous absorption (ATSDR, 2002; NIOSH, 2016a). NIOSH has also designated aldrin as a "potential occupational carcinogen," and has determined an Immediately Dangerous to Life or Health (IDLH) concentration of 25 mg/m^3 (NIOSH, 2016a). NIOSH similarly designated dieldrin as a "potential occupational carcinogen," and has determined an IDLH concentration of 50 mg/m^3 (NIOSH, 2016b).

WHO has established a guideline value of 0.03 µg/L for the sum of aldrin and dieldrin concentrations in drinking-water (WHO, 2003). The United States EPA has not established a maximum contaminant level for aldrin in drinking-water, but has published a variety of non-enforceable health advisory levels that depend on duration of exposure and age (EPA, 2012).

Under the European Union harmonized classification and labelling system, both aldrin and dieldrin are suspected of "causing cancer" (Carc. 2) [H 351] and have been determined to be "very toxic to aquatic life" (Aquatic Acute 1) [H 450] and "very toxic to aquatic life with long lasting effects" (Aquatic Chronic 1) [H 410], "toxic if swallowed" (Acute Tox. 3) [H 311], and to "cause damage to organs through prolonged or repeated exposure" (STOT RE 1) [H 372] (ECHA, 2016a, b). In addition, aldrin has been determined to be "toxic in contact with skin" (Acute Tox. 3) [H 301], whereas dieldrin has been determined to be "fatal in contact with skin" (Acute Tox. 1) [H 310] (ECHA, 2016a, b).

In the USA, aldrin and dieldrin uses were restricted to certain non-food applications in 1974, and the sole manufacturer cancelled all remaining uses in 1989 (ATSDR, 2002). In the 1970s, the use of aldrin was banned or severely restricted in a number of additional countries including Germany, Italy, Japan, Norway, the former Soviet Union, and the United Kingdom (IARC, 1974). Use and export of aldrin and dieldrin are banned in the European Union (European Commission, 2004). There are additional restrictions and requirements regarding the presence of aldrin in seeds, effluent, groundwater, water bodies, hazardous waste, and releases to the environment in the USA (ATSDR, 2002).

Aldrin and dieldrin are listed in Annex A of the Stockholm Convention on Persistent Organic Pollutants (Stockholm Convention, 2008), under which parties must take steps to eliminate production and use unless they have registered for an exemption.

2. Cancer in Humans

2.1 Aldrin

Aldrin and dieldrin are often discussed together because aldrin readily converts into dieldrin, both in the environment and in the human body (see Sections 1 and 4). The studies in this section may therefore also be discussed or referred to in the section on dieldrin (Section 2.2), when results for both compounds were presented in the same study.

2.1.1 Cohort studies

See Table 2.1.

(a) Occupational cohorts

Two studies have published results related to aldrin exposure in occupational cohorts: a study in workers at an insecticide plant in Pernis-Rotterdam, the Netherlands; and the Agricultural Health Study (AHS) of Iowa and North Carolina, USA, among residents licensed to apply restricted-use pesticides. A study in workers at organochlorine pesticide-manufacturing plants in Colorado, USA, was considered uninformative because the plant had produced many different pesticides and no results specific to aldrin (or dieldrin) were presented (Ditraglia et al., 1981; Brown, 1992; Amoateng-Adjepong et al., 1995).

Several studies have been published on a cohort of 570 male workers at a Dutch plant that produced and formulated aldrin and dieldrin (Ribbens, 1985; de Jong et al., 1997; Sielken et al., 1999; Swaen et al., 2002; van Amelsvoort et al., 2009). The most recent publication included employees who had worked for at least 1 year between 1954 and 1970 inclusive and were followed up until 2006 (van Amelsvoort et al., 2009). Standardized mortality ratios (SMRs) were calculated relative to the national population of the Netherlands. Total intake of dieldrin plus aldrin was calculated using models based on blood monitoring that had been carried out during the 1950s for 343 members of the cohort (de Jong, 1991). Blood monitoring of dieldrin was used as a combined measure of exposure to both aldrin and dieldrin. Workers without samples were allocated the same intake as workers in the same job, workplace, and time.

The standardized mortality ratio for all cancers combined was 0.76 (95% CI, 0.61–0.95) for all workers. When the workers were divided into three groups on the basis of dose, the standardized mortality ratios were 1.00 (95% CI, 0.66–1.46) for the group at the lowest dose (mean intake, 270 mg); 0.75 (95% CI, 0.50–1.09) for the group at the moderate dose (mean intake, 540 mg), and 0.66 (95% CI, 0.44–0.96) for the group at the highest dose (mean intake, 750 mg).

The standardized mortality ratio for cancer of the lung was significantly different from expected (SMR, 0.63; 95% CI, 0.41–0.92; 26 cases) and there was no dose–response pattern. Standardized mortality ratios for cancers of the oesophagus, rectum, liver and biliary tract, and skin were elevated based on small numbers of deaths, but were not statistically significant or systematically related to exposure level. [For the other cancers examined, all had fewer than 10 cases and none had statistically significant results. No internal analyses were performed.]

[The Working Group noted that the strengths of this study were that the plant made only aldrin and dieldrin; the exposure assessment was based on biomonitoring and modelling; and there was a small loss to follow-up. The limitations were that exposure assessment did not separate aldrin and dieldrin; the study reported mortality data, rather than incidence data; there was low power for rare cancers; no adjustment for confounders; and there were no internal analyses.]

In the AHS, more than 57 000 pesticide-user licensees in Iowa and North Carolina, USA, were recruited between 1993 and 1997. At enrolment, participants completed a self-administered questionnaire on whether they had ever mixed or applied 50 specific pesticides (including aldrin and dieldrin), which application methods were used, and the use of personal protective equipment. About half of the cohort also reported the number of years and days per year they had personally mixed aldrin or dieldrin.

Lifetime exposure-days of use for each pesticide were calculated as the product of the number of years a participant had personally mixed or applied each pesticide multiplied by the number of days per year that pesticide was used. In addition, an intensity-weighted lifetime exposure-days score was calculated by multiplying lifetime exposure-days by an exposure intensity

Table 2.1 Cohort studies of cancer and exposure to aldrin

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
Ward et al. (2000) Norway 1973–1993 Population-based Nested case–control	Cases: 150; random selection from Janus serum bank with samples taken before diagnosis Controls: 150; matched to cases by date of sample and age Exposure assessment method: personal monitoring; gas chromatography	Breast	Aldrin Above LOD	1	0.5 (0.0–6.5)	Age, time of sample collection	
Flower et al. (2004) Iowa and North Carolina, USA Childhood cancers 1975–1998 in Iowa and 1990–1998 in North Carolina Cohort	50 cases; Agricultural Health Study; children of pesticide licensees, born after 1975 Exposure assessment method: questionnaire; parental pesticide use	Childhood cancer	Aldrin, father's use (prenatal)	6	2.66 (1.08–6.59)	Age of child at enrolment	Strengths: large numbers, individual pesticide use Limitations: self-reported data
Engel et al. (2005) Iowa and North Carolina, USA 1993–2000 Cohort	30 454; Agricultural Health Study; wives of pesticide licensees Exposure assessment method: questionnaire	Breast	Aldrin use By wife By husband By husband (premenopausal) By husband (postmenopausal)	 4 52 6 40	 0.9 (0.3–2.5) 1.9 (1.3–2.7) 1.4 (0.6–3.8) 1.7 (1.1–2.6)	Age, state, race	Strengths: large numbers, individual pesticide use Limitations: self-reported data

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
Purdue et al. (2007) Iowa and North Carolina, USA Recruited, 1993–1997, follow-up, 2002 Cohort	51 011; Agricultural Health Study; pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days, and intensity-weighted exposure days (take into account factors affecting exposure)	All cancers combined: incidence	Aldrin	680	1.0 (0.9–1.1)	Age, state, sex, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	Strengths: large numbers, individual pesticide use Limitations: self-reported data
		Lung: incidence	Aldrin	53	1.0 (0.7–1.4)		
		Colon: incidence	Aldrin	39	0.7 (0.4–1.0)		
		Rectum: incidence	Aldrin	28	1.4 (0.8–2.4)		
		Malignant melanoma: incidence	Aldrin	23	1.1 (0.7–2.0)		
		Leukaemia: incidence	Aldrin	22	1.4 (0.8–2.7)		
van Amelsvoort et al. (2009) Pernis, the Netherlands 1954–2006 Cohort	570; men employed ≥ 1 year in a pesticide production plant, 1954–1970 Exposure assessment method: modelling; exposure modelled from blood measures in subgroup (n = 343) to produce total dose for each worker; range, 11–7755 mg dieldrin and aldrin combined	All cancers combined	Estimated intake of aldrin+dieldrin			Age, time	Earlier publications from this study are Swaen et al. (2002); Sielken et al. (1999); de Jong et al. (1997); Ribbens (1985) Strengths: biomonitoring data modelled to give quantitative exposure assessment Limitations: no internal comparisons made; unable to separate exposure to dieldrin and Aldrin; small numbers
			All	82	0.76 (0.61–0.95)		
			Low	27	1.00 (0.66–1.46)		
			Moderate	27	0.75 (0.50–1.09)		
			High	28	0.66 (0.44–0.96)		
		All cancers combined: Mortality	SMR			Age, time	
			Assistant operator	28	0.86 (0.58–1.25)		
			Maintenance	11	0.66 (0.33–1.19)		
			Operator	41	0.78 (0.56–1.05)		
			Supervisor	2	0.45 (0.06–1.65)		
		Oesophagus	Estimated intake of aldrin+dieldrin			Age, time	
			All	4	1.59 (0.43–4.08)		
			Low	2	2.87 (0.35–10.35)		
			Moderate	1	1.17 (0.03–6.49)		
			High	1	1.08 (0.03–5.99)		

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
van Amelsvoort et al. (2009) (cont.)		Rectum	Estimated intake of aldrin+dieldrin			Age, time	
			All	6	2.15 (0.79–4.68)		
			Low	3	4.42 (0.91–12.91)		
			Moderate	1	1.10 (0.03–6.11)		
			High	2	1.76 (0.21–6.34)		
		Liver and bile ducts	Estimated intake of aldrin+dieldrin			Age, time	
			All	4	2.16 (0.59–5.54)		
			Low	2	4.26 (0.52–15.41)		
			Moderate	2	3.23 (0.39–11.65)		
			High	0	0.00 (0.00–4.14)		
		Lung	Estimated intake of aldrin+dieldrin			Age, time	
			All	26	0.63 (0.41–0.92)		
			Low	7	0.67 (0.27–1.37)		
			Moderate	12	0.86 (0.44–1.5)		
			High	7	0.43 (0.17–0.89)		
		Skin (non-melanoma)	Estimated intake of aldrin+dieldrin			Age, time	
			All	3	3.02 (0.62–8.84)		
			Low	1	3.57 (0.09–19.9)		
			Moderate	2	6.12 (0.74–22.09)		
			High	0	0.00 (0.00–8.44)		

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
Koutros et al. (2013a) Iowa and North Carolina, USA 1993–2007 Cohort	54 412; Agricultural Health Study; pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days and intensity-weighted exposure days	Prostate (total): incidence	Cumulative lifetime exposure to aldrin			Age, state, smoking status, race, family history of prostate cancer, fruit servings, leisure time physical activity in winter	Strengths: large numbers, individual pesticide use
			Q1	65	1.04 (0.80–1.35)		
			Q2	64	0.94 (0.72–1.22)		
			Q3	64	1.14 (0.88–1.48)		
			Q4	64	1.25 (0.97–1.63)		
			Trend-test *P*-value: 0.07				
		Prostate (aggressive/ advanced): incidence	Cumulative lifetime exposure to aldrin				
			Q1	33	0.97 (0.67–1.41)		
			Q2	33	1.09 (0.75–1.57)		
			Q3	34	1.21 (0.84–1.74)		
			Q4	31	1.49 (1.03–2.18)		
			Trend-test *P*-value: 0.02				
		Prostate: family history of prostate cancer	Cumulative lifetime exposure to aldrin				
			Q1	12	1.29 (0.70–2.4)		
			Q2	20	1.95 (1.17–3.25)		
			Q3	17	1.83 (1.08–3.09)		
			Q4	16	2.13 (1.22–3.72)		
			Trend-test *P*-value: 0.005				

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
Koutros et al. (2013b) Iowa and North Carolina, USA 1993–2004 Nested case–control	Cases: 776; prostate cancer cases in AHS who had provided DNA of good quality Controls: 1444; non-cancer subjects in AHS who had provided DNA of good quality Controls: 1444; non-cancer subjects in AHS who had provided DNA of good quality Exposure assessment method: Questionnaire; lifetime exposure days, and intensity-weighted exposure days	Prostate: TET2 Genotype AA	Aldrin, low Aldrin, high Trend-test *P*-value: 0.006 for interaction	10 13	1.86 (0.73–4.75) 3.67 (1.43–9.41)	Age, state	Strengths: large numbers, individual pesticide use
Alavanja et al. (2014) Iowa and North Carolina, USA Recruited, 1993–1997, follow-up, 2011 Cohort	54 306; AHS; pesticide licensees. Exposure assessment method: questionnaire; lifetime exposure days, and intensity-weighted exposure days (take into account factors affecting exposure)	NHL: incidence MM: incidence	Aldrin Aldrin	116 29	0.9 (0.7–1.1) 1.5 (0.9–2.5)	Age, state, sex, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	Strengths: large numbers, individual pesticide use

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
Koutros et al. (2016) Iowa and North Carolina, USA Recruited, 1993–1997, follow-up, 2011 Cohort	57 310; AHS, male pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days, and intensity-weighted exposure days	Urinary bladder: incidence	Ever exposed	88	1.2 (0.92–1.57)	Age, state, smoking status, race	Men only Strengths: large numbers, individual pesticide use. Limitations: self-reported data
		Urinary bladder: incidence	Cumulative intensity weighted days of use			Age, state, education level, smoking status, race	
			Tertile 1	15	0.88 (0.5–1.53)		
			Tertile 2	18	1.61 (0.96–2.68)		
			Tertile 3	17	1.51 (0.89–2.55)		
			Trend-test *P*-value: 0.08				

AHS, Agricultural Health Study; CI, confidence interval; LOD, limit of detection; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; SMR, standardized mortality ratio

score based on modifying factors such as use of personal protective equipment.

Between 1999 and 2005, participants were asked to report all pesticides used in the year before the interview, as well as frequency of use. This interview was completed by only 63% of participants, and in reports after 2012 multiple imputation with logistic regression and stratified sampling were used to impute missing pesticide-exposure information (Heltshe et al., 2012). A wide range of potential confounders including lifestyle factors, other agricultural factors, and medical history were also collected at baseline.

Pertinent results from this study have been published in several publications focused on different cancers. The most recent results for each cancer are reviewed below.

There were no statistically significant increases in risk of all cancers associated with exposure to aldrin, or risk of cancer of the lung, colon, rectum, or melanoma, or leukaemia (Purdue et al., 2007), or of non-Hodgkin lymphoma (NHL) (relative risk, RR, 0.9; 95% CI, 0.7–1.1), or multiple myeloma (Alavanja et al., 2014). For cancer of the bladder, there was no significant association with ever use of aldrin or high use (RR, 1.51; 95% CI, 0.89–2.55) (Koutros et al., 2016). There was a non-statistically significant increase in risk of all prostate cancer associated with aldrin use (RR, 1.25; 95% CI, 0.97–1.63; *P* for trend, 0.07), which was more marked for the highest quartile (RR, 1.49; 95% CI: 1.03–2.18), with a significant exposure–response trend for aggressive prostate cancer (*P* for trend, 0.02) (Koutros et al., 2013a). Cancer of the prostate was also associated with aldrin use in those with a family history of prostate cancer (*P* for trend, 0.005) (Koutros et al., 2013a); and in further gene–environment analyses, men carrying two AA alleles at rs7679673 were at increased risk of prostate cancer when they had high aldrin use (Koutros et al., 2013b). Cancer of the breast in wives of the pesticide licensees was not increased for self-use of aldrin, but was increased for husband's use (RR, 1.9; 95% CI, 1.3–2.7), and this was more marked in postmenopausal women (RR, 1.7; 95% CI, 1.1–2.6; 40 cases) than in premenopausal women (RR, 1.4; 95% CI, 0.6–3.8; 6 cases) (Engel et al., 2005). Finally, prenatal use of aldrin by fathers was associated with an increase in risk of childhood cancer (RR, 2.66; 95% CI, 1.08–6.59), although this was based on only six cases (Flower et al., 2004). [The Working Group noted that the strengths of this study were that it was large, there was adjustment for other pesticides and potential confounding factors (including major risk factors for cancer of the breast), the exposure assessment was extensive, and the authors were able to separate exposures to aldrin, dieldrin, and other pesticides. The limitations included the small numbers of cases for some analyses, especially in early publications.]

(b) Population cohort study

(i) Cancer of the breast

A case–control study nested within the Janus cohort in Norway used serum samples that had been collected between 1973 and 1991 (Ward et al., 2000). Of 25 431 women who were working outside the home or were resident on farms as of the 1970 or 1980 census and who were followed for cancer incidence until 1993, 272 incident cases of cancer of the breast were reported by 1993. Of these, 150 were randomly chosen, and 150 controls who were alive and cancer-free at time of case diagnosis were matched to cases by date of sample and date of birth. Aldrin, and dieldrin (which may reflect exposure to aldrin and/or dieldrin) were measured in the sera. There were only three samples that contained aldrin at a concentration above the limit of detection (LOD) and the matched odds ratio for aldrin was 0.5 (95% CI, 0–6.5).

[The Working Group noted that the strengths of this study were that exposure was measured before diagnosis, while the limitations were that the exposure assessment was based solely

on serum measurements, given conversion of aldrin to dieldrin, and that only three samples contained aldrin at a level above the LOD.]

2.1.2 Case–control studies

See Table 2.2.

The associations between cancer risk and exposure to organochlorine pesticides, including aldrin and dieldrin, have been investigated in case–control studies in the USA, Canada, and countries in Europe.

Exposure assessment in case–control studies has mainly been performed in two ways. First, questionnaires can be used to obtain self-reports of pesticides used by the participant, and often also some information about methods of application and use of personal protective equipment. Studies using such questionnaires were able to report results for dieldrin and aldrin separately. Second, samples of serum or adipose tissue can be collected and analysed for pesticides. Because of the conversion of aldrin to dieldrin noted above, results for serum dieldrin may represent exposure to both aldrin and dieldrin.

The methods used in studies presenting results for both aldrin and dieldrin are given in the section on aldrin (Section 2.1) and are referred to in the section on dieldrin (Section 2.2). Studies reporting only results related to dieldrin (which may include aldrin in the case of serum measurements) are described in the section on dieldrin.

The Working Group excluded two case–control studies that did not report results specifically for aldrin or dieldrin (Cocco et al., 2008; Tomasallo et al., 2010), and three case–control studies that did not adequately report their methods (Shukla et al., 2001; Mathur et al., 2002, 2008). A study in Gran Canaria, Spain, (Boada et al., 2012) measured aldrin and dieldrin in serum samples from 121 cases of breast cancer and 103 women who had given serum samples in a survey several years earlier. The controls were significantly younger than the cases. [The Working Group noted that the reported prevalence of exposure and serum levels of aldrin (mean, 72.5 ng/g lipid for cases, with 74% above the LOD; and 27.1 ng/g lipid for controls, with 38% above the LOD) and dieldrin (mean, 12.6 ng/g lipid for cases, with 22% above the LOD; and mean, 9.5 ng/g lipid for controls, with 32% above the LOD) was unusually high. The very narrow confidence intervals around odds ratios based on small numbers were also unusual (aldrin odds ratio, 1.027; 95% CI, 0.991–1.065; and dieldrin odds ratio, 1.002; 95% CI, 0.956–1.050) given that, in the same model, the results for lindane (with similar numbers of exposed cases as dieldrin) were 1.097 (95% CI, 0.420–28.412). The Working Group therefore had little confidence in the results of this study and it was also excluded.]

(a) Non-Hodgkin lymphoma

Several case–control studies have investigated the association between NHL and exposure to aldrin. Three of these studies used questionnaires to obtain self-reported data separately on aldrin and dieldrin, and four of these studies used serum or tissue levels of dieldrin to measure combined exposure to dieldrin and aldrin (see Section 2.3).

A population-based case–control study included 622 newly diagnosed cases of NHL among white men aged ≥ 30 years from Iowa and Minnesota, USA (Cantor et al., 1992). The controls were 1245 men without haematopoietic or lymphatic cancer, randomly selected from the general population and frequency-matched to NHL cases by 5-year age group, vital status at interview, and state of residence. In-person structured interviews included detailed questions about farming and pesticide-use history. Adjusted odds ratios indicated non-significantly elevated risk among subjects who had ever personally handled, mixed, or applied aldrin on crops (OR, 1.1; 95% CI, 0.7–1.7). The risks were somewhat higher for those who had handled

Table 2.2 Case–control studies of cancer and exposure to aldrin

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
Brown et al. (1990) Iowa and Minnesota, USA 1980–1984	Cases: 578; tumour registry and hospital records Controls: 1245; matched to case by 5-yr age group, vital status and state via random-digit dialling, Medicare records or state death certificates Exposure assessment method: questionnaire; detailed questions with days per year for each pesticide	Leukaemia: newly diagnosed cases	Ever handled aldrin/days per year			Vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, high-risk exposures	US midwest studies. cases and controls residing in cities with little farming activity (i.e. Minneapolis, St Paul, Duluth, and Rochester) were excluded from the study Strengths: large population-based study in farming areas; in-person interviews; detailed questionnaires including quantification; collection of other potential risk factors; reviewed diagnosis Limitations: multiple comparisons; self-report of pesticide use and limited numbers of participants with aldrin and dieldrin use
			Aldrin, ever handled	33	0.9 (0.6–1.4)		
			Aldrin, 1–4 days/year	11	1 (0.5–2)		
			Aldrin 5–9 days/year	7	0.8 (0.3–2)		
			Aldrin 10+ days/year	4	0.5 (0.2–1.4)		
Cantor et al. (1992) Iowa and Minnesota, USA 1980–1983	Cases: 622; health registry and hospital and pathology records Controls: 1245; matched to cases by age, vital status and state via random-digit dialling, Medicare record or state death certificate files Exposure assessment method: questionnaire; in-person interview	NHL: newly diagnosed cases of four subtypes, follicular, diffuse, small lymphocytic, and "other NHL"	Aldrin exposure: ever handled	47	1.1 (0.7–1.7)	Vital status, age, state, smoking, family history of lympho-haematopoietic cancer, high-risk occupation, high-risk exposures	Data subsequently pooled in De Roos et al. (2003); white men only Strengths: large population-based study in farming areas Limitations: not controlled for exposure to other pesticides
			Handled before 1965	34	1.3 (0.8–2.1)		

Table 2.2 (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
McDuffie et al. (2001) Alberta, Saskatchewan, Manitoba, Quebec, Ontario, British Columbia, Canada 1991–1994	Cases: 517; cancer registries Controls: 1506; health insurance and voting records; frequency-matched on province and ± 2 yr to the age distribution of entire case group Exposure assessment method: questionnaire; self-administered postal questionnaire, followed by telephone interview	NHL	Ever use of aldrin			Age, province of residence, medical variables, mecoprop	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 recall bias; poor response rates; most exposed men were exposed to multiple pesticides and multiple classes of pesticides, but risk estimates were not adjusted for other pesticides
			Model adjusted for age and province of residence	10	3.81 (1.34–10.79)		
			Fully adjusted model	10	4.19 (1.48–11.96)		
Schroeder et al. (2001) Iowa and Minnesota, USA 1980–1983	Cases: 622; state health registry and hospital/ pathology laboratory records Controls: 1245; matched to cases by age, state and vital status via random-digit dialling, Medicare records or state death certificate files Exposure assessment method: questionnaire; in-person structured interviews	NHL: t(14;18)-Positive or t(14;18)-negative cases	Ever use of aldrin			Age, state	Same study population as Cantor et al. (1992); the study looked at NHL subtypes but > 70% of cases had missing subtypes; small numbers of cases with aldrin or dieldrin exposure Strengths: large population-based study in farming areas Limitations: relative small numbers of t(14;18)-positive or -negative NHL
			Aldrin: t(14;18)-positive NHL vs controls	11	1.5 (0.8–2.7)		
			Aldrin: t(14;18)-negative NHL vs controls	10	0.7 (0.4–1.4)		

Table 2.2 (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
De Roos et al. (2003) Nebraska, Iowa and Minnesota, Kansas, USA 1979–1986	Cases: 650; Nebraska Lymphoma Study Group, hospitals, state health registry, cancer registry Controls: 1933; matched to cases by race, sex, age, region and vital status via random-digital dialling, Medicare records or state mortality files Exposure assessment method: questionnaire; 47 pesticides	NHL: newly diagnosed cases	Aldrin, ever use Aldrin (logistic regression) Aldrin (hierarchical regression)	 47 47	 0.5 (0.3–0.9) 0.6 (0.4–1.0)	Age, study site, all other pesticides	USA midwest studies (pooled) from 3 previous case–control studies (Zahm, Cantor, Hoar); analysis restricted to potentially carcinogenic pesticides
Ibarluzea et al. (2004) Granada and Almeria provinces, Spain April 1996 to June 1998	Cases: 198; breast cancer histologically diagnosed Controls: 260; matched by age (± 3 yr) and hospital; undergoing gall bladder, inguinal hernia, abdominal, varicose vein or other surgery Exposure assessment method: personal monitoring; adipose tissue; aldrin measured with gas chromatography	Breast Breast (premenopausal) Breast (postmenopausal)	Aldrin > LOD > LOD > LOD	 NR 27 40	 1.55 (1–2.4) 1.07 (0.47–2.42) 1.84 (1.06–3.18)	Age, reference hospital, in BMI, number of children, age first pregnancy, family history of breast cancer, alcohol, tobacco	Strengths: medium-sized study; able to adjust for multiple potential confounders Limitations: aldrin measured after diagnosis

Table 2.2 (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
Lee et al. (2004) Iowa, Minnesota, Nebraska, USA 1980–1986	Cases: 872; state health registry, hospitals and Nebraska Lymphoma Study Group Controls: 2336; matched to case on age, race, and state via random-digit dialling, Medicare records or mortality files Exposure assessment method: questionnaire; telephone or personal interviews with subjects or next-of-kin in Nebraska	NHL	Ever use of aldrin Aldrin among asthmatics Aldrin among non-asthmatics	 10 66	 2.1 (0.9–5.1) 1.0 (0.7–1.5)	Age, vital status, state	Strengths: pooled study so larger numbers Limitations: use of proxy respondents may have led to nondifferential misclassification; no adjustment for co-exposures
Pahwa et al. (2011) Six provinces in Canada 1991–1994	Cases: 357 STS; provincial cancer registries or hospitals Controls: 1506; matched to case by age constraints (± 2 yr) from provincial health insurance records, telephone listings, voters' lists Exposure assessment method: questionnaire; self-administered postal questionnaire and telephone interview	STS	Ever handled aldrin/days per year Aldrin, ever handled	 4	 3.71 (1.00–13.76)	Statistically significant medical variables (history of measles, rheumatoid arthritis, mononucleosis, whooping cough and a positive family history of cancer in a first-degree relative), age group, province of residence	Same controls and data collection methods as McDuffie et al. (2001) Strengths: population-based study; large number of cases; detailed questionnaires on pesticide exposure information; did not use surrogates Limitations: diversity in exposure situations (crops and animals) but no distinction in analysis; self-reported questionnaire; low response from potential controls (48%)

AHS, Agricultural Health Study; CI, confidence interval; LOD, limit of detection; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; SMR, standardized mortality ratio; STS, soft tissue sarcoma; yr, year(s)

these crop insecticides before 1965 (OR, 1.3; 95% CI, 0.8–2.1).

A further analysis (Schroeder et al., 2001) included the same cases and controls as those in the study by Cantor et al. (1992), but investigated subtypes of NHL, t(14;18)-positive or t(14;18)-negative. Because subtype was missing for more than 70% of study cases, an expectation–maximization algorithm was used to impute missing values. Adjusted odds ratios and 95% confidence intervals for various agricultural risk factors and t(14;18)-positive and -negative cases of NHL were estimated based on polytomous logistic regression models. Aldrin use was not significantly associated with t(14;18)-positive NHL or with t(14;18)-negative NHL.

[The Working Group noted that the strengths of this study were that it was a large population-based study with in-person interview on detailed farming and pesticide-use history, there were adequate numbers of exposed cases; and it was possible to differentiate exposures to aldrin and dieldrin. The limitations were the self-reported exposure and the fact that NHL subtypes were missing for more than 70% of the cases.]

A study by De Roos et al. (2003) pooled data from three case–control studies (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) in the midwest USA to examine pesticide exposures in farming as risk factors for NHL in men. Newly diagnosed NHL cases among white men aged ≥ 30 years in Iowa and Minnesota from 1980 to 1983 and aged ≥ 21 years in eastern Nebraska counties from 1983 to 1986, and a random sample of cases among white men aged ≥ 21 years diagnosed between 1979 and 1981 in Kansas were identified. The Minnesota and Iowa portions of this study overlapped with the population studies by Cantor et al. (1992). Population-based controls were randomly selected from the same geographical areas as the cases, frequency-matched to cases by race, sex, age, and vital status at the time of interview via various sources. Interviews were conducted to obtain pesticide uses and other known or suspected risk factors for NHL. Subjects with a missing or "don't know" response for any of the 47 pesticides of interest (about 25% of subjects) were excluded from analyses, resulting in 650 cases and 1933 controls available in the regression analyses. There was a significantly decreased risk of NHL associated with aldrin use (OR, 0.5; 95% CI, 0.3–0.9). Analysis by hierarchical regression gave similar results. [The Working Group noted that this was a large study, which used adjustment for multiple pesticides with hierarchical logistic regression. The limitations were the lack of univariate analyses of single pesticides, and the exclusion of subjects with any missing data. The Working Group noted a difference between the results of this pooled analysis and those of the original analysis by Cantor et al. (1992), which included all subjects and did not adjust for use of other pesticides.]

A further analysis investigated whether asthma modifies the risk of NHL associated with pesticide exposure (Lee et al., 2004). This study included men from Iowa and Minnesota and men and women from Nebraska, and excluded subjects without asthma information (n = 25), leaving 872 cases and 2336 controls for analysis. Odds ratios were adjusted for age, state, and vital status. The risk of NHL was non-significantly elevated with exposure to aldrin (OR, 2.1; 95% CI, 0.9–5.1) in asthmatics compared with non-farmers without asthma. No increase in risk was reported for non-asthmatics. [The Working Group noted the very small numbers of subjects with asthma and aldrin use, resulting in wide confidence intervals.]

The Cross-Canada Study of Pesticides and Health was a population-based case–control study in male residents in six Canadian provinces (McDuffie et al., 2001). Incident cases with first diagnosis of NHL between 1991 and 1994 and randomly selected, age-matched controls were sent postal questionnaires, with follow-up telephone interviews to obtain details of pesticide

use for subjects who reported pesticide exposure of 10 hours per year or more, plus 15% random samples with lower exposure. The results were based on 517 NHL cases (10 exposed to aldrin) and 1506 controls who responded to the postal questionnaires. NHL was significantly associated with reported exposure to aldrin (OR, 3.81; 95% CI, 1.34–10.79) with adjustment for age and province of residence. NHL risk associated with aldrin use increased to 4.19 (95% CI, 1.48–11.96) when statistically significant medical variables were also adjusted. In additional multivariate models with independent predictors, which included histories of measles, previous cancer, first-degree relatives with cancer and allergy desensitization, as well as exposure to mecoprop, aldrin was significantly associated with increased risk of NHL (OR, 3.42; 95% CI, 1.18–9.95). [The Working Group noted that the strengths of the study were the use of postal questionnaire followed by telephone interviews to obtain details of pesticide use, the fact that surrogates were not used, and that many pesticides/chemicals were analysed and many covariates considered. However, there was limited precision for aldrin, and a low response rate from potential controls (48%).]

(b) Leukaemia

One study investigated leukaemia and aldrin exposure (Brown et al., 1990). This population-based case–control interview study included 578 newly diagnosed leukaemia cases among white men and 1245 controls from Iowa and Minnesota, part of the midwest studies by the United States National Cancer Institute (NCI) (Cantor et al., 1992). Additional interviews to obtain number of days of handling pesticides were completed for 86 cases and 203 controls from Iowa who reported agricultural use of pesticides in the initial interview. Odds ratios relative to nonfarmers for 243 cases and 547 controls were adjusted for multiple risk factors. The odds ratio for subjects who had ever personally handled, mixed, or applied aldrin was 0.9 (95% CI, 0.6–1.4). Odds ratios for leukaemia by the number of days per year that aldrin was reportedly handled showed a decreasing dose–response trend. [The Working Group noted that this was a large population-based study with in-person and follow-up phone interviews in farming areas. A limitation was that more surrogates were interviewed for cases (73%) than for controls (28%) in follow-up.]

(c) Soft tissue sarcoma

The association between soft tissue sarcoma (STS) and aldrin exposure was investigated in the previously described Cross-Canada Study of Pesticides and Health (McDuffie et al., 2001). Details of the study methods are given above. The results for STS were based on 357 cases and 1506 controls who responded to the postal questionnaires (Pahwa et al., 2011). STS was associated with reported exposure to aldrin (OR, 3.71; 95% CI, 1.00–13.76; 4 exposed cases) in multivariate models. In additional multivariate models with independent predictors, which included histories of whooping cough and first-degree relatives with cancer as well as exposure to diazinon, the odds ratio for aldrin was 3.35 (95% CI, 0.89–12.56). [The Working Group noted the very small number of exposed cases, resulting in poor precision.]

(d) Cancer of the breast

A hospital-based case–control study recruited residents of two provinces of Spain in 1996–1998 (Ibarluzea et al., 2004). Cases were women undergoing surgery for breast cancer and controls were women undergoing non-cancer-related surgery (gall bladder surgery, 65%). Of 260 eligible cases and 352 controls, 198 (76%) cases and 260 (74%) controls consented and provided adequate adipose tissue samples and interviews. Dieldrin and aldrin were measured using gas chromatography in adipose tissue: more than 40% of subjects had measurable levels of aldrin, while less than 40% had measurable dieldrin. After

adjusting for a range of potential confounders, a positive association was seen between breast cancer and aldrin levels above the LOD (OR, 1.55; 95% CI, 1.0–2.4) and this relationship was stronger in postmenopausal women (OR, 1.84; 95% CI, 1.06–3.18). [The Working Group noted that the strengths of this study were the biomarker assessment of exposure in adipose tissue and adjustment for a range of potential confounders. The Working Group considered that the finding that the concentration of aldrin was higher than that of dieldrin was surprising, given that aldrin should not have been in active use at the time the study was conducted.]

2.2 Dieldrin

2.2.1 Cohort studies

See Table 2.3.

(a) Occupational cohort studies

Workers at an insecticide plant in the Netherlands were exposed to dieldrin and aldrin. The study methods and results are described in Section 2.1.1 because data were reported for both pesticides combined.

Exposure to dieldrin was specifically investigated in the AHS and the methods are presented in Section 2.1.1. For exposure to dieldrin, there were no increases in risk for all cancers, or for cancer of the colon or rectum (Purdue et al., 2007), for total prostate cancer (Koutros et al., 2013a), for NHL (RR, 0.9; 95% CI, 0.6–1.2), or any NHL subtype, including multiple myeloma (Alavanja et al., 2014). Risks were non-significantly increased for leukaemia (RR, 1.7; 95% CI, 0.8–3.6) and melanoma (RR, 1.4; 95% CI, 0.7–2.9) (Purdue et al., 2007), aggressive prostate cancer (RR, 1.39; 95% CI, 0.65–2.94) (Koutros et al., 2013a), and bladder cancer (RR, 1.19; 95% CI, 0.82–1.72) (Koutros et al., 2016). Lifetime days of dieldrin use showed a positive association with incidence of lung cancer in the highest exposure category (hazard ratio, HR, 1.93; 95% CI, 0.70–5.30). The results were very similar for either a 5- or 15-year lag. Additionally, the results using intensity-weighted lifetime days of dieldrin use showed a similar increase of 2-fold in the highest exposure category (HR, 2.06; 95% CI, 0.95–4.43) (Bonner et al., 2017). Risk of cancer of the breast in wives of the pesticide licensees was increased for husband's use of dieldrin (RR, 2.0; 95% CI, 1.1–3.3) (Engel et al., 2005). [The Working Group noted that the strengths of this study were that it was large, and there was adjustment for other pesticides and potential confounding factors, there was an extensive exposure assessment effort, and the study was able to separate exposures to aldrin, and other pesticides. The limitations were the small numbers for some analyses, especially in early publications.]

(b) Population cohort studies

(i) Non-Hodgkin lymphoma

From 25 802 adults in Washington County, Maryland, USA, who enrolled in 1974 in the Campaign Against Cancer and Stroke (CLUE I) study, 74 incident NHL cases with serum samples available and 147 matched controls were included in a nested case–control study (Cantor et al., 2003). The medians of lipid-corrected serum concentrations of dieldrin (which may reflect exposure to aldrin and/or dieldrin) were 129.9 and 116.9 ng/g lipid for cases and controls, respectively (Wilcoxon signed rank test, $P = 0.26$). Odds ratios showed no evidence of an association between NHL risk and quartiles of serum dieldrin (adjusted OR, 0.9; 95% CI, 0.4–2.4 in the highest versus the lowest quartile, P for trend, 0.88). [The Working Group noted that the strengths of the study included the collection of biological samples, and matching and/or adjustment for potential confounders; however, serum aldrin was not considered but may contribute to serum dieldrin.]

Table 2.3 Cohort studies of cancer and exposure to dieldrin

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
Høyer et al. (1998) Denmark Enrolled, 1976, follow-up to 1993 Nested case–control	Cases: 240; all women who developed breast cancer, with enough serum sample Controls: 477; random selection of 2 women matched for age, date of examination, vital status and breast cancer status of case Exposure assessment method: biomarker; gas chromatography	Breast	Dieldrin Q2 Q3 Q4 Trend-test *P*-value: 0.01	 57 66 73	 1.58 (0.93–2.67) 1.96 (1.14–3.39) 2.05 (1.17–3.57)	Age, number of full-term pregnancies, weight	Strengths: serum taken before diagnosis; adequate sample size
Ward et al. (2000) Norway Sera collected 1973–1991, follow-up to 1993 Nested case–control	Cases: 150; random selection from 272 incident breast cancer cases where sera was taken 2+ yr before diagnosis Controls: 150; matched to cases by date of sample and date of birth, alive and free of cancer at time of case diagnosis Exposure assessment method: personal monitoring; gas chromatography	Breast	Dieldrin > LOD	 NR	 1.0 (0.4–2.6)	Age, time of sample collection	Strengths: nested case–control so exposure measured before diagnosis Limitations: very few aldrin-exposed subjects; only 22 discordant pairs for dieldrin; not clear if any confounding factors were added to model

Table 2.3 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Høyer et al. (2001) Denmark Enrolled, 1976–78, follow-up to 1993 Nested case–control	Cases: 161 Controls: 318 Exposure assessment method: personal monitoring; gas chromatography	Breast: estrogen receptor-positive	Dieldrin in quartiles (ng/mL)			Age, number of full-term pregnancies, weight, HRT	Strengths: serum taken before diagnosis; adequate sample size
			Q2, 12.01–28.30	28	1.3 (0.7–2.2)		
			Q3, 28.30–57.11	33	1.5 (0.8–2.7)		
			Q4, > 57.11	28	1.4 (0.8–2.5)		
			Trend-test *P*-value: > 0.20				
		Breast: estrogen receptor-negative	Dieldrin in quartiles (ng/mL)			Age, number of full-term pregnancies, weight, HRT	
			Q2, 12.01–28.30	5	1.2 (0.3–5.4)		
			Q3, 28.30–57.11	13	4.9 (0.9–28.3)		
			Q4, > 57.11	20	7.6 (1.3–46.1)		
			Trend-test *P*-value: 0.01				
Høyer et al. (2002) Denmark Enrolled, 1976–78, follow-up to 1993 Nested case–control	Cases: 240 Controls: 477 Exposure assessment method: personal monitoring; gas chromatography	Breast: wildtype p53	Dieldrin			Age, number of full-term pregnancies, weight, HRT	Strengths: serum taken before diagnosis; adequate sample size
			Q2	28	1.0 (0.49–2.04)		
			Q3	31	1.15 (0.53–2.47)		
			Q4	35	1.2 (0.56–2.58)		
			Trend-test *P*-value: 0.6				
		Breast: p53 mutation	Dieldrin			Age, number of full-term pregnancies, weight, HRT	
			Q2	7	2.07 (0.48–8.88)		
			Q3	13	4.57 (0.94–22.24)		
			Q4	12	3.53 (0.79–15.79)		
			Trend-test *P*-value: 0.12				

Table 2.3 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cantor et al. (2003) Maryland, USA 1974 enrolment in the Campaign Against Cancer and Stroke (CLUE I) and 1989 CLUE II Nested case–control	Cases: 74; Washington County Cancer Registry from CLUE I or II cohort Controls: 147; matched to case on race, sex, date of birth, CLUE I or II or private census between 1963–75, date of blood sample, location of stored serum Exposure assessment method: total lipid corrected serum values	NHL	ng/g lipid 26.6–84.2 85.3–116.7 116.9–153.8 163.0–393.9 Trend-test *P*-value: 0.88	 18 15 17 24	 1.0 1.0 (0.4–2.7) 1.2 (0.4–3) 0.9 (0.4–2.4)	Years of education, ever smoked cigarettes, currently smoking cigarettes, EBV early antigen seropositivity, quartile of PCB concentration	Strengths: most cases confirmed from pathology information; serum collected pre-diagnosis. matched and/or adjusted for potential confounders Limitations: larger than expected levels obtained for some compounds such as PCB and DDT may imply that there was some measurement error. aldrin was not reported
Engel et al. (2005) Iowa and North Carolina, USA 1993–2000 Cohort	30 454; AH; wives of pesticide licensees Exposure assessment method: questionnaire	Breast: incidence in farmers' wives	Dieldrin, husband's use Premenopausal, husband's use Postmenopausal, husband's use	16 NR 12	2.0 (1.1–3.3) – 1.6 (0.9–3)	Age, state, race	Strengths: large numbers, individual pesticide use Limitations: self-reported data
Purdue et al. (2007) Iowa and North Carolina, USA Recruited, 1993–1997, follow-up, 2002 Cohort	51 011; AHS, pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days, and intensity-weighted exposure days (take into account factors affecting exposure)	All cancers combined: incidence Lung: incidence Colon: incidence Rectum: incidence Malignant melanoma: incidence Leukaemia: incidence	Dieldrin	257 21 16 11 10 10	1.0 (0.8–1.1) 1.1 (0.6–1.8) 0.7 (0.4–1.3) 1.1 (0.5–2.4) 1.4 (0.7–2.9) 1.7 (0.8–3.6)	Age, state, sex, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	Strengths: large numbers, individual pesticide use Limitations: self-reported data

Table 2.3 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Koutros et al. (2013a) Iowa and North Carolina, USA 1993–2007 Cohort	54 412; AHS; pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days and intensity-weighted exposure days	Prostate (total): incidence	Dieldrin, quartile of exposure			Age, state, smoking status, race, family history of prostate cancer, fruit servings, leisure time physical activity in winter	Strengths: large numbers, individual pesticide use
			Q1	19	0.94 (0.60–1.49)		
			Q2	19	0.86 (0.54–1.36)		
			Q3	18	0.93 (0.58–1.49)		
			Trend-test *P*-value: 0.68				
		Prostate: aggressive (incidence)	Dieldrin, quartile of exposure				
			Unexposed	429	1.00		
			Q1	8	0.83 (0.41–1.68)		
			Q2	7	2.00 (0.94–4.23)		
			Q3	8	0.68 (0.33–1.37)		
			Q4	7	1.39 (0.65–2.94)		
			Trend-test *P*-value: 0.54				
		Prostate: family history of prostate cancer	Dieldrin, tertile of exposure			Age, state, smoking status, race, fruit servings, leisure time physical activity in winter	
			Unexposed	4	1.00		
			T2	5	1.55 (0.63–3.82)		
			T3	5	1.54 (0.62–3.83)		
			Trend-test *P*-value: 0.29				
Alavanja et al. (2014) Iowa and North Carolina, USA Recruited 1993–1997, follow-up 2011 Cohort	54 306; AHS; pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days, and intensity-weighted exposure days (take into account factors affecting exposure)	NHL: incidence	Dieldrin	35	0.9 (0.6–1.2)	Age, state, sex, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	Strengths: large numbers; individual pesticide use
		MM: incidence	Dieldrin	10	0.9 (0.5–1.4)		

Table 2.3 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Koutros et al. (2016) Iowa and North Carolina, USA Recruited, 1993–1997, follow-up 2011 Cohort	57 310; AHS; male pesticide licensees Exposure assessment method: questionnaire; lifetime exposure days, and intensity-weighted exposure days	Urinary bladder: incidence	Dieldrin	32	1.19 (0.82–1.72)	Age, state, sex, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	Strengths: large numbers; individual pesticide use Limitations: self-reported data; men only
Bonner et al. (2017) Iowa and North Carolina, USA Enrolment, 1993–1997 and follow-up 31 December 2011 Cohort	57 310; AHS; included 57 310 restricted-use pesticides applicators residing in Iowa and North Carolina between 1993 and 1997 Exposure assessment method: questionnaire; information about lifetime pesticide use was ascertained at enrolment (1993–1997) and updated with a follow-up questionnaire (1999–2005)	Lung	Lifetime days of use (exposure tertile)			Age, smoking status and pack-years, sex, total lifetime pesticide use	Strengths: large population of pesticide applicators; initial and follow-up questionnaire; controlled for smoking and other potential confounders Limitations: about 40% of applicators did not complete the follow-up interview so missing pesticide needed to be imputed/estimated
			Non-exposed	230	1.00		
			Dieldrin T1	6	0.58 (0.26–1.31)		
			Dieldrin T2	6	1.49 (0.66–3.37)		
			Dieldrin T3	4	1.93 (0.70–5.3)		
			Trend-test *P*-value: 0.472				
		Lung	Intensity-weighted lifetime days of use (exposure tertile)			Age, smoking status and pack-years, sex, total lifetime pesticide use	
			Non-exposed	230	1.00		
			Dieldrin T1	5	1.01 (0.42–2.47)		
			Dieldrin T2	4	0.5 (0.18–1.34)		
			Dieldrin T3	7	2.06 (0.95–4.43)		
			Trend-test *P*-value: 0.880				
		Lung	15-year lagged lifetime days pesticide exposure (tertile)			Age, smoking status and pack-years, sex, total lifetime pesticide use	
			Non-exposed	230	1		
			Dieldrin T1	6	0.59 (0.26–1.32)		
			Dieldrin T2	6	1.44 (0.64–3.26)		
			Dieldrin T3	4	2.09 (0.76–5.75)		
			Trend-test *P*-value: 0.468				

AHS, Agricultural Health Study; CI, confidence interval; CLUE, Campaign Against Cancer and Stroke; DDT, dichlorodiphenyltrichloroethane; EBV, Epstein–Barr virus; HRT, hormone-replacement therapy; LOD, limit of detection; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; PCB, polychlorinated biphenyl; SMR, standardized mortality ratio; STS, soft tissue sarcoma

(ii) Cancer of the breast

A case–control study on cancer of the breast was nested within the Copenhagen City Heart Study (Høyer et al., 1998). In 1976, 7712 of 10 317 participating women agreed to provide demographic information and a serum sample. The cohort was matched with the Danish Cancer Registry and 240 incident cases of breast cancer to 1993 with sufficient serum for analysis were included, while 477 controls were matched for age and vital status. There was an increase in risk of cancer of the breast with increasing quartile of dieldrin exposure (*P* for trend, 0.01); the odds ratio for the highest quartile was 2.05 (95% CI, 1.17–3.57). An analysis stratified by estrogen-receptor (ER) status was reported in a later publication (Høyer et al., 2001). Serum dieldrin was associated with ER-negative tumours (OR, 7.6; 95% CI, 1.3–46.1 for the highest quartile of exposure; *P* for trend, 0.01). There was no association with ER-positive tumours. A further analysis by *p53* (*TP53*) status (wildtype vs mutation) and found no statistically significant associations or trend with increasing serum dieldrin, although odds ratios for the three highest quartiles were raised for cases with mutant *p53* (OR for highest quartile, 3.53; 95% CI, 0.79–15.79; *P* for trend, 0.12) (Høyer et al., 2002). [The Working Group noted that the strengths of this study included that serum was taken before diagnosis of breast cancer, and that there were controls for multiple confounders.]

In the case–control study nested in the Norwegian Janus cohort of serum donors described above (Ward et al., 2000), there were 11 discordant case–control pairs with serum dieldrin levels (which may reflect exposure to aldrin and/or dieldrin) above the LOD. The matched odds ratio for dieldrin was 1.0 (95% CI, 0.4–2.6). [The Working Group considered that this was a reasonably high-quality study on dieldrin, with serum taken before diagnosis and control for multiple confounders; however, there were relatively small numbers of exposed cases.]

2.2.2 Case–control studies

See Table 2.4.

Several case–control studies that reported results for dieldrin also presented data for aldrin. The methods for these studies are described in detail in Section 2.1.2 and only the findings for dieldrin are presented here. In some other studies, exposures to dieldrin were assessed, but no risk estimates were reported (Cocco et al., 2008), or data for dieldrin were reported only as part of a broader grouping of pesticides (McDuffie et al., 2001; Pahwa et al., 2011). These studies were considered uninformative for dieldrin and are not considered further in this section. A cross-sectional study based on the United States NHANES survey of associations of self-reported cancer of the breast and prostate with serum dieldrin levels was also considered uninformative (Xu et al., 2010).

(a) Non-Hodgkin lymphoma

In the previously described study of NHL in Iowa and Minnesota, USA, by Cantor et al. (1992), a non-significant elevation in risk was observed among subjects who had ever personally handled, mixed, or applied dieldrin (OR, 1.4; 95% CI, 0.7–2.8). The risks were higher for those who had handled dieldrin for crop use before 1965 (OR, 1.9; 95% CI, 0.8–4.4). Additionally, elevated risk was found for dieldrin (OR, 2.2; 95% CI, 1.0–4.9; 13 cases) when pre-1965 use on either animals or crops was considered. In the subanalysis investigating subtypes of NHL (Schroeder et al., 2001), dieldrin was associated with t(14;18)-positive NHL (OR, 3.7; 95% CI, 1.9–7.0; 7 cases), but not with t(14;18)-negative NHL. [The Working Group noted that this was a large population-based study with in-person interviews on detailed farming and pesticide-use history, but the number of dieldrin uses was

Table 2.4 Case–control studies on cancer and exposure to dieldrin

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
Brown et al. (1990) Iowa and Minnesota, USA 1980–1984	Cases: 578; tumour registry and hospital records Controls: 1245; matched to case by 5-year age group, vital status and state via random-digit dialling, Medicare records or state death certificates Exposure assessment method: questionnaire; detailed questions with days per year for each pesticide	Leukaemia: newly diagnosed cases	Ever handled dieldrin Ever handled dieldrin	8	0.8 (0.4–2.0)	Vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, high-risk exposures	USA midwest studies Cases and controls residing in cities with little farming activity (i.e. Minneapolis, St Paul, Duluth, and Rochester) were excluded from the study Strengths: large population-based study in farming areas; in-person interviews; detailed questionnaires including quantification; collection of other potential risk factors; reviewed diagnosis Limitations: multiple comparisons; self-report of pesticide use and limited numbers of aldrin and dieldrin use
Cantor et al. (1992) Iowa and Minnesota, USA 1980–1983	Cases: 622; health registry and hospital and pathology records Controls: 1245; matched to cases by age, vital status and state via random-digit dialling, Medicare record or state death certificate files Exposure assessment method: questionnaire; in-person interview	NHL: newly diagnosed cases divided into four subtypes: follicular, diffuse, small lymphocytic, and "other NHL"	Dieldrin ever handled Dieldrin ever handled before 1965	17 10	1.4 (0.7–2.8) 1.9 (0.8–4.4)	Vital status, age, state, smoking, family history of lympho-haematopoietic cancer, high-risk occupation, high-risk exposures	Data subsequently pooled in De Roos et al. (2003) Strengths: large population-based study in farming areas Limitations: not controlled for exposure to other pesticides; white men only

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
Schroeder et al. (2001) Iowa and Minnesota, USA 1980–1983	Cases: 622; state health registry and hospital/ pathology laboratory records Controls: 1245; matched to cases by age, state and vital status via random-digit dialling, Medicare records or state death certificate files Exposure assessment method: questionnaire; in-person structured interviews	NHL: t(14;18)-positive or t(14;18)-negative cases	Ever use of dieldrin Dieldrin: t(14;18)-positive NHL vs controls	7	3.7 (1.9–7)	Age, state	Same study population as Cantor et al. (1992) Strengths: large population-based study in farming areas Limitations: relative small numbers of t(14;18)-positive or -negative NH; the study looked at NHL subtypes but > 70% of the cases had missing subtypes; small numbers of cases with aldrin or dieldrin exposure
Gammon et al. (2002) Long Island, New York, USA, 1996–1997	Cases: 1508; pathologically diagnosed breast cancer Controls: 1556; frequency-matched to cases by 5-year age group; identified by random-digit dialling Exposure assessment method: personal monitoring; dieldrin in serum	Breast	Dieldrin (ng/g lipid) 14.97–20.90 20.91–26.67 26.68–33.45 33.46–179.29	 38 32 22 46	 1.19 (0.59–2.41) 0.91 (0.45–1.84) 0.64 (0.3–1.35) 1.37 (0.69–2.72)	Age, race	Strengths: serum measures, adjusted for multiple potential confounders Limitations: small numbers (10% of original number of participants); includes in situ breast cancer; blood taken after diagnosis

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
Clary & Ritz (2003) California, USA 1989–1996	Cases: 950; death tape files within three counties (Fresno, Kern, and Tulare) Controls: 9435; all non-cancer deaths that occurred during the same time period in the same three counties Exposure assessment method: residential pesticide measure from the California Department of Pesticide Regulation PUR database	Pancreas (ICD-9, 157)	Dieldrin (tonnage) Highest vs lower three quartiles Highest vs lower three quartiles, ≥ 20 yr residence	 114 98	 1.38 (0.90–2.11) 1.52 (0.94–2.46)	Sex, age, year of death, years of living in county, urban residence, race, education	Strengths: examined all pesticides individually, simultaneously and in various combinations of pesticide subgroups Limitations: mortality and pesticide data without individual measurement or questionnaire conducted; residence duration before death may not represent exposure duration
De Roos et al. (2003) Nebraska, Iowa and Minnesota, Kansas, USA 1979–1986	Cases: 650; Nebraska Lymphoma Study Group, hospitals, state health registry, cancer registry Controls: 1933; matched to cases by race, sex, age, region and vital status via random-digital dialling, Medicare records or state mortality files Exposure assessment method: questionnaire; 47 pesticides	NHL: newly diagnosed cases	Dieldrin – ever use Dieldrin (logistic regression) Dieldrin (hierarchical regression)	 21 21	 1.8 (0.8–3.9) 1.4 (0.8–2.6)	Age, study site, all other pesticides	USA midwest studies (pooled) from three previous case–control studies (Zahm, Cantor, Hoar) analysis restricted to potentially carcinogenic pesticides

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
Ritchie et al. (2003) Iowa, USA 2000–2001 Case–control	Cases: 58; two clinics in Iowa Controls: 99; physical examination and annual check-ups from the university hospital; frequency-matched by age in 5-year increments to cases Exposure assessment method: blood samples collected and analysed questionnaire along with chemical checklist; medical history form for all study participants	Prostate: ICD-O 61.9	Dieldrin (μg/g) Non-detectable 0.006–0.024 > 0.024	 41 12 5	 1.00 0.97 (0.40–2.36) 0.28 (0.09–0.88)	Age, BMI, history of prostatitis	Organochlorine levels were analysed using both the unadjusted and lipid-adjusted serum values Strengths: collected blood samples; questionnaire included demographic and risk characteristics; a medical history for all study participants Limitations: small sample size
Lee et al. (2004) Iowa, Minnesota, Nebraska, USA 1980–86	Cases: 872; State Health Registry, hospitals and Nebraska Lymphoma Study Group Controls: 2336; matched to case on age, race and state via random-digit dialling, Medicare records or mortality files Exposure assessment method: questionnaire; telephone or personal interviews with subjects or next of kin in Nebraska	NHL	Ever use of dieldrin Among asthmatics Dieldrin among non-asthmatics	 5 30	 4.2 (0.98–18.2) 1.2 (0.7–1.9)	Age, vital status, state	Strengths: pooled study so larger numbers; same population as De Roos et al. (2003) Limitations: use of proxy respondents may have led to nondifferential misclassification; no adjustment for co-exposures

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
Quintana et al. (2004) USA 1969–1983 Case–control	Cases: 175; cases without missing lipid-adjusted pesticide exposure data in EPA NHATS data Controls: 481; controls with a diagnosis of accidental injury (or death) or myocardial infarction, matched on age, sex, geographical region and race Exposure assessment method: human adipose tissue samples collected during surgery and post mortem	NHL	Dieldrin exposure (ppm; µg/g lipid) < 0.09 0.09–0.15 0.15–0.24 > 0.24 Trend-test *P*-value: 0.0002	 37 37 38 63	 1.0 1.24 (0.71–2.17) 1.56 (0.88–2.74) 2.70 (1.58–4.61)	Year of sample collection	Strengths: relatively large study size with biological samples collected; analyses with dieldrin as well as other compounds were conducted Limitations: two sources used for sample collection and mostly post mortem (> 90% from cadavers); control selection also from two groups; no information on lifestyle factors; essentially a cross-sectional study
De Roos et al. (2005) Iowa, Los Angeles County, Detroit and Seattle, USA 1998–2000	Cases: 100; SEER registry Controls: 100; matched to cases by age, sex and race via random-digit dialling and Medicare records Exposure assessment method: personal interview and laboratory measurements of organochlorines including aldrin and dieldrin from blood samples	NHL: untreated, newly diagnosed cases	Dieldrin, quartiles (ng/g lipid) ≤ 8.1 > 8.1–10.9 > 10.9–14.3 > 14.3 Continuous (per 10 ng/g lipid) Trend-test *P*-value: 0.82	 31 14 8 25 78	 1.0 0.5 (0.17–1.5) 0.31 (0.1–0.96) 0.76 (0.31–1.88) 0.98 (0.71–1.37)	Sex, study site, birth date, date of blood draw	Strengths: laboratory measurements included aldrin and dieldrin exposures; multiple imputation approach for values below detection limits; potential confounders were considered in analyses with quartiles and continuous exposure Limitations: small numbers of cases and controls relative to the original study; all measurements for some pesticides including aldrin were below LOD

BMI, body mass index; CI, confidence interval; EPA, Environmental Protection Agency; LOD, limit of detection; NHATS, National Human Adipose Tissue Survey; NHL, non-Hodgkin lymphoma; NR, not reported; PUR, Pesticide Use Reporting Database; SMR, standardized mortality ratio; vs, versus

limited. An attempt was made to investigate NHL subtypes, but subtype was missing for more than 70% of the cases.]

A pooled analysis of studies in the midwest USA (De Roos et al., 2003), including the previous study by Cantor et al. (1992), found an elevated risk of NHL associated with dieldrin use, although the effect estimate was not statistically significant (RR, 1.8; 95% CI, 0.8–3.9, with conventional logistic regression; and RR, 1.4; 95% CI, 0.8–2.6, with hierarchical regression). In a further analysis investigating whether asthma modifies the risk of NHL associated with pesticide exposure, risk was non-significantly elevated with exposure to dieldrin (OR, 4.2; 95% CI, 0.98–18.2; 5 exposed cases) in asthmatics compared with non-farmers without asthma (Lee et al., 2004). [The Working Group noted that this was a pooled analysis, which used hierarchical regressions to control for multiple pesticide exposures. A large number (n = 47) of insecticides and herbicides was included in regression modelling, but there was no analysis for single pesticides. Subjects with any missing exposure data were excluded. There were a very small number of subjects with asthma and dieldrin use, resulting in wide confidence intervals.]

In the population-based case–control study of NHL in four different areas of the USA (the state of Iowa, Los Angeles county, and metropolitan areas of Detroit and Seattle) (De Roos et al., 2005), 100 untreated, newly diagnosed NHL cases aged 20–74 years identified between 1998 and 2000 with adequate plasma volume were randomly selected with 100 controls matched by birth date, date of blood draw, sex, and study site. Concentrations of organochlorines including aldrin and dieldrin were measured in blood samples obtained before treatment, but no sample contained aldrin at above detection limits. Plasma dieldrin was not associated with risk of NHL in analyses of quartiles or continuous exposure (OR, 0.98 per 10 ng/g lipid; 95% CI, 0.71–1.37). [The Working Group noted that study strengths included use of a conditional logistic regression analysis with consideration of potential confounders. Analyses of quartiles and of continuous exposure were conducted, although no significant associations were observed. The main study limitation was that biological samples were obtained after diagnosis. The Working Group further noted that measurements of dieldrin may additionally reflect exposure to aldrin.]

Another study used cases and controls from a data set originally collected in the United States EPA National Human Adipose Tissue Survey (NHATS) to examine the relationship between NHL and exposure to organochlorine pesticides (Quintana et al., 2004). Adipose tissue samples from more than 20 000 people were collected during surgery or post mortem between 1969 and 1983 in selected cities in the USA, and lipid-adjusted pesticide exposures were estimated. Cases (n = 175) were those with a diagnosis of NHL. Controls (n = 481) were subjects with a diagnosis of accidental injury or myocardial infarction matched on age, sex, geographical region, and race. Virtually all samples from cases and controls were obtained from cadavers. Dieldrin levels were significantly associated with increased risk of NHL among cases in the quartile of highest exposure (OR, 2.70; 95% CI, 1.58–4.61, with adjustment for year of sample collection; P for trend, 0.0002). Serum dieldrin levels showed moderate correlation with exposure to other compounds. When heptachlor epoxide was included in the model, the odds ratio for the highest quartile of dieldrin exposure was attenuated, while adjustment for β-hexachlorocyclohexane (β-HCH), and *para*,*para*′-dichlorodiphenyldichloroethylene (*p*,*p*′-DDE) did not have a notable effect. [The Working Group noted that the strengths of this study were that it was relatively large, and some biological samples were collected when dieldrin was in active use, with most measurements being above the LOD. The limitations were that it was essentially a

cross-sectional study, and two sources were used for sample collection, mostly post mortem.]

(b) Leukaemia

In the previously cited population-based case–control study in Iowa and Minnesota, USA, a lower risk of leukaemia was observed among subjects who had ever personally handled, mixed, or applied dieldrin (OR, 0.8; 95% CI, 0.4–2.0; 8 exposed cases) (Brown et al., 1990). [The Working Group noted that this was a large population-based study in farming areas. A limited number of subjects using dieldrin were included.]

(c) Cancer of the prostate

A pilot study compared serum levels of organochlorines in cases and controls (Ritchie et al., 2003). Cases (n = 58) were pathologically confirmed, newly diagnosed patients with cancer of the prostate from two clinics in Iowa, USA. Controls (n = 99) were men seen for routine examinations at a university hospital, frequency-matched by age to cases. Polychlorinated biphenyls and 18 organochlorine pesticides were measured in serum. Dieldrin (which may reflect exposure to aldrin and/or dieldrin) was detected in serum from 29.3% of cases and 38.4% of controls (P = 0.25). There was no apparent trend in the regression analysis of association between prostate cancer and dieldrin concentrations, and subjects with the highest levels of dieldrin appeared to have a reduced risk of cancer of the prostate compared with those with non-detectable dieldrin levels (P = 0.13). [The Working Group noted that blood samples were collected after diagnosis; the questionnaire included demographic and risk characteristics. The study was hospital-based, with a small sample size.]

(d) Cancer of the pancreas

A case–control study of mortality from cancer of the pancreas and long-term residential exposure to pesticides used computerized death tape files (1989–1996) and pesticide-use reporting records (1972–1989) from three counties in California (Clary & Ritz, 2003). Between 1989 and 1996, 950 deaths from cancer of the pancreas were identified and 9435 non-cancer deaths were randomly selected as controls within the same time period in these counties. Exposure was assigned based on information on duration of residency and pesticide-use reporting data on pesticide use with date and location of application for 18 chlorinated organic compounds, including dieldrin. Odds ratios and 95% confidence intervals for mortality from cancer of the pancreas were estimated for the quartile of highest pesticide usage at the postal code level (≥ 75%) in comparison with all other quartiles (< 75%). A non-significantly elevated risk of pancreatic cancer was observed for potential dieldrin exposure for all cases (OR, 1.38; 95% CI, 0.90–2.11) and after restricting to subjects with ≥ 20 years of residency (OR, 1.52; 95% CI, 0.94–2.46) in analyses mutually adjusted for the 18 measured pesticides. Single pesticide models (not adjusted for multiple pesticides) did not suggest increases in risk associated with exposure to dieldrin. [The Working Group noted that this study examined all pesticides individually, simultaneously, and in various combinations of pesticide subgroups. Death certificate data only were used. The exposure assessment was ecological.]

(e) Cancer of the breast

A case–control study on cancer of the breast recruited residents of Long Island, New York, USA, in 1996 and 1997 (Gammon et al., 2002). Cases were pathologically diagnosed incident cases of cancer of the breast (both invasive and in situ) and controls were selected by random-digit dialling and frequency-matched to the cases by

5-year age group. Blood samples were available for 646 cases and 429 controls; serum samples for 181 cases and 148 controls contained dieldrin measured at the time of recruitment (i.e. after diagnosis for cases). Geometric mean levels of dieldrin were 20.4 ng/g lipid in cases and 21.3 ng/g lipid in controls. There was a non- significant positive association between dieldrin serum level and breast cancer after adjustment for age and race (OR, 1.37; 95% CI, 0.69–2.72, for the highest compared with the lowest quintile of dieldrin concentration). [The Working Group noted that dieldrin measured in serum may reflect exposure to aldrin and/or dieldrin. A study limitation is that serum dieldrin levels were assessed at the time of breast cancer diagnosis.]

2.3 Exposure assessment in epidemiological studies of aldrin and dieldrin

2.3.1 Exposure questionnaires and interviews

Individual exposure to aldrin and dieldrin has been assessed in epidemiological studies using several different methods. The simplest method, commonly used in case–control studies and also used in some cohort studies, used retrospective interviews or questionnaires to ascertain past use of aldrin, dieldrin, and other pesticides (Brown et al., 1990; Cantor et al., 1992; McDuffie et al., 2001; Schroeder et al., 2001; De Roos et al., 2003; Lee et al., 2004; Engel et al., 2005; Purdue et al., 2007; Pahwa et al., 2011; Koutros et al., 2013a, b, 2016; Alavanja et al., 2014). Such studies may also elicit information on the duration, timing, and frequency of use, specific tasks performed with pesticides, or numbers of animals and crops treated (e.g. Brown et al., 1990; Purdue et al., 2007). At least one study asked about use of pesticides in hobbies or home gardening, as well as farming (McDuffie et al., 2001). It has been argued that workers in stable careers can reliably report on past production methods and frequent chemical use (Friesen et al., 2015; IARC, 2017). For example, orchardists in one study showed good consistency in recalling commonly used pesticides and pesticide categories for repeated exposure questionnaires after 21–25 years; however, long-term recall of specific pesticides can be poor (Engel et al., 2001). In retrospective questionnaires, the types and timing of pesticide use are potentially subject to recall bias (differential accuracy of recall for cases versus controls), particularly if cancers have already occurred when study participants or next-of-kin proxies are interviewed (Nam et al., 2005).

The AHS, a prospective cohort study, collected information on use of specific pesticides from participants before follow-up for health outcomes. Exposure questionnaires collecting information on active ingredients, decades of use, application methods, and use of personal protective equipment were administered both at baseline and after 5 years of follow-up of a cohort (Flower et al., 2004; Koutros et al., 2013a, b; Alavanja et al., 2014; Koutros et al., 2016), rather than after cancer cases had been identified. These studies were unlikely to be affected by recall bias. On the basis of participant responses, the intensity of pesticide use was estimated and combined with information reported on frequency and duration of use to obtain cumulative exposure of each participant to each active ingredient (Dosemeci et al., 2002).

2.3.2 Employment records

An alternative approach was used in a study of workers in a pesticide-production plant in the USA, in which work records such as start dates for work areas and production units, payroll classifications, and job titles were used to classify workers into production unit categories such as “operations” or “maintenance” (Amoateng-Adjepong et al., 1995). [The Working Group noted that although not subject to recall bias, these are crude surrogates for exposure to aldrin

and dieldrin, because a wide variety of chemicals were used and manufactured at the plant.]

2.3.3 Exposure biomarkers

In some studies, pesticide-use questionnaires or work records were supplemented or replaced by measurements of dieldrin and aldrin in the blood (Cantor et al., 2003; Ritchie et al., 2003; De Roos et al., 2005; Cocco et al., 2008; van Amelsvoort et al., 2009), or in adipose tissue (Quintana et al., 2004). Most aldrin is rapidly converted to dieldrin in humans (ATSDR, 2002), so measurements of dieldrin in blood and adipose samples may reflect exposure to aldrin and/or dieldrin. It is unclear whether aldrin measurements in the blood and adipose reflect only recent exposures or long-term storage of unmetabolized aldrin. Most dieldrin in the body is associated with lipids, so biomarker concentrations are typically reported as "lipid-adjusted" values (mass of dieldrin per unit mass of lipids). The mean apparent half-life of dieldrin in humans has been reported as 266–369 days (ATSDR, 2002), so dieldrin concentrations in blood may reflect exposure to aldrin and/or dieldrin in recent years, as well as any dieldrin mobilized from longer-term storage in adipose tissue.

In case–control studies, biomarker measurements were obtained after determination of case status and used as surrogates for past exposure. Such temporal misalignment induces some degree of exposure measurement error, with a larger degree of measurement error with shorter biological half-lives, larger exposure variability, or longer exposure durations (Bartell et al., 2004). Biomarkers may be affected by reverse causation if case status is associated with altered storage, metabolism, or excretion of a toxicant. For example, concentrations of organochlorines increase in plasma and adipose after weight loss (Baris et al., 2000; Pelletier et al., 2003), which results in differential exposure measurement error if cases experienced more weight loss than controls (or vice versa). This may be a concern for interpretation of studies in which cases experienced weight loss before sample collection as a result of illness, chemotherapy, or radiation therapy (De Roos et al., 2005).

In the study by De Roos, serum samples were collected from untreated cases of NHL and matched controls in the USA during 1998–2000. Of the dieldrin measurements, 19% were below the LOD, and an additional 22.5% were unreportable due to interference. The median LOD was 6.5 ng/g lipid and the median serum concentration was 10.9 ng/g lipid. Eighteen quality-control pairs were available for which both measurements were above the LOD; these had an average intrabatch coefficient of variation of 6.6% and an intraclass correlation coefficient of 0.98 (De Roos et al., 2005).

Cocco et al. (2008) measured a variety of polychlorinated biphenyls and organochlorine pesticides in serum samples obtained from NHL cases and controls in France, Germany, and Spain. Among these, 54% of dieldrin measurements were below the LOD in Spain, and 100% were below the LOD in France and Germany. Poor intraclass correlation (< 0.5) was reported for duplicate samples, possibly due to low sample volumes (1 mL).

Ritchie et al. (2003) measured 31 toxicants (including dieldrin) in serum samples in a pilot case–control study of cancer of the prostate in the USA. Serum was collected from newly diagnosed cases and controls in 2000–2001; 71% of cases and 62% of controls had serum dieldrin concentrations that were below the LOD.

In a study by Quintana and colleagues, samples of adipose tissue were collected from a nested case–control study of cadavers and surgery patients in the USA National Human Adipose Tissue Survey (NHATS) from 1969 to 1983. About 14% of NHL cases were excluded due to missing lipid-adjusted pesticide concentrations or low lipid content in the adipose samples. Fewer than 2% of the remaining samples contained

dieldrin at less than the LOD. Median adipose dieldrin concentrations were 180 ng/g lipid and 150 ng/g lipid for cases and controls, respectively (Quintana et al., 2004).

Several studies used stored blood samples to conduct cohort-based studies using prediagnostic biomarkers (Ward et al., 2000; Høyer et al., 2001; Gammon et al., 2002; Cantor et al., 2003; van Amelsvoort et al., 2009). The case–cohort study by Cantor and colleagues used a cohort with stored serum samples collected in the USA in 1974, identifying incident NHL cases from 1975–1994. Median serum dieldrin concentrations were 129.9 ng/g lipid for cases and 116.9 ng/g lipid for controls. Intraset and interset coefficients of variation for serum dieldrin were 0.22 and 0.30, respectively. The few values below the LOD were retained (Cantor et al., 2003). [The Working Group noted that although this design also had temporal misalignment of the exposure measurement and disease outcome, the resulting exposure measurement error was most likely to be non-differential due to the use of prediagnostic rather than postdiagnostic serum samples.]

The cohort study by van Amelsvoort and colleagues of workers at plants manufacturing aldrin and dieldrin in the Netherlands also used dieldrin concentration in prediagnostic blood samples (from 1963–1970) to assess exposure, and followed participants for cause-specific mortality until 2006 (van Amelsvoort et al., 2009). Aldrin and dieldrin exposures were substantially decreased for these workers after 1970 due to improved production processes. Blood samples were collected one to four times per year as part of routine biomonitoring at the plant; repeated dieldrin measurements were available for 60% of participants. The study used a one-compartment pharmacokinetic model and a piecewise constant-exposure model to estimate total intake of aldrin and dieldrin for each worker over time, imputing missing values based on measurements in workers with the same job and work dates (de Jong, 1991). [The Working Group considered that this exposure assessment was of relatively high quality because of the use of repeated prediagnostic biomarkers sampled during the years of peak exposure.]

2.3.4 *Pesticide-use reporting and residential locations*

Clary & Ritz (2003) used a different approach to exposure assessment for their epidemiological analysis, relying on geographical information systems and the California pesticide-use reporting database. They sorted 102 zip (postal) codes by relative commercial use of each of 18 organochlorine pesticides (including dieldrin) from 1972 to 1989, matching each study participant to a postal code using residential address at death. Duration of residency in county of residence was also available from death records. In California, reporting for commercial use of pesticides has been mandatory since the 1970s and recent data are highly resolved spatially and temporally, but earlier records were often incomplete and usage was likely underreported due to lack of enforcement (Clary & Ritz, 2003). [The Working Group noted that it was unclear to what extent dieldrin use by zip (postal) code is a reasonable surrogate for personal exposure.]

3. Cancer in Experimental Animals

3.1 Aldrin

See Table 3.1.

3.1.1 *Mouse*

Oral administration

A group of 215 young male and female C3HeB/Fe mice [age, numbers, and sex were not reported; mice were divided approximately equally by sex] were fed diets containing aldrin [purity not reported] at a concentration of

10 ppm for up to 2 years (Davis & Fitzhugh, 1962). The control group consisted of 217 male and female mice. Treated mice died 2 months earlier than controls: the average survival time in treated mice was 51.8 weeks compared with 59.8 weeks for the controls. Survival at 18 months was decreased in treated mice (32/215; 15%) compared with the control group (47/217; 22%). All survivors at 2 years were killed and autopsied. Pneumonia and intestinal parasitism probably contributed to the decreased survival of the mice. It was reported that caging of mice in groups of 5–8 contributed to the spread of disease within groups. Partial re-evaluation by Reuber and others of the available histopathology data from Davis & Fitzhugh (1962) and from Davis (1965) indicated that most tumours initially classified by Davis & Fitzhugh (1962) as "hepatic cell adenoma" were actually hepatocellular carcinomas (Epstein, 1975; Reuber, 1975, 1976a). A statistically significant increase in the incidence of "hepatic cell adenoma" [hepatocellular carcinoma] was noted in treated mice when compared with the control group. On average, treated mice developed "hepatic cell adenomas" [hepatocellular carcinomas] after 80 weeks on study compared with 89 weeks on study for control mice. [The Working Group noted that the limitations of this study included low survival rate, combination of data for both sexes, lack of detailed histopathology, reports of disease, pneumonia, and intestinal parasitism, and the disposal of a large number of animals at autopsy. The Working Group considered that the re-evaluation by Epstein (1975) was accurate, but limited by the number of cases reviewed.]

In a subsequent study, groups of 100 male and 100 female C3H mice were fed diets containing aldrin [purity not reported] at a concentration of 0 or 10 ppm for up to 2 years (Davis, 1965, reported in Epstein, 1975). The number of survivors at 104 weeks was 64 and 31 for control and treated mice, respectively. Whereas the reported number of hepatic carcinomas [hepatocellular carcinomas] was about the same, the incidence (for both sexes combined) of "benign hepatomas" [hepatocellular carcinomas] in the treated group (10 ppm) was significantly elevated, being approximately double that of controls, (Epstein, 1975). An independent partial re-evaluation of the Davis & Fitzhugh (1962) and Davis (1965) by Reuber and others concluded that most of the "benign hepatomas" were hepatocellular carcinomas. This re-evaluation indicated significant increases in the incidence of hepatocellular carcinoma in males and females in the treated group compared with the control groups (Epstein, 1975; Reuber, 1976a). Morphological descriptions of the liver lesions were reported by Reuber (1975) and Reuber (1976a). There were often two hepatocellular carcinomas present at the same time in treated animals, while solitary hepatocellular carcinomas were reported in the control animals (Reuber, 1976a). In addition, transplantation studies were conducted in which hepatocellular carcinomas were transplanted into mice [sex not reported] with a similar genetic background. Nine out of ten tumours from mice fed diets containing aldrin at 10 ppm grew when transplanted and histologically resembled the primary tumours (Reuber, 1976b). [The Working Group noted that the limitations of this study included the combination of data for both sexes, lack of detailed histopathology, and the absence of report on the number of animals evaluated for histopathology. The Working Group considered that the re-evaluation by Epstein (1975) was accurate, but limited by the number of cases reviewed.]

In a study by the NCI, groups of 50 male and 50 female $B6C3F_1$ mice were fed diets containing aldrin (technical grade; purity, 95% [impurities unspecified]) at a concentration of 4 or 8 ppm (time-weighted exposure) for males, and 3 or 6 ppm (time-weighted exposure) for females, for 80 weeks, and then held untreated for an additional 10–13 weeks (NTP, 1978a). The matched-control group consisted of 20 males

Table 3.1 Studies of carcinogenicity in experimental animals exposed to aldrin

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, C3HeB/Fe (M+F combined) NR 2 yr Davis & Fitzhugh (1962)	Oral Aldrin, purity NR Diet 0, 10 ppm, ad libitum 217, 215 47, 32 (at 18 mo)	*Liver* Hepatic cell adenoma [hepatocellular carcinoma]: 9/134 (7%), 35/151* (23%)	*$P < 0.001$, statistical test NR	Principal strengths: adequate duration Principal limitations: low survival rate; data combined for sexes; lack of detailed histopathology; disease, pneumonia and intestinal parasitism reported; large numbers of animals discarded at autopsy Partial re-evaluation of hepatic lesions of the combined studies by Davis & Fitzhugh (1962) and Davis (1965) by Reuber and others reported in Epstein (1975) (Table 3) – most tumours classified as hepatic cell adenomas were re-evaluated as hepatocellular carcinomas. Total hepatocellular carcinomas reported in Reuber (1976a): control male – 22/73, 30%; aldrin male – 75/91 [$P < 0.0001$], 82%; control female – 2/53, 4%; aldrin female – 72/85, 85% [$P < 0.0001$]
Full carcinogenicity Mouse, C3H (M+F combined) NR 2 yr Davis (1965)	Oral Aldrin, NR Diet 0, 10 ppm, ad libitum 200, 200 64, 31 (at 104 wk)	*Liver* Benign hepatoma [hepatocellular carcinoma]: 27/200, 65/200* Hepatic carcinoma [hepatocellular carcinoma]: 4/200, 3/200	*[$P < 0.0001$] [NS]	Principal strengths: adequate duration Principal limitations: data combined for sexes, lack of detailed histopathology, number of animals evaluated for histopathology not reported Davis (1965) is reported in Epstein (1975). Data presented in Table 2 of Epstein (1975). Partial re-evaluation of hepatic lesions of the Davis & Fitzhugh (1962) and Davis (1965) combined studies by Reuber and others reported in Epstein (1975) (Table 3) – most tumours classified as benign hepatomas were re-evaluated as hepatocellular carcinomas. Total hepatocellular carcinomas reported in Reuber (1976a): control male – 22/73, 30%; aldrin male – 75/91, 82% [$P < 0.0001$]; control female – 2/53, 4%; aldrin female – 72/85, 85% [$P < 0.0001$]

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 35 days 90–93 wk NTP (1978a)	Oral Aldrin, 95% (technical grade; impurities, NR) Diet 0, 0, 4 (TWA), 8 (TWA) ppm, ad libitum; treated for 80 wk then control diet for 10–13 wk 20, 92, 50, 50 NR	*Liver* Hepatocellular carcinoma: 3/20* (matched control), 17/92** (pooled control), 16/49***, 25/45***,****	*P = 0.001 by the Cochran-Armitage trend test **P < 0.001 by the Cochran-Armitage trend test ***P = 0.048 by the Fisher exact test vs pooled control group for intermediate-dose group, and P < 0.001 for high-dose group ****P = 0.002 by the Fisher exact test vs matched control group	Principal strengths: adequate duration; studies in M and F; complete histopathology
Full carcinogenicity Mouse, B6C3F$_1$ (F) 35 days 90–91 wk NTP (1978a)	Oral Aldrin, 95% (technical grade; impurities, NR) Diet 0, 0, 3 (TWA), 6 (TWA) ppm, ad libitum; treated for 80 wk then control diet for 10–11 wk 10, 79, 50, 50 NR	*Liver* Hepatocellular carcinoma: 0/10, 3/78, 5/48, 2/43	NS	Principal strengths: adequate duration; studies in M and F; complete histopathology

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Osborne-Mendel (M+F combined) 3 wk 104 wk Fitzhugh et al. (1964)	Oral Aldrin, ≥ 99% Diet 0, 0.5, 2, 10, 50, 100, 150 ppm, ad libitum 24, 24, 24, 24, 24, 24, 24 50%, 50%, 50%, 42%, 25%, 17%[a], 4%[b]	All sites combined 3/17, 10/19*, 7/19, 8/22, 5/18, 5/11, 1/9	*[$P = 0.041$, Fisher's exact test; increase]	Principal limitations: data combined for sexes; only 68% of animals treated with aldrin (or dieldrin) were examined histologically Survival was significantly decreased in M and F (combined) exposed to 100 or 150 ppm at 24 mo ([a]$P \leq 0.01$ or [b]$P \leq 0.05$, respectively). Tumours reported as "pulmonary lymphosarcoma," "fibroadenoma of breast," "carcinoma of breast," "lymphoid except lung," "fibrosarcoma," and "other", were confirmed by independent re-evaluations by Reuber and others (Epstein, 1975). No liver tumours were initially reported, but a partial re-evaluation of the liver histopathology identified a total of 18 liver carcinomas in rats fed diets containing aldrin or dieldrin
Full carcinogenicity Rat, Osborne-Mendel (M) NR (weanling) 25 mo Deichmann et al. (1967)	Oral Aldrin, 95% (technical grade) Diet 0, 5 ppm, ad libitum 30, 30 50%, 66% (at 24 mo)	All tumours: 1/30, 2/30 Total tumours: 1, 2	[NS]	Principal limitation: only one dose group
Full carcinogenicity Rat, Osborne-Mendel (F) NR (weanling) 25 mo Deichmann et al. (1967)	Oral Aldrin, 95% (technical grade) Diet 0, 5 ppm, ad libitum 30, 30 60%, 63% (at 24 mo)	All tumours: 13/30, 13/30 Total tumours: 14, 13	[NS]	Principal limitation: only one dose group

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Osborne-Mendel (M) NR (weanling) ≤ 31 mo Deichmann et al. (1970)	Oral Aldrin, 95% (technical grade) Diet 0, 20, 30, 50 ppm, ad libitum 100, 50, 50, 50 NR	All tumours: 19/75, 5/45, 7/46, 4/45 Total tumours: 46, 15, 15, 13	NS	Principal limitations: histopathology limited to examination of the lung, kidney, liver and all macroscopic changes Doses during the first 10 wk (0, 10, 15, 25 ppm) were half the final concentrations. Maximum survival of controls was only 27 mo. Tumour incidence: total number of rats with tumours/number of rats examined histologically
Full carcinogenicity Rat, Osborne-Mendel (F) NR (weanling) > 27–< 31 mo Deichmann et al. (1970)	Oral Aldrin, 95% (technical grade) Diet 0, 20, 30, 50 ppm, ad libitum 100, 50, 50, 50 NR	All tumours 60/88, 20/47, 24/44, 11/31 Total tumours: 104, 26, 28, 16	NS	Principal limitations: histopathology limited to examination of the lung, kidney, liver and all macroscopic changes Doses during the first 10 wk (0, 10, 15, 25 ppm) were half the final concentrations. Maximum survival of controls was only 27 mo. Tumour incidence: total number of rats with tumours/number of rats examined histologically
Full carcinogenicity Rat, Osborne-Mendel (M) 35 days 111–112 wk NTP (1978a)	Oral Aldrin, 95% (technical grade; impurities NR) Diet 0, 0, 30, 60 ppm, ad libitum; treated for 74 wk then control diet for 37–38 wk 10, 58, 50, 50 NR	*Thyroid* Follicular cell adenoma or carcinoma (combined): 3/7 (matched control), 4/48 (pooled control), 14/38*, 8/38 Follicular cell carcinoma: 0/7 (matched control), NR (pooled control), 4/38, 2/38 *Pancreas* Islet cell adenoma or carcinoma (combined): 0/9 (matched control), 1/52 (pooled control), 5/37*, 2/39	*$P = 0.002$ by the Fisher exact test vs pooled control group NS *$P = 0.043$ by the Fisher exact test vs pooled control group	Principal strengths: adequate duration; covered most of the life span; studies in M and F; complete histopathology

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Osborne-Mendel (F) 35 days 112–113 wk NTP (1978a)	Oral Aldrin, 95% (technical grade; impurities NR) Diet 0, 0, 30, 60 ppm, ad libitum; treated for 80 wk then control diet for 32–33 wk 10, 60, 50, 50 NR	*Adrenal gland* Cortical adenoma: 0/10, 0/55, 8/45*, 1/48 *Thyroid* Follicular cell adenoma or carcinoma (combined): 1/9, 3/52, 10/39*, 7/46 Follicular cell carcinoma: 0/9 (matched control), NR (pooled control), 2/39, 4/46	*$P = 0.002$ by the Fisher exact test vs pooled control group *$P = 0.009$ by the Fisher exact test vs pooled control group NS	Principal strengths: adequate duration; covered most of the life span; studies in both M and F; complete histopathology

F, female; M, male; mo, month; NR, not reported; NS, not significant; ppm, parts per million; TWA, time-weighted average; wk, week(s); yr, year(s)

and 10 females, and the study duration was 90–93 weeks. Time-weighted doses were used to assess the results, because the concentration of aldrin was reduced after study start due to toxicity. Because the number of matched-control mice was small, pooled controls were also used for statistical comparisons. The pooled-control groups consisted of the matched controls from the bioassay of aldrin combined with matched controls from contemporary bioassays with dieldrin, chlordane, heptachlor, dichlorvos, and dimethoate, giving groups of 92 male and 79 female mice. There was no significant effect on the survival of male mice. There was a significant ($P = 0.037$) dose-related trend in the mortality of female mice, primarily due to the early deaths in the groups at the higher dose. Mean body weights of males and females were similar to those of the controls.

In comparisons with the matched or pooled controls, the incidence of hepatocellular carcinoma was significantly increased at 4 and 8 ppm in males, with a significant positive trend. The incidence of hepatocellular carcinoma in the treated groups was above the mean for incidence in historical controls (44/285, 16.8%). There were no other significant increases in tumour incidence compared with the matched or pooled controls. There was no significant increase in the incidence of tumours in female mice (NTP, 1978a).

3.1.2 Rat

A study in male and female Carworth rats fed diets containing aldrin (Treon & Cleveland, 1955; Cleveland, 1966; also reported in Epstein, 1975) was judged inadequate for the evaluation by the Working Group because of the lack of histopathological evaluation, difficulties in interpretation of the mortality data, limited reporting, and discrepancies between Treon & Cleveland (1955) and Cleveland (1966).

Groups of 12 male and 12 female Osborne-Mendel rats were fed diets containing aldrin (purity, not less than 99%) at a concentration of 0, 0.5, 2, 10, 50, 100, or 150 ppm for 2 years (Fitzhugh et al., 1964). Survival was significantly decreased in males and females (combined) at 100 or 150 ppm at 24 months. Mean body weights of males and females were similar to those of the controls. Six tumour categories were identified, including "pulmonary lymphosarcoma", "fibroadenoma of breast", "carcinoma of breast", "lymphoid except lung", "fibrosarcoma", and "other". Epstein (1975) reported that independent histopathological re-evaluations by Reuber and others confirmed these multiple site tumours. No benign or malignant liver tumours were initially reported by Fitzhugh et al. (1964), but a partial re-evaluation of the liver histopathology identified a total of 18 hepatocellular carcinomas in rats fed diets containing aldrin or dieldrin (Epstein, 1975). [The Working Group noted that the limitations of this study were that only 68% of the animals treated with aldrin (or dieldrin) were examined histologically, and that the data were combined for both sexes.]

Groups of 30 male and 30 female weanling Osborne-Mendel rats [age not reported] were fed diets containing aldrin (purity, 95%) at a concentration of 0 or 5 ppm for 25 months (Deichmann et al., 1967). Survival at 24 months was 50% and 66% for control and treated male rats, respectively, and 60% and 63% for control and treated female rats, respectively. Mean body weights were similar between control and treated groups. Tumour incidence (all sites) was not significantly increased in male or female rats relative to that in the respective control groups. [As a limitation of the study, the Working Group noted that only one dose concentration was used.]

Groups of 50 male and 50 female weanling Osborne-Mendel rats [age not reported] were fed diets containing aldrin (purity, 95%) at a concentration of 20, 30, or 50 ppm for 31 months (Deichmann et al., 1970). Control groups were

comprised of 100 males and 100 females. Doses during the first 10 weeks were half the final concentrations. Mean survival of the control male and female rats was 19.7 and 19.5 months, respectively. The survival rate was not affected in treated males, but the mean survival of female rats at 50 ppm (13.0 months) was significantly decreased relative to the control group. The maximum survival of control males and control females was 27 months. Mean body-weight gain was similar for treated and control groups. Tumour incidence (all sites) was not significantly increased in male or female rats relative to the respective control groups. No benign or malignant tumours of the liver were found in treated animals. [The Working Group noted that limitations of this study included that not all tissues were examined histologically.]

In a study by the NCI, groups of 50 male and 50 female Osborne-Mendel rats (age, 35 days) were fed diets containing aldrin (purity, 95% [impurities not reported]) at a concentration of 30 or 60 ppm (NTP, 1978a). Male rats were treated 74 weeks followed by 37–38 weeks of observation, and female rats were treated for 80 weeks followed by 32–33 weeks of observation. For matched controls (10 males and 10 females per group) the study duration was 111 weeks for males and 111–112 weeks for females. The pooled-control groups consisted of the matched controls from the bioassay of aldrin combined with matched controls from the contemporary bioassays of dieldrin, chlordane, heptachlor, dichlorvos and dimethoate, giving groups of 58 male and 60 female rats. There was no significant effect on the survival of males or females. Mean body weights of the treated male and female rats were lower than those of the controls during the second year of the study. The incidences of follicular cell adenoma or carcinoma (combined) of the thyroid gland increased in male and female Osborne-Mendel rats (NTP, 1978a). The increases were significant in groups at the lower dose, but not in the groups at the higher dose for males, or for females when compared with the pooled controls, but were not significant when compared with the matched controls. The incidence of follicular cell carcinoma of the thyroid gland was not increased significantly in males or females. A significant increase in the incidence of adenoma or carcinoma (combined) of pancreatic islet cells was observed in males at the lower dose, but not at the higher dose, when compared with the pooled control group. A significant increase in the incidence of cortical adenoma of the adrenal gland was also observed in females at the lower dose, but not at the higher dose when compared with the pooled control group. [The Working Group noted that these increases in tumour incidence were only for the groups at the lower dose, and only when compared with the pooled control group, and thus concluded that they were not treatment-related.]

3.2 Dieldrin

See Table 3.2.

Dieldrin was reviewed in *IARC Monographs* Volume 5 (IARC, 1974) and Supplement 7 (IARC, 1987). The previous *IARC Monographs* Working Group (IARC, 1987) concluded that there was *limited evidence* in experimental animals for the carcinogenicity of dieldrin. This section provides an evaluation of the animal carcinogenesis studies reviewed in previous *Monographs* and Supplement and a review of any studies published since the earlier reviews.

3.2.1 Mouse

(a) Dietary administration

In a study by Davis & Fitzhugh (1962), a group of 218 young [age not reported] male and female C3HeB/Fe mice [numbers and sex were not reported; mice were divided approximately equally by sex] were fed diets containing dieldrin [purity not reported] at a concentration of 10 ppm for up to 2 years. The control group

Table 3.2 Studies of carcinogenicity in experimental animals exposed to dieldrin

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, C3HeB/Fe (M+F combined) NR 2 yr Davis & Fitzhugh (1962)	Oral Dieldrin, NR Diet 0, 10 ppm, ad libitum 217, 218 47, 33 (at 18 mo)	*Liver* Hepatic cell adenoma [hepatocellular carcinoma]: 9/134, 36/148* (24%)	$P < 0.001$, statistical test NR	Principal strength: adequate duration Principal limitations: low survival rate; lack of detailed histopathology; disease, pneumonia and intestinal parasitism reported; large numbers of animals discarded at autopsy; data combined for both sexes Partial re-evaluation of hepatic lesions of the Davis & Fitzhugh (1962) and Davis (1965) combined studies by Reuber and others reported in Epstein (1975) (Table 3) – most tumours classified as hepatic cell adenomas were re-evaluated as hepatocellular carcinomas. Total hepatocellular carcinomas reported in Reuber (1976a): control male – 22/73, 30%; dieldrin male – 62/71 [$P < 0.0001$], 87%; control female – 2/53, 4%; dieldrin female – 62/71, 87% [$P < 0.0001$]
Full carcinogenicity Mouse, C3H (M+F combined) NR 2 yr Davis (1965)	Oral Dieldrin, NR Diet 0, 10 ppm, ad libitum 200, 200 64, 39 (at 104 wk)	*Liver* Benign hepatoma [hepatocellular carcinoma]: 27/200, 69/200* Hepatic carcinoma [hepatocellular carcinoma]: 4/200, 5/200	*[$P < 0.0001$] [NS]	Principal strength: adequate duration Principal limitations: lack of detailed histopathology; number of animals evaluated for histopathology not reported; data combined for both sexes Davis (1965) is reported in Epstein (1975). Data presented in Table 2 of Epstein (1975). Partial re-evaluation of hepatic lesions of the Davis & Fitzhugh (1962) and Davis (1965) combined studies by Reuber and others reported in Epstein (1975) (Table 3) – most tumours classified as benign hepatomas were hepatocellular carcinomas. Total hepatocellular carcinomas reported in Reuber (1976a): control male – 22/73 (30%); dieldrin male – 62/71 (87%) [$P < 0.0001$]; control female – 2/53 (4%); dieldrin female – 62/71 (87%) [$P < 0.0001$]

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, C57BL/6J, C3H/He, B6C3F$_1$ (M) NR (weanling) ≤ 132 wk Meierhenry et al. (1983)	Oral Dieldrin, > 99% Diet C57BL/6J : 0, 10 ppm; C3H/He: 0, 10 ppm; B6C3F$_1$: 0, 10 ppm, ad libitum; dieldrin was given for 85 wk 69, 71, 50, 50, 76, 62 NR	*Liver* Benign hepatoma [benign hepatocellular tumour]: 10/69 (14%), 20/71* (28%), 9/50 (18%), 10/50 (20%), 3/76 (4%), 18/62* (29%) Hepatocellular carcinoma: 0/69, 21/71* (30%), 6/50 (12%), 19/50* (38%), 3/76 (4%), 26/62* (42%)	*$P < 0.01$ compared with control using the one-tailed test for the difference of proportions *$P < 0.01$ compared with control using the one-tailed test for the difference of proportions	Principal limitations: no data on survival or body weight
Full carcinogenicity Mouse, C3H/He (M) NR (weanling) 2 yr Ruebner et al. (1984)	Oral Dieldrin, 99% Diet 0, 10 (dieldrin "stopped"), 10 (dieldrin "continued") ppm, ad libitum 21, 12, 11 NR	*Liver* Hepatocellular adenoma: 6/21, 10/12*, 3/11	*[$P < 0.004$ by Fisher's exact test]	Principal limitations: small number of animals; limited exposure duration; number of animals at start not reported "stop-dieldrin" group: dieldrin fed until mice were aged 57 wk; "continue-dieldrin" group: dieldrin fed until mice were aged 67 wk
Full carcinogenicity Mouse, CF-1 (M) 4 weeks 132 wk Walker et al. (1973); Hunt et al. (1975)	Oral Dieldrin, > 99% Diet 0, 0.1, 1.0, 10 ppm, ad libitum 300, 125, 125, 200 NR	*Liver* Hepatocellular adenoma: 16%, 22%, 23%, 37% Hepatocellular carcinoma: 4%, 5%, 9%, 58% Hepatocellular adenoma and carcinoma (combined): 20%, 27%, 32%, 95% *Lung* Adenoma: 32%, 38%, 37%, 18% Carcinoma: 7%, 11%, 13%, 1%	NR	Principal limitations: neoplasm incidences not reported; effective number of animals unclear; statistics cannot be calculated Study 1 (Experiment 1); data reported in this table are from the values given in Hunt et al. (1975). Total liver tumours: type (a) (simple nodular growth of parenchymal cells) + type (b) (areas of papilliform and adenoid growth of tumour cells). Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (F) 4 wk 132 wk Walker et al. (1973); Hunt et al. (1975)	Oral Dieldrin, > 99% Diet 0, 0.1, 1.0, 10 ppm, ad libitum 300, 125, 125, 200 NR	*Liver* Hepatocellular adenoma: 12%, 18%, 23%, 37% Hepatocellular carcinoma: 0%, 3%, 5%, 59% Hepatocellular adenoma and carcinoma (combined): 12%, 21%, 28%, 96% *Lung* Adenoma: 17%, 19%, 25%, 11% Carcinoma: 6%, 10%, 10%, 0%	NR	Principal limitations: neoplasm incidences not reported; effective number of animals unclear; statistics cannot be calculated Study 1 (Experiment 1); data reported in this table are from the values given in Hunt et al. (1975). Total liver tumours: type (a) (simple nodular growth of parenchymal cells) + type (b) (areas of papilliform and adenoid growth of tumour cells). Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively
Full carcinogenicity Mouse, CF-1 (M) 4 wk 128 wk Walker et al. (1973)	Oral Dieldrin, > 99% Diet 0, 1.25, 2.5, 5, 10, 20 ppm, ad libitum 78, 30, 30, 30, 30, 30 NR	*Liver* Hepatocellular adenoma: 12%, 13%, 40%, 77%, 36%, 18% Hepatocellular carcinoma: 0%, 7%, 3%, 10%, 9%, 53% Hepatocellular adenoma and carcinoma (combined): 12%, 20%, 43%, 87%, 45%, 71% *Lung* Adenoma: 58%, 57%, 37%, 47%, 18%, 6% Carcinoma: 1%, 3%, 3%, 3%, 0%, 0%	NR	Principal limitations: neoplasm incidences not reported; effective number of animals unclear; statistics cannot be calculated Study 2 – Experiment 2.1; animals received ethylene oxide-sterilized diet (standard procedure at that time). Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (F) 4 wk 128 wk Walker et al. (1973)	Oral Dieldrin, > 99% Diet 0, 1.25, 2.5, 5, 10, 20 ppm, ad libitum 78, 30, 30, 30, 30, 30 NR	*Liver* Hepatocellular adenoma: 10%, 17%, 39%, 43%, 41%, 24% Hepatocellular carcinoma: 0%, 0%, 4%, 17%, 12%, 14% Hepatocellular adenoma and carcinoma (combined): 10%, 17%, 43%, 60%, 53%, 38% *Lung* Adenoma: 31%, 23%, 11%, 10%, 6%, 0% Carcinoma: 10%, 0%, 0%, 3%, 0%, 0% *Ovary* Tumour, NOS: 26%, 40%, 14%, 10%, 6%, 0%	NR	Principal limitations: neoplasm incidences not reported; effective number of animals unclear; statistics cannot be calculated Other comments: Study 2 – Experiment 2.1; animals received ethylene oxide-sterilized diet (standard procedure at that time). Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (M) 4 wk Unsterilized diet experiment (104 wk), γ-irradiated diet experiment (128 wk), γ-irradiated diet and bedding experiment (100 wk) Walker et al. (1973)	Oral Dieldrin, > 99% Diet Unsterilized diet: 0, 10 ppm; irradiated diet: 0, 10 ppm; irradiated diet and bedding: 0, 10 ppm, ad libitum 24, 24, 30, 30, 24, 24 NR	*Liver* Hepatocellular adenoma: 30%, 58%, 20%, 40%, 42%, 63% Hepatocellular carcinoma: 4%, 25%, 3%, 20%, 0%, 23% Hepatocellular adenoma and carcinoma (combined): 34%, 83%, 23%, 60%, 42%, 86% *Lung* Adenoma: 30%, 17%, 43%, 10%, 46%, 36% Carcinoma: 0%, 0%, 3%, 0%, 4%, 0% *Lymphoid tissue* Tumour, NOS: 13%, 4%, 37%, 10%, 13%, 5% *Kidney* Tumour, NOS: 4%, 4%, 13%, 0%, 4%, 9%	NR	Principal limitations: few dose groups; neoplasm incidences not reported; effective number of animals unclear; statistics cannot be calculated Study 2 – Experiment 2.2; diet sterilization. Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively

Table 3.2 (continued)

Study design **Species, strain (sex)** **Age at start** **Duration** **Reference**	**Route** **Agent tested, purity** **Vehicle** **Dose(s)** **No. of animals at start** **No. of surviving animals**	**Incidence of tumours**	**Significance**	**Comments**
Full carcinogenicity Mouse, CF-1 (F) 4 wk Unsterilized diet experiment (104 wk), γ-irradiated diet experiment (128 wk), γ-irradiated diet and bedding experiment (100 wk) Walker et al. (1973)	Oral Dieldrin, > 99% Diet Unsterilized diet: 0, 10 ppm; irradiated diet: 0, 10 ppm; irradiated diet and bedding: 0, 10 ppm, ad libitum 24, 24, 30, 30, 24, 24 NR	*Liver* Hepatocellular adenoma: 23%, 36%, 11%, 32%, 17%, 42% Hepatocellular carcinoma: 0%, 23%, 0%, 11%, 0%, 21% Hepatocellular adenoma and carcinoma (combined): 23%, 59%, 11%, 43%, 17%, 63% *Lung* Adenoma: 32%, 9%, 18%, 0%, 17%, 29% Carcinoma: 0%, 0%, 0%, 0%, 13%, 0% *Ovary* Tumour, NOS 23%, 0%, 25%, 5%, 29%, 17% *Lymphoid tissue* Tumour, NOS: 32%, 5%, 32%, 0%, 2%, 21%	NR NR NR NR NR NR NR	Principal limitations: few dose groups; neoplasm incidences not reported; effective number of animals unclear; statistics cannot be calculated Study 2 – Experiment 2.2; diet sterilization. Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Co-carcinogenicity Mouse, CF-1 (M) 4 wk 112 wk Walker et al. (1973)	Oral Dieldrin, > 99% Diet 0, 50 (DDT), 100 (DDT), 5 +50 (dieldrin+DDT) ppm, ad libitum 48, 32, 32, 32 NR	*Liver* Hepatocellular adenoma: 13%, 28%, 44%, 38% Hepatocellular carcinoma: 0%, 9%, 9%, 50% Hepatocellular adenoma and carcinoma (combined): 13%, 37%, 53%, 88% *Lung* Adenoma: 38%, 41%, 50%, 34% Carcinoma: 0%, 0%, 0%, 3% *Testes* Tumour, NOS: 0%, 0%, 6%, 3%	NR	Principal limitations: few dose groups.; neoplasm incidences not reported.; effective number of animals unclear; statistics cannot be calculated Study 2 – Experiment 2.3; DDT and dieldrin co-carcinogenicity. Animals received ethylene oxide-sterilized diet (standard procedure at that time). Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively. As reported in Epstein (1975), Reuber re-evaluated the liver histopathology data and reported the following incidences for hepatocellular adenoma and carcinoma (combined): control, 0%; 50 ppm DDT, 6%; 5 ppm dieldrin+50 ppm DDT, 58%
Co-carcinogenicity Mouse, CF-1 (F) 4 wk 112 wk Walker et al. (1973)	Oral Dieldrin, > 99% Diet 0, 50 (DDT), 100 (DDT), 5 +50 (dieldrin+DDT) ppm, ad libitum 48, 32, 32, 32 NR	*Liver* Hepatocellular adenoma: 17%, 43%, 63%, 28% Hepatocellular carcinoma 0%, 7%, 13%, 50% Hepatocellular adenoma and carcinoma (combined): 17%, 50%, 76%, 78% *Lung* Adenoma: 40%, 20%, 22%, 28% *Lung* Carcinoma: 6%, 17%, 3%, 6%	NR	Principal limitations: few dose groups; effective number of animals unclear; neoplasm incidences not reported; statistics cannot be calculated Study 2 – Experiment 2.3; DDT and dieldrin co-carcinogenicity. Animals received ethylene oxide-sterilized diet (standard procedure at that time). Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively. As reported in Epstein (1975), Reuber re-evaluated the liver histopathology data and reported the following incidences for hepatocellular adenoma and hepatocellular carcinoma (combined): control, 0%; 50 ppm DDT, 16%; 5 ppm dieldrin+50 ppm DDT, 94%

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (M) 4 wk 104 wk Walker et al. (1973)	Oral Dieldrin, > 99% Diet 10 ppm fed for 0 wk, 2 wk, 4 wk, 8 wk, 16 wk, 32 wk, 64 wk, ad libitum 29, 29, 29, 29, 29, 29, 29 NR	*Liver* Hepatocellular adenoma: 2/18, 2/13, 0/10, 3/10, 4/11, 4/10, 6/13*	*[$P < 0.043$ by Fisher's exact test]	Study 2 – Experiment 2.4; limited exposure Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively
		Hepatocellular carcinoma: 0/18, 0/13, 1/10, 1/10, 0/11, 0/10, 7/13	[NS]	
		Hepatocellular adenoma and carcinoma (combined): 2/18, 2/13, 1/10, 4/10, 4/11, 4/10, 13/13*	*[$P < 0.0001$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	
		Lung Tumour, NOS: 8/18, 6/13, 3/10, 6/10, 6/11, 5/10, 7/13	[NS]	
		Spleen/lymphatic tissue Tumour, NOS: 0/18, 2/13, 1/10, 3/10, 0/11, 1/10, 2/13	[NS]	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (F) 4 wk 104 wk Walker et al. (1973)	Oral Dieldrin, > 99% Diet 10 ppm fed for 0 wk, 2 wk, 4 wk, 8 wk, 16 wk, 32 wk, ad libitum 29, 29, 29, 29, 29, 29, 29 NR	*Liver* Hepatocellular adenoma: 1/16, 2/9, 3/12, 4/12, 3/8, 4/10, 6/9*	*[$P < 0.003$ by Fisher's exact test]	Study 2 – Experiment 2.4; limited exposure Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively
		Hepatocellular carcinoma: 0/16, 0/9, 1/12, 0/12, 0/8, 0/10, 2/9	[NS]	
		Hepatocellular adenoma and carcinoma (combined): 1/16, 2/9, 4/12, 4/12, 3/8, 4/10, 8/9*	*[$P < 0.0001$ by Fisher's exact test]; [$P = 0.004$ by Cochran-Armitage trend-test]	
		Lung Tumour, NOS: 4/16, 7/9*, 2/12, 6/12, 3/8, 4/10, 2/9	*[$P < 0.017$ by Fisher's exact test]	
		Ovary Tumour, NOS: 4/16, 3/9, 3/12, 4/12, 2/8, 3/10, 3/9	[NS]	
		Spleen/lymphatic tissue Tumour, NOS: 2/16, 1/9, 1/12, 2/12, 0/8, 3/10, 1/9	[NS]	
		Other tissues Tumour, NOS: 2/16, 2/9, 1/12, 0/12, 0/8, 0/10, 2/9	[NS]	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (M) 4 wk 110 wk Thorpe & Walker (1973)	Oral Dieldrin, > 99% Diet 0, 10 ppm, ad libitum 45, 30 NR	*Liver* Hepatocellular adenoma and carcinoma (combined): 24%, 100%*	*$P < 0.01$ by a 2 × 2 contingency table	Principal limitations: few dose groups; neoplasm incidences not reported; statistics cannot be calculated Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively
Full carcinogenicity Mouse, CF-1 (F) 4 wk 110 wk Thorpe & Walker (1973)	Oral Dieldrin, > 99% Diet 0, 10 ppm, ad libitum 45, 30 NR	*Liver* Hepatocellular adenoma and carcinoma (combined): 23%, 93%*	*$P < 0.01$ by a 2 × 2 contingency table	Principal limitations: few dose groups; neoplasm incidences not reported; statistics cannot be calculated Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively
Full carcinogenicity Mouse, CF-1 (M) NR (weanling) ≤ 65 wk of age Tennekes et al. (1979)	Oral Dieldrin, NR Diet (SSD or CD) SSD/FPB, 0, 10; SSD/SB, 0, 10; CD/FPB, 0, 10; CD/SB, 0, 10 mg/kg diet, ad libitum 15, 15, 15, 12, 15, 16, 15, 16 NR	*Liver* Hepatocellular adenoma: 2/15 (13.3%), 7/15 (46.7%), 1/15 (6.7%), 10/12 (83.3%)*, 0/15, 9/16 (56.3%)**, 0/15, 7/16 (43.7%)*** Hepatocellular carcinoma: 0/15, 4/15 (26.7%), 0/15, 2/12 (16.7%), 0/15, 4/16 (25%), 0/15, 5/16 (31.3%)* Hepatocellular adenoma and carcinoma (combined): 2/15 (13.3%), 11/15 (73.3%)*, 1/15 (6.7%), 12/12**, 0/15, 13/16 (81.3%)**, 0/15, 12/16 (75.0%)**	*[$P < 0.0001$] **[$P \leq 0.0008$] ***[$P < 0.007$] *[$P < 0.05$] *[$P \leq 0.0025$] **[$P < 0.0001$]	Principal limitations: few dose groups; small number of animals per group SSD: semisynthetic diet; FPB: filter paper bedding; SB: sawdust bedding; CD: conventional diet. Liver neoplasms were diagnosed as type (a) and type (b). In current terminology, these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (M) NR (weanling) 110 wk Tennekes et al. (1981)	Oral Dieldrin, > 99% Diet (SSD or CD) SSD/FPB, 0, 10; SSD/SB, 0, 10; CD/FPB, 0, 10; CD/SB, 0, 10 mg/kg diet, ad libitum 55, 31, 47, 19, 68, 51, 82, 38 NR	*Liver* Hepatocellular adenoma: 2/55, 10/31*, 12/47, 13/19**, 4/68, 23/51***, 5/82, 13/38**** Hepatocellular carcinoma: 1/55, 11/31*, 0/47, 3/19**, 0/68, 21/51*, 1/82, 19/38* Hepatocellular adenoma and carcinoma (combined): 3/55 (5.5%), 21/31 (67.7%)*, 12/47 (25.5%), 16/19 (84.2%)*, 4/68 (5.9%), 44/51 (86.3%)*, 6/82 (7.3%), 32/38 (84.2%)*	*[$P = 0.0005$] **[$P \leq 0.0019$] ***[$P < 0.0001$] ****[$P = 0.0002$] *[$P < 0.0001$] **[$P = 0.0212$] *[$P < 0.0001$]	Principal limitation: few dose groups SSD: semi-synthetic diet; FPB: filter paper bedding; SB: sawdust bedding; CD: conventional diet. On average, only 10% of dieldrin-treated mice survived to 100 wk (controls, 40%). Lung metastases were observed in hepatocellular carcinoma-bearing treated mice
Full carcinogenicity Mouse, CF-1 (M) 4 wk ≤ 132 wk Tennekes et al. (1982)	Oral Dieldrin, > 99.9% NR 0, 0.1, 1, 10 ppm, ad libitum 289, 124, 111, 176 NR	*Liver* Hepatocellular carcinoma: 11/289, 6/124, 10/111*, 102/176** Hepatocellular adenoma and carcinoma (combined): 58/289, 33/124, 35/111*, 167/176**	*[$P < 0.046$ by Fisher's exact test]; **[$P < 0.0001$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test] *[$P < 0.018$ by Fisher's exact test]; **[$P < 0.0001$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	Re-evaluation of Walker et al. (1973). Publication includes data from two different long-term feeding studies: Experiment 1: dieldrin at 0, 0.1, 1, and 10 ppm; Experiment 2.1: dieldrin at 0, 2.5, 5, and 20 ppm. At 20 ppm, 5/17 males died from "acute intoxication" within the first 13 wk of treatment

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (F) 4 wk Up to 132 wk Tennekes et al. (1982)	Oral Dieldrin, > 99.9% NR 0, 0.1, 1, 10 ppm, ad libitum 297, 120, 117, 148 NR	*Liver* Hepatocellular carcinoma: 0/297, 4/120*, 6/117**, 88/148**	*[$P < 0.007$ by Fisher's exact test]; **[$P < 0.0001$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	Re-evaluation of Walker et al. (1973). Publication includes data from two different long-term feeding studies: Experiment 1: dieldrin at 0, 0.1, 1 and 10 ppm; Experiment 2.1: dieldrin at 0, 2.5, 5, 10, and 20 ppm. At 20 ppm, 11/21 females died from "acute intoxication" within the first 13 wk of treatment
		Hepatocellular adenoma and carcinoma (combined): 37/297, 25/120*, 33/117**, 142/148**	*[$P < 0.034$ by Fisher's exact test]; **[$P = 0.0002$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	
Full carcinogenicity Mouse, CF-1 (M) 4 wk Up to 132 wk Tennekes et al. (1982)	Oral Dieldrin, > 99.9% NR 0, 2.5, 5, 20 ppm, ad libitum 78, 30, 30, 17 NR	*Liver* Hepatocellular carcinoma: 0/78, 2/30, 3/30*, 9/17**	*[$P < 0.020$ by Fisher's exact test]; **[$P < 0.0001$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	Re-evaluation of Walker et al. (1973). Publication includes data from two different long-term feeding studies: Experiment 1: dieldrin at 0, 0.1, 1, and 10 ppm; Experiment 2.1: dieldrin at 0, 2.5, 5, and 20 ppm. At 20 ppm, 5/17 males died from "acute intoxication" within the first 13 wk of treatment
		Hepatocellular adenoma and carcinoma (combined): 9/78, 14/30*, 26/30*, 12/17*	*[$P < 0.0002$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, CF-1 (F) 4 wk Up to 132 wk Tennekes et al. (1982)	Oral Dieldrin, > 99.9% NR 0, 2.5, 5, 10, 20 ppm, ad libitum 78, 28, 30, 17, 21 NR	Hepatocellular carcinoma: 0/78, 2/28, 5/30*, 2/17**, 3/21***	*[$P < 0.0014$ by Fisher's exact test]; **[$P < 0.031$ by Fisher's exact test]; ***[$P < 0.009$ by Fisher's exact test] [$P = 0.013$ by Cochran-Armitage trend-test]	Re-evaluation of Walker et al. (1973). Publication includes data from two different long-term feeding studies: Experiment 1: dieldrin at 0, 0.1, 1, and 10 ppm; Experiment 2.1: dieldrin at 0, 2.5, 5, 10, and 20 ppm. At 20 ppm, 11/21 females died from "acute intoxication" within the first 13 wk of treatment
		Hepatocellular adenoma and carcinoma (combined): 8/78, 13/28*, 18/30*, 9/17*, 8/21**	*[$P < 0.0001$ by Fisher's exact test]; **[$P = 0.0002$ by Fisher's exact test]; [$P < 0.001$ by Cochran-Armitage trend-test]	
Full carcinogenicity Mouse, B6C3F$_1$ (M) 35 days 91–93 wk NTP (1978a)	Oral Dieldrin (technical grade), > 96% (impurities, NR) Diet 0, 0, 2.5, 5 ppm, ad libitum; mice treated for 80 wk, followed by observation periods of 11–13 wk 20, 92, 50, 50 NR	*Liver* Hepatocellular carcinoma: 3/18 (matched control), 17/92* (pooled control), 12/50, 16/45**	*$P = 0.020$; Cochran-Armitage trend test **$P = 0.025$; Fisher exact test vs pooled control group	Principal strengths: adequate duration; studies in M and F; complete histopathology

Table 3.2 (continued)

Study design **Species, strain (sex)** **Age at start** **Duration** **Reference**	**Route** **Agent tested, purity** **Vehicle** **Dose(s)** **No. of animals at start** **No. of surviving animals**	**Incidence of tumours**	**Significance**	**Comments**
Full carcinogenicity Mouse, B6C3F$_1$ (F) 35 days 90–93 wk NTP (1978a)	Oral Dieldrin (technical grade), > 96% (impurities NR) Diet 0, 0, 2.5, 5 ppm, ad libitum; mice treated for 80 wk, followed by observation periods of 10–13 wk 20, 79, 50, 50 NR	*Liver* Hepatocellular carcinoma: 0/20 (matched control), 3/78 (pooled control), 6/50, 2/49	 NS	Principal strengths: adequate duration; studies in M and F; complete histopathology
Full carcinogenicity Mouse, Balb/c (M) NR (young) 52 and 75 wk Lipsky et al. (1989)	Oral Dieldrin, NR Diet 0 (52 wk), 10 (52 wk), 0 (75 wk), 10 (75 wk) ppm 10, 10, [unclear], 20 NR	*Liver* Hepatocellular adenoma: Incidence: 0/10, 2/10, 2/36, 16/20* Total tumours: 0, 2, 7, 29 Hepatocellular carcinoma: Incidence: 0/10, 1/10, 1/36, 3/20 Total tumours: 0, 1, 1, 3 Hepatocellular adenoma or carcinoma (combined): 0/10, 2/10 (20%), 3/36 (8%), 16/20 (80%)*	 *[$P < 0.0001$] [NS] *[$P < 0.0001$]	Principal limitation: number of 75-wk control animals at start unclear
Full carcinogenicity Mouse, Swiss-Webster (M) NR (weanling) ≤ 30 mo Epstein (1975)	Oral Dieldrin, technical grade NR 0, 3, 10 ppm, ad libitum 125, 129, 130 NR	*Liver* Nodules: 0/93, 2/81 (2%), 32/91* (35%) Hepatoma: 0/93, 0/81, 0/91	 *[$P < 0.0001$ by Fisher's exact test] [$P < 0.001$ by Cochran-Armitage trend-test] NS	Re-evaluation of some of the histopathology data by Reuber and others concluded that more than half of the re-examined liver lesions from high-dose mice were hepatocellular carcinomas

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, Swiss-Webster (F) NR (weanling) ≤ 32 mo Epstein (1975)	Oral Dieldrin, technical grade NR 0, 3, 10 ppm, ad libitum 100, 100, 100 NR	*Liver* Nodules: 0/71, 2/78 (3%), 44/70* (63%) Hepatoma: 2/71, 0/78, 0/70	*[$P < 0.0001$ by Fisher's exact test] [$P < 0.001$ by Cochran-Armitage trend-test] NS	Re-evaluation of some of the histopathology data by Reuber and others concluded that more than half of the re-examined liver lesions from high-dose mice were hepatocellular carcinomas
Full carcinogenicity Mouse (C57BL/6J × C3HeB/FeJ)F_1 (M) 1 or 5 wk Up to 90 wk Vesselinovitch et al. (1979)	Gavage and/or oral Dieldrin, NR NR 0 µg (untreated control); 12.5 µg daily by gavage from age 1 to 5 wk; 10 ppm in the diet from age 5 to 90 wk; 12.5 µg daily by gavage from age 1 to 5 wk, then 10 ppm in the diet from age 5 to 90 wk NR NR	*Liver* Hepatocellular tumours: 1/58 (2%), 3/46 (7%), 7/60 (12%), 21/70 (30%)*	$P < 0.001$	Principal limitations: number of animals at start, NR; lack of vehicle control; no data on survival or body weight; purity, NR; statistical test, NR

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse (transgenic), FVB/N-TgMMTV/neu (offspring) (F) NA Offspring killed at 22 wk Cameron & Foster (2009)	Transplacental/lactation/gavage Dieldrin, NR Corn oil 0, 0.45, 2.25, 4.5 µg/g bw Dams: gavage for 5 days, 2 wk before mating, 1×/week throughout gestation and lactation until weaning (age 3 wk); offspring: 1×/week until age 9 wk NR 84, 79, 81, 19	*Mammary* Total tumours: Tumour multiplicity: 4.62, 4.82, 4.54, 7.58* Thoracic tumours: Tumour multiplicity: 3.81, 4.24, 3.82, 6.37* Inguinal tumours: Tumour multiplicity: 0.75, 1.00, 0.73, 1.21	*$P < 0.05$ as determined by one way ANOVA and appropriate post hoc test *$P < 0.05$ as determined by one way ANOVA and appropriate post hoc test NS	Tumours were primarily adenocarcinoma of the mammary gland. There was also an increased ($P < 0.05$) volume of thoracic mammary tumours: 49.12, 45.55, 18.28, and 77.30* mm^3, respectively. Preliminary evidence of increased incidence of ovarian and liver tumours in groups at the intermediate and highest dose
Full carcinogenicity Rat, Carworth Farm "E" (M) 5 wk 2 yr Walker et al. (1969)	Oral Dieldrin, > 99% Diet 0, 0.1, 1.0, 10 ppm, ad libitum 45, 25, 25, 25 NR	All tumours 12/43, 6/23, 5/23, 8/23 *Pituitary gland* Tumour: 2/43, 2/23, 1/23, 2/23 *Thyroid gland* Tumour: 3/43, 2/23, 2/23, 4/23	NS NS NS	Stevenson et al. (1976) re-evaluated the study and concluded again there was not a treatment-related increase in tumour incidence. Number of males with tumours was 12/43, 9/23, 5/23, and 9/23, respectively
Full carcinogenicity Rat, Carworth Farm "E" (F) 5 wk 2 yr Walker et al. (1969)	Oral Dieldrin, > 99% Diet 0, 0.1, 1.0, 10 ppm, ad libitum 45, 25, 25, 25 NR	*All tumours* 19/43, 15/23, 14/23, 12/23 *Pituitary gland* Tumour: 2/43, 1/23, 1/23, 2/23 *Thyroid gland* Tumour: 3/43, 6/23, 4/23, 3/23	NS NS NS	Stevenson et al. (1976) re-evaluated the study and concluded again there was not a treatment-related increase in tumour incidence. Number of females with tumours was 18/43,18/23,16/23,and 13/23, respectively

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Carworth Farm "E" (F) 5 wk 2 yr Walker et al. (1969) (cont.)		*Mammary gland* Tumour: 13/43, 11/23, 10/23, 8/23 *Other tumours* 3/43, 2/23, 4/23, 0/23	 NS NS	
Full carcinogenicity Rat, Osborne-Mendel (M+F combined) 3 wk 104 wk Fitzhugh et al. (1964)	Oral Dieldrin, 100% Diet 0, 0.5, 2, 10, 50, 100, 150 ppm, ad libitum 24, 24, 24, 24, 24, 24, 24 50%, 42%, 63%, 25%, 21%[a], 13%[b], 4%[a]	*All tumours* 3/17, 8/22, 8/23, 4/18, 4/20, 3/18, 0/11	NS	Principal limitations: data combined for sexes; only 68% of animals treated with dieldrin (or aldrin) were examined histologically Survival was significantly decreased in M and F (combined) at 50, 100 or 150 ppm at 24 mo ([a]$P \leq 0.05$, [b]$P \leq 0.01$). Tumours reported as "pulmonary lymphosarcoma," "fibroadenoma of breast," "carcinoma of breast," "lymphoid except lung," "fibrosarcoma," and "other were confirmed by" independent re-evaluations by Reuber and others (Epstein, 1975). No liver tumours were initially reported, but a partial re-evaluation of the liver histopathology identified a total of 18 liver carcinomas in rats fed diets containing dieldrin or aldrin
Full carcinogenicity Rat, Osborne-Mendel (M) NR (weanling) < 31 mo Deichmann et al. (1970)	Oral Dieldrin, 100% Diet 0, 20, 30, 50 ppm, ad libitum 100, 51, 50, 50 NR	*All tumours* 19/75, 4/48, 7/38, 1/44 Total tumours: 46, 10, 19, 1	NS	Doses during the first 10 wk were half the final concentrations. Maximum survival of controls was only 27 mo. Histopathology was re-evaluated in limited samples of the group receiving dieldrin at 30 ppm: as reported in Epstein (1975), the total number of rats (M and F combined) with malignant tumours was reported as 12.6% (10/79) in Deichmann et al. (1970), whereas a re-evaluation by Reuber reported 34.2% (26/76). Tumour incidence: total number of rats with tumours/number of rats examined histologically

Table 3.2 (continued)

Study design **Species, strain (sex)** **Age at start** **Duration** **Reference**	**Route** **Agent tested, purity** **Vehicle** **Dose(s)** **No. of animals at start** **No. of surviving animals**	**Incidence of tumours**	**Significance**	**Comments**
Full carcinogenicity Rat, Osborne-Mendel (F) NR (weanling) < 31 mo Deichmann et al. (1970)	Oral Dieldrin, 100% Diet 0, 20, 30, 50 ppm, ad libitum 100, 50, 48, 50 NR	*All tumours* 60/88, 23/48, 16/41, 16/41 Total tumours: 104, 33, 23, 23	NS	Doses during the first 10 wk were half the final concentrations. Maximum survival of controls was only 27 mo. Histopathology was re-evaluated in limited samples of the group receiving dieldrin at 30 ppm: as reported in Epstein (1975), the total number of rats (M and F combined) with malignant tumours was reported as 12.6% (10/79) in Deichmann et al. (1970), whereas a re-evaluation by Reuber reported 34.2% (26/76). Tumour incidence: total number of rats with tumours/number of rats examined histologically
Full carcinogenicity Rat, Osborne- Mendel (M) 35 days 110–111 wk NTP (1978a)	Oral Dieldrin (technical grade), > 96% (impurities NR) Diet Matched controls – 0, pooled controls – 0, 29 (TWA), 65 (TWA) ppm, ad libitum; low-dose rats treated for 80 wk, followed by observation periods of 30 wk; high-dose rats treated for 59 wk followed by observations periods of 52 wk 10, 58, 50, 50 NR	Any tumour type No significant increase	NS	Principal strengths: adequate duration; covered most of the life span; studies in M and F; complete histopathology

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Osborne- Mendel (F) 35 days 110–111 wk NTP (1978a)	Oral Dieldrin (technical grade), > 96% (impurities NR) Diet Matched controls – 0, pooled controls – 0, 29 (TWA), 65 (TWA) ppm, ad libitum; Low-dose rats treated for 80 wk, followed by observation periods of 30–31 wk; high-dose rats treated for 59 wk followed by observation periods of 51–52 wk 10, 60, 50, 50 NR	*Adrenal gland* Cortical adenoma or carcinoma (combined): 0/9, 0/55, 6/45*, 2/40	*P = 0.007 by the Fisher exact test when compared with the pooled-control group	Principal strengths: adequate duration; covered most of the life span; studies in M and F; complete histopathology
Full carcinogenicity Rat, F344 (M) 51–55 days 104–105 wk NTP (1978b)	Oral Dieldrin, technical grade, purified Diet 0, 2, 10, 50 ppm, ad libitum 24, 24, 24, 24 22, 18, 18, 16	No increase in incidence of any tumour type	NS	Principal limitation: small number of animals
Full carcinogenicity Rat, F344 (F) 51–55 days 104–105 wk NTP (1978b)	Oral Dieldrin, technical grade, purified Diet 0, 2, 10, 50 ppm, ad libitum 24, 24, 24, 24 21, 21, 20, 17	No increase in incidence of any tumour type	NS	Principal limitation: small number of animals

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Hamster, Syrian golden (M) NR Lifetime (up to 120 wk of age) Cabral et al. (1979)	Diet Dieldrin, 99% Diet 0, 20, 60, 180 ppm, ad libitum 40, 34, 32, 41 2, 3, 5, 13 (at age 90 wk)	All tumours: 3/40 (7.5%), 5/32 (15.6%), 5/32 (15.6%), 10/40 (25%) Total tumours: 3, 5, 8, 11	NS	Tumour sites were reported as [all], thyroid gland, adrenal gland, liver, and "other"
Full carcinogenicity Hamster, Syrian golden (F) NR Lifetime (up to 120 wk of age) Cabral et al. (1979)	Diet Dieldrin, 99% Diet 0, 20, 60, 180 ppm, ad libitum 40, 33, 34, 38 3, 0, 3, 4 (at age 90 wk)	All tumours: 5/39 (12.8%), 1/32 (3.2%), 5/34 (14.7%), 5/38 (13.2%) Total tumours: 5, 1, 7, 9	NS	Tumour sites were reported as [all], thyroid gland, adrenal gland, liver, and "other"

DDT, dichlorodiphenyl trichloroethane; F, female; M, male; mo, month; NOS, not otherwise specified; NR, not reported; NS, not significant; ppm, parts per million; TWA, time-weighted average; wk, week; yr, year

consisted of 217 male and female mice. Treated mice died 2 months earlier than controls; the average survival time in the treated mice was 51.4 weeks compared with 59.8 weeks for the controls. Survival at 18 months was decreased in treated mice (33/218, 15%) compared with the control group (47/217, 22%). All survivors at 2 years were killed and autopsied. Pneumonia and intestinal parasitism were observed in the study and probably contributed to the decreased survival of the mice. Caging of mice in groups of 5–8 contributed to the spread of disease within groups (Davis & Fitzhugh, 1962). Partial re-evaluation by Reuber and others of the histopathology data of the Davis & Fitzhugh (1962) and Davis (1965) studies indicated that most tumours initially classified by Davis & Fitzhugh (1962) as "hepatic cell adenomas" were hepatocellular carcinomas (Epstein, 1975; Reuber 1975, 1976a). A statistically significant increase in the incidence of "hepatic cell adenoma" [hepatocellular carcinoma] (36/148, 24%; $P < 0.001$) was noted in treated mice when compared to the control group (9/134, 7%). On average, treated mice developed "hepatic cell adenomas" [hepatocellular carcinomas] after 77 weeks on study compared with 89 weeks on study for control mice. [Limitations of this study included the low survival rate, combination of data for both sexes, lack of detailed histopathology, reports of disease, pneumonia and intestinal parasitism, and the disposal of a large number of animals at autopsy. The Working Group noted that the re-evaluation by Epstein (1975) was accurate, but limited by the number of cases reviewed.]

In a subsequent study, groups of 100 male and 100 female C3H mice were fed diets containing dieldrin [purity not reported] at a concentration of 0 or 10 ppm for up to 2 years (Davis, 1965, reported in Epstein, 1975). The number of survivors at 104 weeks was 64 and 39 for control and treated mice, respectively. The incidence (for both sexes combined) of "benign hepatoma" [hepatocellular carcinoma] in the treated group was significantly increased and approximately double that of controls, whereas the number of hepatic carcinomas [hepatocellular carcinoma] was about the same (Epstein, 1975). An independent partial re-evaluation of the Davis & Fitzhugh (1962) and Davis (1965) combined studies by Reuber and others concluded that most of the "benign hepatomas" were hepatocellular carcinomas. This re-evaluation indicated significant increases in the incidence of hepatocellular carcinoma in the treated compared with the control group in males and females (Epstein, 1975; Reuber 1976a). Morphological descriptions of the liver lesions were reported by Reuber (Reuber, 1975, 1976a). There were often two hepatocellular carcinomas present at the same time in treated animals compared with a solitary hepatocellular carcinoma in the control animals (Reuber, 1976a). In addition, transplantation studies were conducted in which hepatocellular carcinomas were transplanted into mice [sex not reported] with a similar genetic background. Eight out of nine tumours from mice fed dieldrin at 10 ppm grew when transplanted and histologically resembled the primary tumours (Reuber, 1976b). [Limitations of this study included the combination of data for both sexes, lack of detailed histopathology and the absence of report on the number of animals evaluated for histopathology. The Working Group noted that the re-evaluation by Epstein (1975) was accurate but limited by the number of cases reviewed.]

Groups of 71 C57BL/6, 50 C3H/He and 62 B6C3F$_1$ weanling male mice [age not reported] were fed diets containing dieldrin (purity, > 99%) at a concentration of 10 ppm for 85 weeks and observed up to age 132 weeks (Meierhenry et al., 1983). Control groups consisted of 69, 50, and 76 mice per strain, respectively. Hepatic tumours [hepatocellular tumours] developed earlier in mice treated with dieldrin than in controls, particularly in the C3H/He strain, in which the first tumour was observed in dieldrin-treated animals 25 weeks earlier (12 weeks)

than in the controls (37 weeks). There was a statistically significant increase in the incidence of benign hepatocellular neoplasms in C57BL/6J and B6C3F$_1$ mice fed diets containing dieldrin compared with controls. The incidence of hepatocellular carcinoma was significantly increased in all strains of mice treated with dieldrin compared with controls. [The Working Group noted that limitations of this study included the absence of data on survival and body weight.]

A subsequent study investigated the histological progression of hepatocellular adenomas to carcinomas in sequential liver biopsies in two groups of C3H/He weanling male mice [age not reported] that were fed diets containing dieldrin (purity, 99%) at a concentration of 10 ppm until the mice reached either age 57 or 67 weeks (Ruebner et al., 1984). A control group was untreated. The animals were killed at age 2 years. There was a significant increase in the incidence of hepatocellular adenoma in the dieldrin-treated group (for 57 weeks) compared with the control group. More frequent progression of hepatocellular lesions from adenoma to carcinoma was observed in dieldrin-treated mice than in control mice. [The Working Group noted that limitations of this study included that the number of animals at start was not reported, the small number of animals, and the short exposure duration.]

Bauer-Hofmann et al. (1992) evaluated the frequency and pattern of c-Ha-*ras* mutations in hepatocellular lesions induced in 20 male C3H/He mice (age, 4 weeks) fed diets containing dieldrin at a concentration of 10 ppm for 52 weeks. A control group of 40 animals was fed basal diet. There was an increase in the incidence [not significant] and multiplicity of hepatocellular lesions in dieldrin-treated mice relative to controls. [This mechanistic study was not a carcinogenicity study: a distinction between neoplastic and non-neoplastic lesions was not made. Limitations of this study also included the limited number of dose groups and short exposure duration. The Working Group considered this study inadequate for the evaluation.]

Walker et al. (1973) conducted several studies in which male and female CF-1 mice (age, 4 weeks) were fed diets containing dieldrin (purity, > 99%) at concentrations ranging from 0.1 to 20 ppm for up to 132 weeks.

In the first study, male and female CF-1 mice were fed diets containing dieldrin (purity, > 99%) at a concentration of 0, 0.1, 1.0, or 10 ppm for 132 weeks (Walker et al., 1973; Epstein, 1975; Hunt et al., 1975). Groups consisted of 600, 250, 250, and 400 mice, respectively, divided equally by sex. By experimental month 15, half of the males and females fed diet containing dieldrin at 10 ppm had died or been killed, while the controls reached 50% mortality by experimental months 20–24. The increase in incidence of hepatocellular carcinoma [type (b) tumours] was dose-related and markedly increased in groups of males and females at the highest dose compared with their respective controls. The increases in incidence of hepatocellular adenoma [type (a) tumours] and carcinoma [type (b) tumours] (combined) were also dose-related and strongly increased in groups of males and females at the highest dose compared with their respective controls. [The Working Group noted that the limitations of the study included that the incidence of neoplasms was not reported and that the effective number of animals was unclear. Liver neoplasms were diagnosed as type (a) and type (b) tumours; in current terminology (Thoolen et al., 2010), these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively.]

In the first study ["Experiment 2.1"] of a second series of studies ["Experiments 2.1-2.4" on the original publication] by Walker and colleagues (Walker et al., 1973; Epstein, 1975), groups of 30 male and 30 female CF-1 mice were given diet containing dieldrin (purity, > 99%) at a concentration of 1.25, 2.5, 5, 10, or 20 ppm for 128 weeks. Control groups consisted of 78 males and 78 females. The incidences of hepatocellular

adenoma and carcinoma (combined) were increased in all the dose groups relative to controls, with the highest incidence observed in males and females given a diet containing dieldrin at a concentration of 5 ppm. In a second study ["Experiment 2.2"], similar incidences of hepatocellular adenoma, hepatocellular adenoma or carcinoma (combined), and hepatocellular carcinoma were observed in groups of male and female CF-1 mice given non-irradiated diet and bedding, gamma-irradiated diet, or gamma-irradiated diets and bedding, with clearly higher incidences in the dieldrin-treated groups; the diet contained dieldrin (purity, > 99%) at concentrations of 0 or 10 ppm. A third (co-carcinogenicity) study ["Experiment 2.3"] investigated the influence of dieldrin (purity, > 99%) exposure (5 ppm) on groups of 32 male and 32 female CF-1 mice given a diet containing 4,4′-dichlorodiphenyltrichloroethane (DDT) at a concentration of 50 ppm for 112 weeks. An untreated control group consisted of 48 male and 48 female mice. The incidence of hepatocellular adenoma or carcinoma (combined) (but also of hepatocellular carcinoma) was increased in male and female mice fed dieldrin at 5 ppm and DDT at 50 ppm compared with controls and in groups fed DDT alone at 50 ppm. Reuber re-evaluated the histopathology data and diagnosed fewer liver neoplasms in the control and DDT groups than Walker et al. did (Walker et al., 1973; Epstein, 1975), resulting in a more pronounced effect of dieldrin on the incidence of hepatocellular neoplasms: males, 0 ppm (control), 0%; 50 ppm DDT, 6%; 5 ppm dieldrin+50 ppm DDT, 58%; and females: 0 ppm (control), 0%; 50 ppm DDT, 16%; 5 ppm dieldrin+50 ppm DDT, 94%. Epstein (1975) indicated that Walker et al. "overestimated the incidence of total liver tumours in the DDT groups, largely by inclusion of hyperplastic and nodular lesions as type (a) tumours." In a fourth study ["Experiment 2.4"], Walker et al. (1973) conducted a time course in which groups of 29 male and 29 female CF-1 mice were given a diet containing dieldrin (purity, > 99%) at a concentration of 10 ppm for varying periods of time from 0 (control) up to 64 weeks, and were maintained until experimental week 104. The incidences of hepatocellular adenoma and carcinoma (combined) were significantly increased in males and in females fed dieldrin at 10 ppm for 64 weeks. There was also a significant positive trend in the incidence of hepatocellular adenoma or carcinoma (combined) in males and females. [The Working Group noted that limitations of some of the studies included that neoplasm incidence was not reported, the effective number of animals was unclear, and the number of dose groups was limited. Liver neoplasms were diagnosed as type (a) and type (b) tumours; in current terminology (Thoolen et al., 2010), these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively.]

Tennekes et al. (1982) re-evaluated the dose–response relationship for the data on tumours of the liver from two long-term studies conducted by Walker et al. (1973) [Experiment 1 and Experiment 2.1]. In both sexes, treatment appeared to result in dose-related increases in the incidence of both hepatocellular adenoma and carcinoma (combined) and hepatocellular carcinoma, up to 10 ppm; the somewhat lower incidence at 20 ppm was hypothesized to result from considerable toxicity and lethality at that concentration. Dieldrin also induced a dose-dependent reduction in tumour latency periods; the lowest doses associated with a significant reduction in median time-to-tumour formation were 0.1 and 1.0 ppm for females and males, respectively.

In another study in CF-1 mice, groups of 30 males and 30 females were fed diets containing dieldrin (purity, > 99%) at a concentration of 10 ppm for 110 weeks (Thorpe & Walker, 1973). The control group consisted of 45 males and 45 females. Mortality increased in male mice fed diets containing dieldrin at 10 ppm after 22

months. A statistically significant increase in the incidence of hepatocellular adenoma and carcinoma (combined) was found in treated males and females compared with controls. The liver tumours appeared much earlier in treated animals than in controls. [The Working Group noted that limitations of the study included the lack of reporting on neoplasm incidence and the small number of dose groups. Liver neoplasms were diagnosed as type (a) and type (b) tumours; in current terminology (Thoolen et al., 2010), these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively.]

In a study by Tennekes et al. (1979), eight groups of 12–16 male weanling CF-1 mice [age not reported] were fed diets containing dieldrin [purity not reported] at a concentration of 0 or 10 ppm until age 65 weeks. The incidence of benign and malignant liver tumours (hepatocellular adenoma and hepatocellular carcinoma, respectively) or their combination was significantly increased in some groups fed dieldrin relative to the respective control groups. The Working Group noted that limitations of the study included the small number of animals per group and the small number of dose groups. Liver neoplasms were diagnosed as type (a) and type (b) tumours; in current terminology (Thoolen et al., 2010), these neoplasms correspond to hepatocellular adenoma and hepatocellular carcinoma, respectively.]

In a subsequent study by Tennekes et al. (1981), eight groups of 19–82 male weanling CF-1 mice [age not reported] were fed diets containing dieldrin (purity, > 99%) at a concentration of 0 or 10 ppm over the duration of their lifespan (for up to 110 weeks). Dieldrin had no effect on the mean body weights of treated mice relative to controls. Survival was significantly reduced in mice fed diets containing dieldrin at 10 ppm. On average, 10% of mice fed dieldrin survived to 100 weeks compared with 40% of control mice. A significant increase in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) was observed in all four groups of mice fed diets containing dieldrin at 10 ppm. Several dieldrin-treated mice with hepatocellular carcinomas had lung metastases.

In a study by the NCI, groups of 50 male and 50 female B6C3F$_1$ mice were fed diets containing dieldrin (technical grade; purity, > 96% [impurities not reported]) at a concentration of 2.5 or 5 ppm for 80 weeks, and then held untreated for an additional 10–13 weeks (NTP, 1978a). The matched-control group consisted of 20 male and 20 female mice, and the study duration was 91–93 weeks. Because the number of matched-control mice was small, pooled controls were used for statistical comparisons. The pooled-control groups consisted of the matched controls from the bioassay of dieldrin combined with matched controls from contemporary bioassays of aldrin, chlordane, heptachlor, dichlorvos, and dimethoate, giving groups of 92 male and 79 female mice. There was no significant effect on the survival or mean body weights of males and females compared with the controls.

In males, a significant positive trend in the incidence of hepatocellular carcinoma was noted when the treated groups were compared with the pooled controls. The incidence of hepatocellular carcinoma was significantly increased in males at 5 ppm (16/45; 36%), and exceeded the incidence for historical controls (48/285, 16.8%). The incidence of other neoplasms was not significantly increased when compared with the matched or the pooled controls. There was no significant increase in the incidence of neoplasms in female mice (NTP, 1978a).

In a study by Lipsky et al. (1989), groups of young [number of control animals at start unclear, and age not further specified] male Balb/c mice were fed diets containing dieldrin [purity not reported] at a concentration of 0 or 10 ppm for 2, 4, 8, 16, 36, 52, or 75 weeks. Hepatocellular adenomas were reported in the groups at 52

and 75 weeks. The incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in mice fed diets containing dieldrin at 10 ppm for 52 weeks and 75 weeks when compared with controls.

Epstein (1975) reviewed and provided re-evaluation of the slides from a study (see also EPA, 1974) in which groups of 125–130 male and 100 female Swiss-Webster mice were fed diets containing dieldrin (technical grade) [purity not reported] at a concentration of 0, 3, or 10 ppm for up to 32 months. The treated animals were initially given dieldrin at 1.5 or 5 ppm for the first 2 months of the study. Only 71% of the mice were examined histologically. According to the authors, dieldrin was not carcinogenic, but it increased the incidence of various non-neoplastic lesions of the liver (including liver hepatomas and nodules). A re-evaluation of some of the histopathology data by Reuber and others concluded that more than half of the re-examined liver lesions from male and female mice at the highest dose were hepatocellular carcinomas. [The Working Group noted the incomplete histopathological examination and re-evaluation, and the limited reporting in this study.]

(b) Gavage plus dietary administration

Four groups of male (C57BL/6J × C3HeB/FeJ)F_1 mice [number of animals at start, not reported] were treated with dieldrin [purity not reported]. Group I received 12.5 µg of dieldrin daily by gavage from age 1 week to age 4 weeks. Group II was given diet containing dieldrin at a concentration of 10 ppm from age 5 weeks to age 90 weeks. Group III received 12.5 µg of dieldrin daily by gavage from age 1 week to age 4 weeks, and was subsequently given diet containing dieldrin at a concentration of 10 ppm from age 5 weeks to age 90 weeks. Group IV (control) was untreated. The experiment was terminated at age 90 weeks. Histopathological examination was performed on the liver only. Only when both treatment schedules were combined (group III) did dieldrin significantly increase the incidence of liver [hepatocellular] tumours (30% vs 2% in controls; $P < 0.001$) (Vesselinovitch et al., 1979). [The Working Group noted the lack of vehicle controls, and the lack of data on survival and body weight.]

(c) Transplacental exposure, lactation, and gavage

In a study by Cameron & Foster (2009), four groups of 29–30 transgenic FVB/N-TgMMTV-neu female mice were given vehicle (corn oil) or dieldrin [purity not reported] at a dose of 0.45, 2.25, or 4.5 µg/g bw daily by gavage for 5 days 2 weeks before mating, and then once per week throughout gestation and lactation until weaning (age, 3 weeks). At weaning, four groups of female pups [number of animals at start, not reported] began weekly dosing (same doses as their respective groups of dams) by gavage until age 9 weeks and were killed at 22 weeks. Treatment with dieldrin had no effect on litter size, birth weight, or the number of pups surviving to weaning. The highest dose of dieldrin (4.5 µg/g bw) resulted in an increased multiplicity of thoracic mammary tumours [primarily mammary adenocarcinomas] per mouse and in increased volume of incident thoracic tumours. The multiplicity of total mammary tumours was also significantly increased at the highest dose. In contrast, the mean number of inguinal mammary tumours was not significantly increased. Preliminary histopathological assessment of the ovaries revealed an increased incidence of ovarian tumours in groups receiving dieldrin at 2.25 (7.5%) and 4.5 (10.5%) g/g bw compared with controls (2.65%). An increase in the incidence of liver tumours was also found in groups receiving dieldrin at 2.25 (18.8%) and 4.5 (52.6%) µg/g bw compared with controls (11.8%).

3.2.2 Rat

A study in male and female Carworth rats fed diets containing dieldrin (Treon & Cleveland, 1955; Cleveland, 1966; also reported in Epstein, 1975) was judged inadequate by the Working Group because of the lack of histopathological evaluation, difficulties in interpretation of the mortality data, limited reporting, and discrepancies between Treon & Cleveland (1955) and Cleveland (1966).

Three groups of 25 male and 25 female Carworth (Farm "E") rats (age, 5 weeks) were fed diets containing dieldrin (purity, > 99%) at a concentration of 0.1, 1.0, or 10 ppm for 2 years (Walker et al., 1969). Control groups consisted of 45 males and 45 females. Survival and body weight were not affected by feeding with dieldrin for 2 years. The incidence of tumours was not increased in treated groups relative to the controls for any of four tissue sites, including the thyroid, pituitary, and mammary gland, or "other" after 2 years.

Groups of 12 male and 12 female Osborne-Mendel rats were fed diets containing dieldrin (purity, 100%) at a concentration of 0, 0.5, 2, 10, 50, 100, or 150 ppm for 2 years (Fitzhugh et al., 1964). Survival was significantly decreased in males and females (combined) at 50, 100, or 150 ppm at 24 months. Mean body weights of males and females were similar to those of the controls. The incidence of tumours (all six categories listed below) in treated males and females (combined) was not increased compared with the control group. Six tumour categories were identified, including "pulmonary lymphosarcoma", "fibroadenoma of breast", "carcinoma of breast", "lymphoid except lung", "fibrosarcoma", and "other". Epstein (1975) reported that independent histopathological re-evaluations by Reuber and others confirmed these multiple-site tumours. No benign or malignant tumours of the liver were initially reported by Fitzhugh et al. (1964), but a partial re-evaluation of the liver histopathology identified a total of 18 hepatocellular carcinomas in rats fed diets containing dieldrin or aldrin (Epstein, 1975). [The Working Group noted that limitations of this study included that only 68% of animals treated with dieldrin (or aldrin) were examined histologically, and that the data were combined for both sexes.]

Groups of [about] 50 male and 50 female weanling Osborne-Mendel rats [age not reported] were fed diets containing dieldrin (purity, 100%) at a concentration of 20, 30, or 50 ppm for less than 31 months (Deichmann et al., 1970). Control groups were comprised of 100 males and 100 females. Doses during the first 10 weeks were half the final concentrations. The mean survival of the control male and female rats was 19.7 and 19.5 months, respectively. The survival rate was not affected in treated males, but the mean survival of females at 30 ppm (17.4 months) and 50 ppm (16.6 months) was significantly lower than that in the control group. Mean body-weight gain was similar in treated and control groups. The tumour incidence (all sites) was not significantly increased in male or female rats relative to the respective control groups. No benign or malignant tumours of the liver were found in the treated animals. [The Working Group noted that limitations of this study included that not all tissues were examined histologically, and that partial re-evaluation of the histopathology indicated that the authors may have underestimated or underreported the incidence of malignant tumours by approximately 3-fold (Epstein, 1975).]

In a study by the NCI, groups of 50 male and 50 female Osborne-Mendel rats (age, 35 days) were fed diets containing technical-grade dieldrin (purity, > 96% [impurities not reported]) at a concentration of 29 or 65 ppm (time-weighted average) (NTP, 1978a). Rats at the lower dose were treated for 80 weeks, followed by observation periods of 30–31 weeks. Rats at the higher dose were treated for 59 weeks, followed by 51–52 weeks of observation. For matched

controls (10 males and 10 females per group), the study duration was 110 weeks. Time-weighted doses were used to assess the results, because the concentration of dieldrin was reduced after study start due to toxicity with initial exposures. The pooled-control groups consisted of the matched controls from the bioassay of dieldrin combined with matched controls from the contemporary bioassays of aldrin, chlordane, heptachlor, dichlorvos and dimethoate, giving groups of 58 male and 60 female rats. There was no significant effect on the survival of rats at the end of the study because there was decreased survival in male and female rats during the first 90 weeks of the study and in the control groups during the remaining 20 weeks. Mean body weights of the treated male and female rats were lower than those of the controls during the second year of the study.

There was no statistically significant increase in the incidence or positive trend in the incidence of any tumour in treated males or females when compared with the matched controls. There was a significant increase in the incidence of adrenal cortical adenoma or carcinoma (combined) in female rats at the lower dose compared with the pooled controls. [The Working Group noted that the increase in tumour incidence was only for the group at the lower dose, and only when compared with the pooled-control group, and concluded that it was not treatment-related.]

In a second study by the NCI (NTP, 1978b), groups of 24 male and 24 female Fischer 344 rats were fed diets containing dieldrin (technical grade, purified) at a concentration of 0, 2, 10, or 50 ppm for 104–105 weeks. There was no significant effect on the survival or mean body weights of rats of either sex relative to matched controls. There was no treatment-related increase in the incidence of tumours in males or females.

3.2.3 Hamster

Four groups of 32–41 male and four groups of 33–40 female Syrian golden hamsters were fed diets containing dieldrin (purity, 99%) at a concentration of 0, 20, 60, or 180 ppm for their life span (up to age 120 weeks) (Cabral et al., 1979). The survival rate at age 50 weeks was comparable to that of controls (males: 0 ppm (control), 32/40; 20 ppm, 24/34; 60 ppm, 27/32; 180 ppm, 35/41; females: 0 ppm (control), 25/40; 20 ppm, 14/33; 60 ppm, 26/34; 180 ppm, 25/38). Only 0–13 hamsters per group survived to age 90 weeks. Male and female hamsters fed diets containing dieldrin at 20 and 180 ppm showed a marked retardation of growth. Tumour sites were reported as [all], thyroid gland, adrenal gland, liver, and "other". The percentage of tumour-bearing animals did not differ significantly between control and treated groups.

3.2.4 Dog

Groups of five male and five female beagle hounds (age, 4–7 months) were fed gelatin capsules containing dieldrin (purity, > 99%) at a dose of 0, 0.005, or 0.05 mg/kg bw per day for 2 years (Walker et al., 1969). Survival and body weight were not affected by feeding with dieldrin for 2 years. In females, the liver weights and liver:body weight ratios in the group at 0.05 mg/kg bw per day dose were increased. No tumours or other specific lesions attributable to dieldrin were reported. [Limitations of this study included the small number of animals. The Working Group concluded that this study was inadequate for the evaluation.]

3.2.5 Monkey

Epstein (1975) summarized the findings from an unpublished study in five groups of five male rhesus monkeys (age, 4 years) given a diet containing dieldrin at a concentration of 0.1, 0.1, 0.5, 0.1, or 1.75 ppm for 5.5–6 years.

An untreated control group consisted of five males and one female. Monkeys in the group receiving the highest dose received dieldrin at 5.0 ppm for 4 months, then 2.5 ppm for approximately 2.5 months, and finally 1.75 ppm for the remainder of the study; for one monkey in the group, dieldrin concentrations were gradually increased to 5 ppm, and were maintained at this concentration for 5 years. No histological differences were observed in the liver or other tissues when the treated monkeys and the controls were compared. [The Working Group noted that the limitations of this study included the short duration, the small number of animals, and the lack of detailed histopathology data.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Introduction

Aldrin is readily converted to epoxide-containing dieldrin in the environment and in living organisms (see Fig. 4.1), thus exposures related to aldrin also involve exposure to dieldrin (Jorgenson, 2001). Overall, there was less information available on the toxicokinetics and disposition of aldrin than of dieldrin. Toxicokinetic data on dieldrin were briefly reviewed by the *IARC Monographs* Working Group more than 40 years before the present meeting (see *IARC Monographs* Volume 5; IARC, 1974). The present Working Group updated its review of the literature encompassing both aldrin and dieldrin, with separate discussions on each where possible.

4.1.2 Absorption

(a) Humans

(i) Aldrin

Several studies indicated that aldrin is absorbed by humans, mainly on the basis of its detection in blood, adipose tissue, and breast milk (Mick et al., 1971; Feldmann & Maibach, 1974; Nair et al., 1992; Stevens et al., 1993; Teixeira et al., 2015). However, it was unclear which route of exposure – oral, dermal, or inhalation – was the most important quantitatively for absorption. Moreover, aldrin was detected less frequently than dieldrin in humans, which is probably due to the ease of conversion of aldrin to dieldrin in the environment and body (IARC, 1974).

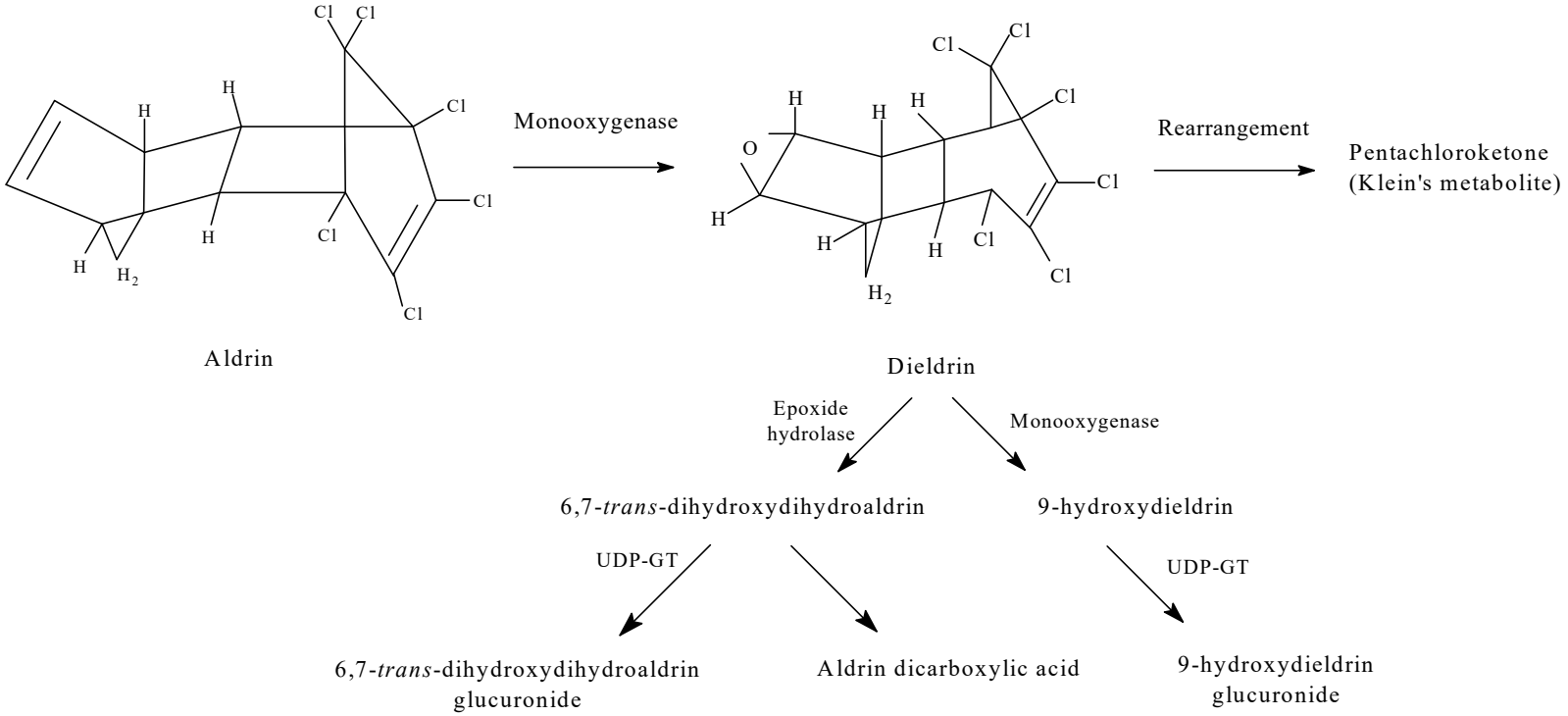
Evidence for the absorption of aldrin in humans comes from occupational as well as non-occupational exposures (see Table 1.2 and Table 1.3). Direct evidence for percutaneous absorption came from studies of deliberate exposure to aldrin (Feldmann & Maibach, 1974). For example, dermal application of [^{14}C]-labelled aldrin (single dose, 0.004 mg/cm^2) to the forearm of six subjects resulted in its rapid absorption, based on the excretion of radiolabel in the urine within 4 hours after administration (Feldmann & Maibach, 1974).

(ii) Dieldrin

On the basis of detection in blood, adipose tissue, and breast milk, dieldrin can be absorbed systemically by humans (Hunter & Robinson, 1967; Hayes & Curley, 1968; Mick et al., 1971; Feldmann & Maibach, 1974; Nair et al., 1992; Stevens et al., 1993; Teixeira et al., 2015). Detection of dieldrin after occupational as well as non-occupational exposures (see Table 1.2 and Table 1.3) indicated that dieldrin was absorbed, or that dieldrin was produced in vivo after exposure to and absorption of aldrin.

When humans were exposed for up to 2 years, concentrations in blood and adipose tissue were strongly correlated with the orally administered

Fig. 4.1 Major biotransformation pathways of aldrin to the epoxide-containing dieldrin metabolite and polar metabolites excreted via faeces and urine in experimental animals



The Chemical Abstracts Service numbering system was used in the designation of aldrin and its downstream metabolites.
UDP-GT, uridine 5′-diphospho-glucuronosyltransferase
Structures of aldrin and dieldrin are from Wikipedia Commons, the remaining metabolites are designated by their names.
Adapted with permission from Matthews et al. (1971). Dieldrin metabolism, excretion, and storage in male and female rats, *Journal of Agricultural and Food Chemistry*, Volume 19, issue 6, pages 1244-1248. Copyright (1971) American Chemical Society; adapted from *Biochemical Pharmacology*, Volume 36, issue 16, Wolff & Guengerich (1987). Rat liver cytochrome P-450 isozymes as catalysts of aldrin epoxidation in reconstituted monooxygenase systems and microsomes, Pages 2581-2588, Copyright (1987), with permission from Elsevier.

dose of dieldrin (Hunter et al., 1967, 1969; Hunter & Robinson, 1967). Direct evidence for percutaneous absorption came from the deliberate exposure of volunteers to dieldrin (Feldmann & Maibach, 1974). Dermal application of [^{14}C]-labelled dieldrin (single dose, 0.004 mg/cm^2) to the forearm of six subjects resulted in its rapid absorption, on the basis of excretion of radiolabel in the urine within 4 hours after administration (Feldmann & Maibach, 1974).

(b) Experimental systems

(i) Aldrin

Multiple studies in experimental animals demonstrated absorption of aldrin via oral and dermal routes; however, no studies were available on exposure to aldrin by inhalation. In dogs, rats, mice, and hens, oral treatment with aldrin resulted in rapid absorption into the systemic circulation (Brown et al., 1964; Korte & Kochen, 1966; Furusawa, 2002). In addition, dose-dependent increases in dieldrin levels in adipose tissue were seen in rats fed diets supplemented with aldrin for several months (Quaife et al., 1967).

In female rats, dermal administration of aldrin at increasing doses (0.1, 1, and 10 mg/kg per bw) resulted in detectable amounts of aldrin and dieldrin in the skin and in the blood stream (Graham et al., 1991). The amount of aldrin absorbed was proportional to the dose administered. This observation was supported by studies in vitro (Macpherson et al., 1991). Aldrin applied onto isolated rat skin was absorbed into the skin. Although percutaneous absorption of aldrin occurs, its major metabolite (dieldrin) is persistent in the skin (Macpherson et al., 1991).

Although the literature on absorption of aldrin in experimental systems was sparser than that for dieldrin, aldrin can penetrate the body after oral and dermal exposures. [Because of its highly lipophilic nature, aldrin is most likely to be absorbed into the body and tissues via processes involving first-order passive diffusion.]

(ii) Dieldrin

Several studies in experimental animals have shown absorption of dieldrin via oral and dermal routes. Mice, rats, rabbits, rhesus monkeys, and chimpanzees all effectively absorbed an oral dose of [^{14}C]-labelled dieldrin (0.5 mg/kg) (Müller et al., 1979). Absorption into the blood stream within 2 hours was noted in rats given a single oral dose of dieldrin (10 mg/kg) (Hayes, 1974). Absorption of dieldrin from the gastrointestinal tract was not complete, because unmetabolized dieldrin was detected in the faeces within 24–48 hours after administration, indicating the presence of unabsorbed compound.

Studies ex vivo examining the kinetics of dieldrin absorption in the mouse intestinal tract have also been conducted (Shah & Guthrie, 1970). The rate constant for penetration of the upper intestinal wall by dieldrin was 0.268×10^{-3} min^{-1}, suggesting that intestinal absorption of dieldrin is slow.

Thus dieldrin is absorbed at variable rates into the body after oral and dermal exposures. [Because of its highly lipophilic nature, dieldrin, like aldrin, is likely to be absorbed into the body via passive diffusion through membranes.]

4.1.3 Distribution

(a) Humans

(i) Aldrin

After its absorption into the body, aldrin is distributed to systemic tissues, with adipose tissues being an important storage depot (Mick et al., 1971; Nair et al., 1992; Botella et al., 2004; Teixeira et al., 2015). While aldrin bioaccumulates in adipose tissues and can be detected in breast milk, no information was available to the Working Group concerning levels in non-adipose tissues (except for blood) in exposed populations or individuals. On the other hand, numerous

studies have reported on the distribution of dieldrin in human tissues, as discussed below.

(ii) Dieldrin

After its absorption into the body, dieldrin is distributed via the circulation to systemic tissues, with adipose, mammary glands, and breast milk being notable storage depots (Mick et al., 1971; Nair et al., 1992; Botella et al., 2004; Teixeira et al., 2015). Dieldrin was detected at levels ranging from 0.13 to 0.36 mg/kg in adipose tissue obtained from autopsy patients (Ahmad et al., 1988; Adeshina & Todd, 1990). In subjects deliberately exposed to dieldrin for up to 24 months (0.1, 0.7, or 3 µg/kg per day), dieldrin concentrations in either blood or adipose tissue correlated strongly with the dose administered (Hunter & Robinson, 1967; Hunter et al., 1967, 1969). In addition, dieldrin concentrations in blood and adipose tissue were also strongly correlated with each other. The average ratio of steady-state dieldrin concentrations in adipose tissue versus blood was 156:1, indicating poor excretability and avid affinity for adipose tissues. When exposure was terminated, the concentration of dieldrin in the blood decreased exponentially, with an average half-life of 369 days (Hunter & Robinson, 1967), indicating slow elimination from the body. [Whereas tissue levels of dieldrin have been reported in the literature, the Working Group noted that quantitative levels of dieldrin-derived polar metabolites (Fig. 4.1) in human tissues were not available. This is mainly due to the metabolic stability of dieldrin (see Section 4.1.4).]

Transport of lipophilic dieldrin in the blood stream involves its avid interaction with albumin, α-globulins, and lipoprotein particles (Moss & Hathway, 1964; Tanaka et al., 1981; Maliwal & Guthrie, 1982). Studies in vitro indicated that dieldrin bound to albumin could be exchanged with human lipoproteins for subsequent transport (Maliwal & Guthrie, 1982). For instance, dieldrin was found to undergo efficient exchange reactions with all lipoprotein types in human plasma within 1 minute. [Similar interactions between aldrin and plasma proteins and lipoproteins in the blood are likely, although no specific data for aldrin were available to the Working Group.]

(b) Experimental systems

(i) Aldrin

Aldrin is widely distributed in the body (Korte & Kochen, 1966; Rumsey & Bond, 1974; Cooke et al., 2001). Intravenous injection of [^{14}C]-labelled aldrin in rats resulted in a broad tissue distribution of radiolabel after about 48 hours, with abdominal fat and subcutaneous fat exhibiting the highest amounts (nearly 15% and 7% of the administered dose, respectively), followed by liver (about 1.5%), and intestines (1%) (Korte & Kochen, 1966).

(ii) Dieldrin

Several studies on dieldrin demonstrated rapid and wide distribution in experimental animals (Bäckström et al., 1965; Robinson et al., 1969; Hayes, 1974; Iatropoulos et al., 1975). In rats given a single oral dose (10 mg/kg), dieldrin was absorbed into the blood stream within 2 hours, and then distributed systemically (Hayes, 1974). Maximum concentrations of dieldrin in muscle, liver, brain, and kidney were reached within 2–4 hours, whereas the maximum concentration in adipose tissue was attained by 24 hours. Over the 10 days after dosing, concentrations of dieldrin slowly declined in all tissues (by day 10: adipose tissue, 5–6% of administered dose; muscle, 0.1% of administered dose). The rank order of dieldrin concentrations (ppm) in tissues was: adipose tissue > > liver > kidney > brain > muscle > plasma, with adipose having by far the highest concentrations of dieldrin over the 10-day period. Thus, after its absorption, dieldrin was distributed rapidly to all systemic tissues, with slow redistribution from non-adipose tissues to adipose tissue for long-term storage (Hayes, 1974).

There were also data indicating that dieldrin can distribute through the body via the lymphatic system (Iatropoulos et al., 1975). The levels of dieldrin in mesenteric lymph nodes in Sprague-Dawley rats gradually increased over a 48-hour period after administration of a single oral dose (150 µg).

4.1.4 Metabolism and modulation of metabolic enzymes

The primary metabolic transformation of aldrin in the body is its rapid conversion to epoxide-containing dieldrin, followed by subsequent slow metabolism of dieldrin to polar metabolites that are excreted (Fig. 4.1).

(a) Humans

(i) Aldrin

No studies were found that examined the metabolism of aldrin in exposed humans; however, epoxidation of aldrin to dieldrin was demonstrated in human liver microsomes and in a human hepatoma cell line (Limbosch, 1983; McManus et al., 1984). The rate of aldrin epoxidation correlated with cytochrome P450 content in liver microsomes and varied by 2.4-fold across samples from 28 individuals (McManus et al., 1984). Comparison of rates of aldrin epoxidation activity with aryl hydrocarbon hydroxylase activity provided context for the rate of conversion of aldrin to dieldrin in human liver. From Wolff & Strecker (1985), it was estimated that aldrin epoxidase activity in human liver microsomes ranged from ~50 to 200 pmol/min per mg protein, whereas the benzo[*a*]pyrene aryl hydrocarbon hydroxylase activity ranged from 0.5 to 1.75 pmol/min per mg protein (an approximately 100-fold difference in rates). Although liver is the most important site of aldrin metabolism (McManus et al., 1984), other tissues probably have minor roles depending on their cytochrome P450 content. [The Working Group noted that the human cytochrome P450 isoforms responsible for aldrin epoxidation have yet to be characterized.]

(ii) Dieldrin

No studies directly examined the metabolism of dieldrin in exposed humans. 9-Hydroxydieldrin, an oxidation product of the metabolism of dieldrin in vivo, was detected in the faeces of occupationally exposed workers (Richardson & Robinson, 1971), indicating that this biotransformation reaction can occur in humans. Hunter et al. (1969) reported on the disposition of dieldrin in subjects given dieldrin for 18–24 months, but did not provide information on metabolites. Most of the information regarding dieldrin metabolism was obtained from experimental animals, as discussed below.

(b) Experimental systems

(i) Aldrin

The primary metabolic transformation of aldrin in rodents and other animal species is its conversion to epoxide-containing dieldrin, particularly in the liver and to a lesser degree in extrahepatic tissues. Nicotinamide adenine dinucleotide phosphate reduced (NADPH)-dependent epoxidation of aldrin was evident in rat liver, lung, and skin microsomes (Wong & Terriere, 1965; Wolff et al., 1979; Lambotte-Vandepaer et al., 1981; Graham et al., 1991), and mouse liver and skin microsomes (Williams & Woodhouse, 1996). Aldrin metabolism in rat liver microsomes was substantially faster than in lung and skin. In addition, the rate of aldrin epoxidation was sex-dependent in adult Sprague-Dawley rats; catalysis of this reaction was more efficient in liver microsomes obtained from males than in those obtained from females (Wolff & Guengerich, 1987). Aldrin epoxidation was sensitive to monooxygenase inhibitors in intact living rats (Clark & Krieger, 1976), and in vitro in rat liver microsomes (Wolff et al., 1979).

Aldrin was also metabolized to dieldrin in the skin. For instance, after dermal administration of

aldrin to rats (0.1, 1.0, or 10mg/kg bw), dieldrin was detectable in the skin at the application site after 1 hour (Graham et al., 1991). Studies in vitro in isolated rat skin preparations (Macpherson et al., 1991) or in rabbit lung (Mehendale & El-Bassiouni, 1975) showed that metabolism of aldrin to dieldrin could occur in these tissues.

In terms of catalysts of aldrin epoxidation in experimental models, cytochrome P450 monooxygenases were identified as the major enzymes responsible for aldrin epoxidation in rat liver (Wolff & Guengerich, 1987). [The Working Group noted that the rodent cytochrome P450 isoforms responsible for aldrin epoxidation have yet to be characterized.]

(ii) Dieldrin

Biotransformation of dieldrin was studied in several animal models and experimental systems. In general, the rate of metabolism of dieldrin is considered to be very slow, but excretion via formation of water-soluble metabolites has been reported (Matthews & Matsumura, 1969).

Despite the relative stability of dieldrin with regard to metabolic transformation, two sites on dieldrin, the epoxide moiety and the non-chlorinated methylene carbon, are susceptible to metabolic attack (Lykken & Casida, 1969). The epoxide can be opened by epoxide hydrolases to yield 6,7-*trans*-dihydroxydihydroaldrin, although this reaction is slow because of steric hindrance (Moody et al., 1991). In addition, the non-chlorinated methylene carbon is susceptible to hydroxylation producing 9-hydroxydieldrin, with the hydroxyl group oriented *syn* to the epoxide moiety. Most species can perform these metabolic transformations, although at variable rates between species or between sexes within a species (Matthews et al., 1971; Müller et al., 1979). Furthermore, the metabolites 6,7-*trans*-dihydroxydihydroaldrin and 9-hydroxydieldrin are often conjugated with glucuronic acid to give terminal products that are excreted (Fig. 4.1) (Matthews & Matsumura, 1969; Matthews et al., 1971).

Compared with epoxide opening, the formation of 9-hydroxydieldrin is the more quantitatively important reaction in rats (Matthews et al., 1971), although all species appear to perform this hydroxylation, including humans (Lykken & Casida, 1969; Richardson & Robinson, 1971). The metabolite 6,7-*trans*-dihydroxydihydroaldrin was also formed in several species, including rats, rabbits, sheep, rhesus monkeys, and chimpanzees (Korte & Arent, 1965; Feil et al., 1970; Müller et al., 1979). In addition to these main reactions, dieldrin can also be oxidatively dechlorinated to give the pentachloro-bridged ketone (pentachloroketone metabolite) (Fig. 4.1; Lykken & Casida, 1969). This product, also termed Klein's metabolite, is most important in male rats; it is detected in relatively high levels in the kidney and urine of males, while females make and excrete little (Matthews et al., 1971).

Studies of metabolism in vitro indicated that rat liver microsomes supplemented with uridine diphosphoglucuronic acid and NADPH could metabolize dieldrin to glucuronides of 9-hydroxydieldrin and 6,7-*trans*-dihydroxydihydroaldrin (Matthews & Matsumura, 1969). In addition, 6,7-*trans*-dihydroxydihydroaldrin can be further oxidized to give aldrin dicarboxylic acid (Baldwin et al., 1972; Hutson, 1976).

Collectively, metabolism of dieldrin to yield polar products does occur and can be modified by competing pathways (Fig. 4.1). The rate of overall biotransformation of dieldrin, however, is deemed to be very slow, accounting for its poor excretion and persistence in the body. Furthermore, on the basis of its half-lives in humans (Hunter & Robinson, 1967) and rodents (Robinson et al., 1969), dieldrin appears to persist longer in humans. [The Working Group noted that this is either because of slower degradation by human enzymes than by rodent enzymes, or slower release from human fat than rodent fat.]

(c) Modulation of metabolic enzymes

Multiple studies indicated that dieldrin can modulate metabolic enzymes. For example, exposure to dieldrin could induce the synthesis of xenobiotic metabolizing enzymes in the liver of many different species, including rats, mice, cattle, fish, and birds (Davison & Sell, 1972; Campbell et al., 1983; Abdelsalam & Ford, 1986; Haake et al., 1987; Barber et al., 2007; Dail et al., 2007). Mixed-function oxidases (i.e. cytochrome P450s) were the most affected by dieldrin (Campbell et al., 1983), and induction of hepatic enzymes by dieldrin could modulate the metabolism of carcinogens and hormones.

Dieldrin is a ligand for the xenoreceptors constitutive androstane receptor (CAR) and pregnane X receptor (PXR), resulting in the increased transcription of cytochrome P450 2B and 3A genes in mice (Zhang et al., 2004). PXR-dependent induction of human CYP3A4 gene expression by dieldrin in cultured cell lines was also reported (Coumoul et al., 2002). Furthermore, a double-null mouse lacking CAR and PXR was completely insensitive to broad-range xenobiotics, such as dieldrin, that activate both types of receptor (Zhang et al., 2004).

[The Working Group considered that, taken together, these data supported the idea that dieldrin (and perhaps aldrin indirectly) can activate xenobiotic receptors that regulate the expression of xenobiotic metabolic enzymes.]

4.1.5 Excretion

(a) Humans

Aldrin and dieldrin

9-Hydroxydieldrin was detectable in the faeces of occupationally exposed workers, suggesting that this is an important route of elimination of aldrin- or dieldrin-derived metabolites in humans (Richardson & Robinson, 1971). Furthermore, aldrin and dieldrin were excreted in the breast milk of nursing mothers (Sant'Ana et al., 1989; Nair et al., 1992), suggesting that this is an important route of excretion in lactating women.

(b) Experimental systems

(i) Aldrin

One study in rats indicated that metabolites of aldrin were predominantly excreted via the faecal route, whereas urinary excretion was a minor route (Korte & Kochen, 1966). For example, in rats given an intravenous injection of [^{14}C]-labelled aldrin, 15% and 5% of the administered dose was excreted in the faeces and urine, respectively, within about 48 hours (Korte & Kochen, 1966). Polar metabolites accounted for the bulk of the radiolabel in the excreta, with only trace amounts of aldrin detected.

(ii) Dieldrin

Because aldrin is converted to dieldrin in vivo, studies on the excretion of dieldrin are also informative for aldrin. Faecal excretion was the major route of elimination of dieldrin and its metabolites, whereas urinary excretion was a minor route (Matthews et al., 1971; Hutson, 1976; Müller et al., 1979). Single oral doses of [^{14}C]-labelled dieldrin (0.5 mg/kg) administered to rats, mice, monkeys, and chimpanzees resulted in the faecal excretion of 10% (average of male and female Sprague-Dawley rats), 36% (average of male and female Swiss white mice), 16% (male rhesus monkeys), and 5% (female chimpanzees) of the administered [^{14}C]-labelled dose within 10 days, whereas urinary excretion accounted for only 0.6–4.4% of the administered dose (Müller et al., 1979). Thus, the bulk of the total radiolabel recovered in the excreta from these different species was present in the faeces (79–95% of excreted radiolabel).

In a separate study, 62% and 7% of a single oral dose of [^{14}C]-labelled dieldrin (3 mg/kg bw) was excreted in the faeces and urine, respectively, within 8 days after administration to male CFE rats (Hutson, 1976). Unchanged dieldrin and

9-hydroxydieldrin and its glucuronide were the major ^{14}C-labelled compounds detected in the faeces, with lesser amounts of 6,7-*trans*-dihydroxydihydroaldrin and aldrin dicarboxylic acid detected.

After an oral dose, the presence of [^{14}C]dieldrin-derived radiolabel in the faeces could indicate incomplete absorption. However, intraperitoneal and intravenous injections of [^{14}C]-labelled dieldrin in male rats also resulted in the excretion of most of the radiolabel by the faecal route (Cole et al., 1970) (Chipman & Walker, 1979). This suggested that biliary excretion of dieldrin and its metabolites is important for its elimination. Indeed, perfusion of isolated rat liver with [^{14}C]-labelled dieldrin resulted in significant biliary excretion of [^{14}C]-labelled dieldrin equivalents (Cole et al., 1970). Using this same approach, endrin, a stereoisomer of dieldrin, was excreted at a significantly higher rate than dieldrin was (Cole et al., 1970). This was attributed to faster metabolism of endrin in the liver when compared with dieldrin, and the subsequent biliary excretion of endrin metabolite 9-hydroxyendrin (Hutson et al., 1975). Elimination via the bile was also measured directly in bile-cannulated rats after an intraperitoneal dose of [^{14}C]-labelled dieldrin (Chipman & Walker, 1979). Interestingly, when dieldrin was compared with another chlorinated cyclodiene analogue (termed HCE), which is metabolically labile, its rate of biliary excretion was substantially slower than that of HCE (3.17 and 204 nmol/min per kg bw for dieldrin and HCE, respectively) (Chipman et al., 1979). [This result further supported the notion that the excretion rates for chlorinated cyclodienes are dependent on their metabolism rates.]

In general, 9-hydroxydieldrin and 6,7-*trans*-dihydroxydihydroaldrin and their glucuronides were the major ^{14}C-labelled compounds detected in rat, mouse, and monkey faeces (via bile excretion), with lesser amounts of unchanged dieldrin detected (Matthews et al., 1971; Hutson, 1976; Müller et al., 1979). On the basis of the profile of metabolites in faecal extracts, male rats excreted greater proportions of 9-hydroxydieldrin and 6,7-*trans*-dihydroxydihydroaldrin than females, whereas female rats excreted more unchanged dieldrin than male rats (Matthews et al., 1971). This result was consistent with a faster rate of dieldrin metabolism in male rats than in female rats. Furthermore, 9-hydroxydieldrin was also detectable in mouse and monkey urine, but not in rat urine (Hutson, 1976; Müller et al., 1979).

A comparison of excretion rates in mice and rats indicated that mice excreted 37–39% of an oral dose of [^{14}C]-labelled dieldrin within 10 days, whereas rats excreted 10–12% of the dose, signifying a species difference in excretion (Müller et al., 1979). In both rodent species, 95% of the radiolabel recovered in the excreta was present in the faeces. Further, substantially more 6,7-*trans*-dihydroxydihydroaldrin was excreted by mice than by rats.

Overall, these studies indicated that faecal excretion of aldrin and dieldrin metabolites via bile is the major route of elimination by rodents, whereas urinary excretion is a minor route. Several polar metabolites and trace amounts of unchanged dieldrin could be detected in the faeces and urine, while aldrin was generally not detectable in excreta (Fig. 4.1). For most species, the overall excretion rate of aldrin and dieldrin was generally slow. Whereas aldrin is rapidly converted to dieldrin in vivo, the slow excretion rate of dieldrin was attributable both to its slow release from fat as well as its inefficient metabolism to water-soluble products.

4.2 Mechanisms of carcinogenesis

This section summarizes in the following order the available evidence for the key characteristics for carcinogens, concerning whether aldrin or dieldrin is genotoxic; modulates receptor-mediated effects; induces inflammation and is immunosuppressive; induces oxidative stress; and alters cell proliferation, cell death, and

nutrient supply. For the other key characteristics of human carcinogens, insufficient data were available for evaluation.

4.2.1 Genetic and related effects

(a) Humans

(i) Exposed humans

See Table 4.1.

Aldrin

DNA damage in lymphocytes was not correlated with levels of aldrin or of other organochlorine pesticides in peripheral blood from mothers, or in umbilical cord blood in a study of mother–infant pairs (Alvarado-Hernandez et al., 2013). Aldrin was detected in maternal blood (median concentration, 412 ng/g lipid) and in umbilical cord blood (median concentration, 906 ng/g lipid); however, no correlation was found between pesticide levels and the frequency of micronucleus formation, chromatin buds, nucleoplasmic bridges, or DNA strand breaks as measured by the comet assay. Edwards & Priestly (1994) did not find increased frequencies of sister-chromatid exchange in the lymphocytes of pest-control workers and pesticide-treatment company employees exposed to aldrin. Aldrin exposures were confirmed by plasma dieldrin detection; median plasma levels ranged from 4.8 ng/mL to 16.0 ng/mL in the lowest and highest exposure groups, respectively. The plasma levels of dieldrin in exposed workers correlated with the duration of employment.

Dieldrin

Chromosomal aberrations were analysed in the lymphocytes of current and former dieldrin-manufacturing plant workers (Dean et al., 1975). The incidence of chromatid and chromosome-like aberrations was not increased in plant workers when compared with matched controls.

(ii) Human cells in vitro

See Table 4.2.

Exposure to aldrin or dieldrin induced unscheduled DNA synthesis, with and without the addition of rat liver S9 microsomal fraction, in SV-40 transformed human fibroblasts (Ahmed et al., 1977a). Aldrin induced chromosome aberrations (gaps, breaks, deletions, and fragments) in human peripheral blood lymphocytes exposed for 22 hours in vitro (Georgian, 1975). [The Working Group noted the lack of methodological detail reported in Georgian (1975).]

Dieldrin induced chromosomal aberrations in cultured human embryonic lung cells at cytotoxic exposures (Majumdar et al., 1976).

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3.

Aldrin

Aldrin induced chromosomal aberrations in bone marrow cells in mice and rats given a single intraperitoneal dose (Georgian, 1975; see comment above). Aldrin exposure via drinking-water for 2 days did not increase the frequency of micronucleus formation in the bone marrow of mice (Usha Rani et al., 1980).

Dieldrin

Bachowski et al. (1998) investigated oxidative damage to DNA and unscheduled DNA synthesis in mice and rats fed diets containing dieldrin for up to 90 days. In the urine of male mice, 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels increased up to day 28. This increase correlated with increased hepatic DNA synthesis, although 8-OHdG levels were not changed in mouse liver (Klaunig et al., 1995). No increases in 8-OHdG formation or unscheduled DNA synthesis were detected in the liver or urine of rats (Klaunig et al., 1995).

Ha-*ras* proto-oncogene codon 61 mutations were not detected in tumours of the liver of dieldrin-exposed CF1 mice (Bauer-Hofmann et al., 1990, 1992).

Table 4.1 Genetic and related effects of aldrin and dieldrin in exposed humans

End-point	Tissue, cell line	Description of exposure and controls	Response[a]/ significance	Comments	Reference
Aldrin					
DNA strand breaks, micronucleus formation	Blood, lymphocytes	50 mother–infant pairs in rural agricultural region of San Luis Potosi, Mexico	–	Multiple pesticides were detected; no exposure information	Alvarado-Hernandez et al. (2013)
	Umbilical cord blood, lymphocytes		–		
Sister-chromatid exchange	Blood, lymphocytes	29 pest-control workers in south Australia Exposure time: range, 3 mo to 20 yr; split into 4 groups based on job duties; 3 matched controls Plasma dieldrin levels were 4.8, 5.8, 7.0, 5.3, and 16.0 ng/mL in groups 1, 1a, 2, 3, and 4, respectively	–		Edwards & Priestly (1994)
		33 pesticide-treatment company employees; Australia	–		
Dieldrin					
Chromosomal aberrations	Blood, lymphocytes	9 former and 12 current dieldrin-plant workers; 17 matched controls	–	No exposure information	Dean et al. (1975)

[a] –, negative; mo, month(s); yr, year

Table 4.2 Genetic and related effects of aldrin and dieldrin in human cells in vitro

End-point	Tissue, cell line	Results[a]		Dose (LED or HID)	Comments	Reference
		With metabolic activation	Without metabolic activation			
Aldrin						
Unscheduled DNA synthesis	Fibroblasts	+	+	NR		Ahmed et al. (1977a)
Chromosomal aberrations	Lymphocytes (primary)	(+)	NT	9.56 µg/mL	Lack of methodological detail	Georgian (1975)
Dieldrin						
Unscheduled DNA synthesis	Fibroblast	+	+	1 µM	No positive controls	Ahmed et al. (1977a)
Chromosomal aberrations	Embryonic lung, WI-38	+	NT	1 µg/mL	No positive controls; cytotoxicity observed	Majumdar et al. (1976)

[a] +, positive; (+), positive in a study of limited quality; the level of significance was set at $P < 0.05$ in all cases

HID, highest ineffective dose; LED, lowest effective dose; NR, not reported; NT, not tested

Table 4.3 Genetic and related effects of aldrin and dieldrin in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Aldrin							
Chromosomal aberrations	Mouse, AKR (M) Rat, Wistar (M)	Bone marrow	(+)	9.56 µg/g bw	i.p.; one injection of 9.56, 19.125, 38.25, or 76.50 µg/g bw, 24 h before the harvesting of the bone marrow; controls received an equivalent volume of vehicle	Lack of methodological detail	Georgian (1975)
Micronucleus formation	Mouse, Swiss albino (M)	Bone marrow (PCE)	–	13 mg/kg	Drinking-water; 2 d (1 × 24 h)		Usha Rani et al. (1980)
Dieldrin							
8-OHdG, unscheduled DNA synthesis	Rat, F344 (M)	Liver, urine	–	10 mg/kg diet	0.1, 1.0, or 10 mg/kg diet; 7, 14, 28, and 90 d		Bachowski et al. (1998)
8-OHdG	Mouse, $B6C3F_1$ (M)	Liver	–	10 mg/kg diet	0.1, 1.0, or 10 mg/kg diet; 7, 14, 28, and 90 d		Bachowski et al. (1998)
8-OHdG	Mouse, $B6C3F_1$ (M)	Urine	+	10 mg/kg diet	0.1, 1.0, or 10 mg/kg diet; 7, 14, 28, and 90 d	Increased at d 14 and 28	Bachowski et al. (1998)
Unscheduled DNA synthesis	Mouse, $B6C3F_1$ (M)	Liver	+	1.0 mg/kg diet	0.1, 1.0, or 10 mg/kg diet; 7, 14, 28, and 90 d		Bachowski et al. (1998)
c-Ha-*ras* proto-oncogene codon 61 mutations	Mouse, C3H (M)	Liver tumours	–	10 ppm [10 000 µg/L]	10 ppm in the diet; 52 wk		Bauer-Hofmann et al. (1992)
Ha-*ras* mutations at codons 12 or 61	Mouse, CF1 (M)	Liver tumours	–	10 ppm [10 000 µg/L]	10 ppm in the diet; 96 wk		Bauer-Hofmann et al. (1990)
Dominant lethal test	Mouse, CF1 (M)	Germinal tissue	–	25 mg/kg bw	Oral; HEOD at 12.5, 25, or 50 mg/kg; 8 wk (1×/wk)	Purity, > 99% (HEOD); vehicle, DMSO	Dean et al. (1975)
Chromosomal aberrations	Hamster, Chinese (M, F)	Bone marrow	–	60 mg/kg bw	Oral; HEOD at 30 or 60 mg/kg bw; 8 or 24 h	Purity, > 99% (HEOD); vehicle, DMSO	Dean et al. (1975)
Chromosomal aberrations	Mouse, STS (M)	Bone marrow	+	1 mg/kg bw	i.p.; single dose, 24 h	No positive controls; 4 animals/dose group; mitotic index decreased 40%	Majumdar et al. (1976)

Table 4.3 (continued)

End-point	Species, strain (sex)	Tissue	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Micronucleus formation	Mouse, CBA (M)	Bone marrow (PCE)	+	60 mg/kg bw	i.p.; 24 and 48 h	No concurrent cytotoxicity; positive and dose-dependent at lethal and sublethal doses; most micronuclei were kinetochore-negative	Cicchetti et al. (1999)

[a] +, positive; (+), positive in a study of limited quality; –, negative; the level of significance was set at $P < 0.05$ in all cases

bw, body weight; d, day; DMSO, dimethyl sulfoxide; F, female; h, hour; HEOD, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4α,5,6,7,8,8α-octahydro-*exo*-1,4-*endo*-5,8-dimethanonapthalene (the major constituent of dieldrin); HID, highest ineffective dose; i.p., intraperitoneal; LED, lowest effective dose; M, male; mo, month; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PCE, polychromatic erythrocytes; ppm, parts per million; wk, week

In the dominant-lethal assay in mice exposed orally to dieldrin for 8 weeks, no significant differences in fetal implantation rates or early fetal deaths were detected in the offspring of exposed male mice (Dean et al. (1975). In the same study, chromosomal aberrations were not induced in the bone marrow of Chinese hamsters 8 or 24 hours after a single oral dose of dieldrin . In two studies in male mice exposed intraperitoneally to dieldrin, chromosomal aberrations (Majumdar et al., 1976) and micronucleus formation (Cicchetti et al., 1999) were significantly induced in bone marrow.

(ii) Non-human mammalian cells in vitro

See Table 4.4.

No studies on aldrin were available to the Working Group.

Dieldrin induced 8-OHdG lesions in actively proliferating and in differentiated rat PC12 cells (Stedeford et al., 2001), and in mouse but not rat hepatocytes (Klaunig et al., 1995).

Dieldrin induced forward mutation at the thymidine kinase locus in the mouse lymphoma assay in two out of three replicate experiments (McGregor et al., 1991). The increases in mutant fraction correlated with dose, but the lowest effective concentration reduced the relative total cell growth to 40%.

Ahmed et al. (1977b) reported a significant induction in the frequency of ouabain-resistant mutants in Chinese hamster V79 cells exposed to nontoxic concentrations of dieldrin.

Dieldrin also increased the frequency of micronucleus formation in mouse primary lung fibroblasts (Cicchetti & Argentin, 2003).

In Chinese hamster ovary cells, an increased incidence of sister-chromatid exchange was observed after exposure to dieldrin, both with and without metabolic activation (S9 microsomal fraction), but there was no increase in chromosomal aberrations at up to toxic concentrations (Galloway et al., 1987). [At concentrations that induced sister-chromatid exchange, a precipitate formed.]

(iii) Non-mammalian systems in vivo

See Table 4.5.

Aldrin

Aldrin induced chromosomal aberrations in the plant species *Vicia faba* (Pandey, 2008), but did not increase micronucleus formation in *Tradescantia* clone 4430 (Sandhu et al., 1989).

Dieldrin

Dieldrin was studied in fish, insects, and plants. In fish, significant increases in the frequency of oxidative damage to DNA were seen 7 days after a single intraperitoneal injection of dieldrin in the gilthead seabream *Sparus aurata* (Rodríguez-Ariza et al., 1999).

Dieldrin gave negative results in the somatic mutation and recombination test (SMART) in *Drosophila melanogaster*, and was toxic to larvae at 0.005 mM (Osaba et al., 1999).

In plants, chromosomal damage was significantly increased by dieldrin exposures. Chromosomal aberrations were induced in *Vicia faba* bean (Pandey, 2008), and increased micronucleus formation was reported in *Tradescantia* (Sandhu et al., 1989; Gill & Sandhu, 1992).

(iv) Non-mammalian systems in vitro

See Table 4.6.

Aldrin

Aldrin gave an equivocal response in strain TA100 in the presence of hamster liver S9 (NTP, 2016a), but otherwise gave negative results when tested with and without S9 fractions in *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and in *Escherichia coli* (strain WP2 *hcr*) (Moriya et al., 1983; NTP, 2016a). Aldrin did not induce DNA adducts in calf thymus DNA (Decloître et al., 1975), or DNA strand breaks in ColE1 plasmid DNA (Griffin & Hill, 1978).

Table 4.4 Genetic and related effects of dieldrin in non-human mammals in vitro

End-point	Species, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
8-OHdG	Rat adrenal gland pheochromocytoma, PC12	+	NT	100 µM [38.1 µg/mL]		Stedeford et al. (2001)
8-OHdG	Rat, hepatocytes	–	NT	50 µM		Klaunig et al. (1995)
8-OHdG	Mouse, hepatocytes	+	NT	10 µM		Klaunig et al. (1995)
Tk mutation	Mouse L5178Y lymphoma cells	+	NT	20 µg/mL	Vehicle, DMSO Positive in 2/3 replicate experiments with dose–response relationship; relative total growth, approx. 40% at 20 µg/mL	McGregor et al. (1991)
Mutation	Chinese hamster fibroblasts, V79	+	NT	10 µM [3.8 µg/mL]	No positive controls; 77.8% cell survival	Ahmed et al. (1977b)
Micronucleus formation	Mouse lung fibroblasts (primary)	+	NT	25 µM [9.5 µg/mL]		Cicchetti & Argentin (2003)
Chromosomal aberrations	Chinese hamster ovary, CHO-W-B1	–	–	60 µg/mL (–S9); 800 µg/mL (+S9)		Galloway et al. (1987)
Sister-chromatid exchange	Chinese hamster ovary, CHO-W-B1	+	+	< 40 µg/mL (–S9); < 300 µg/mL (+S9)	Doses induced cell cycle delay and formed precipitate	Galloway et al. (1987)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

DMSO, dimethyl sulfoxide; HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; S9, 9000 × *g* supernatant

Table 4.5 Genetic and related effects of aldrin and dieldrin in non-mammalian experimental systems in vivo

Test system (species, strain)	End-point	Results	Dose (LED or HID)	Comments	Reference
Aldrin					
Vicia faba (bean)	Chromosomal aberrations	+	50 ppm [50 000 µg/L]	Toxic at ≥ 500 ppm	Pandey (2008)
Tradescantia clone 4430 (spiderworts)	Micronucleus formation	–	36.59 µg/mL	Vehicle, DMSO; precipitated out of solution when water was added. Reported as ppm	Sandhu et al. (1989)
Dieldrin					
Sparus aurata (gilthead seabream)	8-OHdG	+	0.6 mg/kg	Levels significant ($P < 0.05$) in liver and not blood or gills	Rodríguez-Ariza et al. (1999)
Drosophila melanogaster	Somatic mutation and recombination test (SMART)	–	0.005 mM	Highly toxic to larvae	Osaba et al. (1999)
Vicia faba (bean)	Chromosomal aberrations	+	50 ppm [50 µg/mL]	Toxic at ≥ 500 ppm	Pandey (2008)
Tradescantia clone 4430 (spiderwort)	Micronucleus formation	+	3.81 µg/mL	Vehicle, DMSO	Sandhu et al. (1989)
Tradescantia (spiderwort)	Micronucleus formation	+	4 µg/mL	Also positive at 4 mg/kg in soil Vehicle, DMSO	Gill & Sandhu (1992)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

DMSO, dimethyl sulfoxide; h, hour; HID, highest ineffective dose; LED, lowest effective dose; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; ppm, parts per million

Table 4.6 Genetic and related effects of aldrin and dieldrin in non-mammalian experimental systems in vitro

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Aldrin						
Salmonella typhimurium TA98, TA1535, TA1537, TA1538	Reverse mutation	–	–	10 000 µg/plate	Vehicle, DMSO Incubations with rat and hamster liver S9 fractions at 10% and 30% were tested; highest two doses had observable precipitate	NTP (2016a)
Salmonella typhimurium TA100	Reverse mutation	–	+/–	10 000 µg/plate	Vehicle, DMSO Two replicate experiments with 30% hamster liver S9 fractions induced equivocal and negative results, respectively, with precipitate observed	NTP (2016a)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	5000 µg/plate	Vehicle, DMSO	Moriya et al. (1983)
Escherichia coli WP2 hcr	Reverse mutation	–	–	5000 µg/plate	Vehicle, DMSO	Moriya et al. (1983)
Calf thymus DNA	DNA adducts	NT	–	26.3 µM		Decloître et al. (1975)
ColE1 plasmid DNA	DNA strand breaks	–	NT	1 mg/mL		Griffin & Hill (1978)
Dieldrin						
Aspergillus nidulans 35 (haploid)	Forward mutation	–	NT	26 mM [9.9 mg/mL] [converted from 26 mM]	Purity, 97% No decrease in survival	Crebelli et al. (1986)
Aspergillus nidulans P1 (diploid)	Aneuploidy	–	NT	26 mM [9.9 mg/mL] [converted from 26 mM]	Purity, 97% 61% survival	Crebelli et al. (1986)
Saccharomyces cerevisiae D4	Gene conversion	–	NT	50 mg/kg bw	Purity, > 99% (HEOD); vehicle, DMSO Host-mediated assay of male CF1 mice dosed orally with dieldrin and injected i.p. with yeast	Dean et al. (1975)
Salmonella typhimurium TA98, TA100, TA1535	DNA strand breaks	+	+	1 µg/mL	No positive control; only group not positive was TA1535 –S9	Majumdar et al. (1977)
Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Reverse mutation	–	–	1000 µg/plate	Vehicle, DMSO Highest dose +S9 was toxic	Marshall et al. (1976)

Table 4.6 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA98, TA100	Reverse mutation	–	–	1 mg	Vehicle, DMSO	Wade et al. (1979)
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	–	–	3333 µg/plate	Vehicle, DMSO Incubations with 10% rat and hamster liver S9 fractions were tested; highest three doses had observable precipitate	NTP (2016b)
Salmonella typhimurium TA98, TA100	Reverse mutation	–	NT	3000 µg/plate	Concentrations of ≥ 300 µg/plate had visible precipitate, but were not toxic Results reported from other experiments, all negative: TA1535 –S9, TA1537 –S9, TA98 +S9 ± TCPO, TA100 +S9 (Oesch & Daly, 1972)	Glatt et al. (1983)
Salmonella typhimurium TA98, TA100	Reverse mutation	–	NT	1000 µg/plate	Positive with UVC light exposure	De Flora et al. (1989)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	5000 µg/plate	Vehicle, DMSO	Moriya et al. (1983)
Calf thymus DNA	DNA adducts	NT	–	31.6 µM		Decloître et al. (1975)
ColE1 plasmid DNA	DNA strand breaks	–	NT	0.1 mg/mL		Griffin & Hill (1978)

[a] –, negative; +, positive; +/–, equivocal (variable response in several experiments within an adequate study); the level of significance was set at $P < 0.05$ in all cases

bw, body weight; DMSO, dimethyl sulfoxide; h, hour; HEOD, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4α,5,6,7,8,8α-octahydro-*exo*-1,4-*endo*-5,8-dimethanonapthalene (the major constituent of dieldrin); HIC, highest ineffective concentration; i.p., intraperitoneal; LEC, lowest effective concentration; NT, not tested; S9, 9000 × *g* supernatant; TCPO, hypoxide hydrolase inhibitor; UVC, ultraviolet C

Dieldrin

Dieldrin did not induce forward mutation or aneuploidy in *Aspergillus nidulans* strains 35 and P1 (Crebelli et al., 1986). Dieldrin gave negative results in the host-mediated assay, in which mice orally exposed to dieldrin were injected intraperitoneally with *Saccharomyces cerevisiae* strain D4 (Dean et al., 1975).

Majumdar et al. (1977) reported DNA strand breaks in *S. typhimurium* strains TA98 and TA100 (with or without S9), and in TA1535 (with S9 only).

Dieldrin did not induce reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1536, TA1537, and TA1538, with or without S9 microsomal fraction (Marshall et al., 1976; Wade et al., 1979; Glatt et al., 1983; Moriya et al., 1983; De Flora et al., 1989; NTP, 2016b).

Dieldrin did not induce DNA adducts in calf thymus DNA (Decloître et al., 1975), or DNA strand breaks in ColE1 plasmid DNA (Griffin & Hill, 1978).

4.2.2 Receptor-mediated effects

(a) Humans

(i) Exposed humans

No studies on aldrin or dieldrin in exposed humans were available to the Working Group.

(ii) Human cells in vitro

Aldrin

Aldrin increased aromatase activity and CYP19 mRNA aromatase expression in the human choriocarcinoma JEG3 cell line (Laville et al., 2006). While aldrin bound human estrogen receptor α (ERα), it had greater affinity for the human progesterone receptor (Scippo et al., 2004). However, aldrin did not have estrogenic activity in transcriptional activation assays using human cell lines that either expressed ERα (MCF-7 cells) or that were stably transfected with human ERα receptors (HeLa cells) (Tully et al., 2000; Mumtaz et al., 2002; Kim et al., 2011). Lemaire et al. (2006) demonstrated antagonism of the ER by aldrin (0.1–10 μM), suggesting a potential anti-estrogenic effect, in HELN cells expressing human ER subtypes ERα and ERβ.

Aldrin has been shown to activate human retinoic acid receptors (Lemaire et al., 2005), although other studies were unable to demonstrate similar results (Laville et al., 2006).

Dieldrin

The receptor-mediated effects of dieldrin are summarized in Table 4.7, Table 4.8, and Table 4.9.

Dieldrin bound to the human ER and induced estrogen-dependent cell proliferation in human breast cancer cell lines at concentrations of 1 μM or above (Soto et al., 1994, 1995; Rasmussen & Nielsen, 2002) Activation of ERs in transactivation assays was also reported in several different human breast cell lines (Legler et al., 1999; Andersen et al., 2002; Charles et al., 2002; Buteau-Lozano et al., 2008). Dieldrin did not elicit estrogenic responses in MCF-7 or HeLa cells in other studies (Arcaro et al., 1998; Tully et al., 2000; Mumtaz et al., 2002). Dieldrin treatment induced activation of the pregnane X receptor in MCF-7 and HepG2 cells in culture (Coumoul et al. 2002), but did not appear to activate peroxisome proliferator-activated receptor gamma (PPARγ) (Moreno-Aliaga & Matsumura, 1999).

(b) Experimental systems

(i) Aldrin

Aldrin was weakly estrogenic in an assay in zebra fish (Hodges et al., 2000).

(ii) Dieldrin

Several studies in experimental systems demonstrated estrogenic effects, while others have been unable to document similar findings, either with dieldrin alone or in combination with other estrogenic contaminants (Ratnasabapathy et al., 1997; Wade et al., 1997). Dieldrin did not bind to ERs

Table 4.7 Estrogenic activity of dieldrin

Assay system	Cell line	Agent	Concentration	Results	Reference
Breast cancer cell lines	MCF-7	Dieldrin + 9 pesticides	1.0 pM–10 μM	Induced cell proliferation at 10 μM dose only Mixture of 10 pesticides induced cell proliferation at concentrations that were ineffective on their own	Soto et al. (1994)
	MCF-7	Dieldrin + estrogenic compounds	1–10 μM	Dieldrin treatment induced cell proliferation at 10 μM and pS2 expression at 1–10 μM Cell proliferation was increased by chemical mixture containing dieldrin (1.0 μM) showing additivity	Soto et al. (1995)
	MCF7-BUS	Dieldrin	0.1–100 μM	Significant increase in cell proliferation beginning at 5 mM, reaching a maximum at 25 mM, and EC_{50} of 7.0 mM Effects mediated via ER-mediated transactivation of the reporter gene	Rasmussen & Nielsen (2002)
	MCF-7	Dieldrin	1.0 μM–10 μM	Treatments induced PXR transactivation	Coumoul et al. (2002)
	MCF-7	Dieldrin	1.0 pM–10 nM	Dieldrin failed to induce an estrogenic response	Arcaro et al. (1998)
	MELN	Dieldrin	1.0 pM–10 μM	Dieldrin-induced transactivation of the ER and upregulated VEGF expression at 10 μM concentration	Buteau-Lozano et al. (2008)
	T47D	Dieldrin + others	0.1 nM–10 μM	Lowest concentration of dieldrin to cause estrogen receptor transactivated luciferase induction was 1.0 μM Dieldrin and endosulfan acted additively in the range of 3–6 μM	Legler et al. (1999)
	MCF-7	Ternary mixture including dieldrin	0.1–1.0 μM	Estrogenic effects even at highest concentrations were no more than additive	Charles et al. (2002)
Other mammalian cell lines	HELN ERα & ERβ	PCP, dieldrin & aldrin	0.1–10 μM	Pentachlorophenol, aldrin& dieldrin demonstrated antagonism towards hERα & hERβ Dieldrin (10 μM) treatment also caused significant transactivation of ERα but not ERβ	Lemaire et al. (2006)
	HeLa	4,4-DDT, 4,4-DDD, 4,4-DDE, aldrin, dieldrin, or endrin	1.0 nM–10 μM	No estrogenic effects alone or in binary mixtures	Mumtaz et al. (2002)
	HeLa	Aldrin & dieldrin	1.0 nM–10 μM	No estrogenic effects alone or in binary mixtures	Tully et al. (2000)
	GH3/B6 pituitary cells	Dieldrin	1.0 pM–10 nM	Dieldrin-induced Ca^{++} fluxes and PRL release at all concentrations tested although dose–response relationship for PRL release was not evident Effects thought to be mediated via activation of membrane ERα	Wozniak et al. (2005)
	HepG2 cells	Dieldrin	1.0 μM–10 μM	Treatment (10 μM) caused transactivation of PXR	Coumoul et al. (2002)

Table 4.7 (continued)

Assay system	Cell line	Agent	Concentration	Results	Reference
	Eker rat leiomyoma cells	Dieldrin	10 nM–10 μM	Dieldrin exposure did not induce cell proliferation but did upregulate PR message	Hodges et al. (2000)
Yeast gene reporter		Dieldrin	0.1 nM–10 mM	Estrogenic response at concentrations above 1.0 μM	Graumann et al. (1999)
	rtER	PCP and/or + dieldrin	0.1 pM–100 μM	PCP inhibited estrogen-dependent cell growth, whereas dieldrin was weakly estrogenic in both yeast cells expression a rainbow trout ER	Petit et al. (1997)

Ca^{++}, calcium; DDD, dichlorodiphenyl dichloroethane; DDE, dichlorodiphenyl dichloroethylene; DDT, bis(*p*-chlorophenyl)-2,2,2-trichloroethane; EC_{50}, half maximal effective concentration; ER, estrogen receptor; PCP, pentachlorophenol; PR, progesterone; PRL, prolactin; PXR, pregnane X receptor; VEGF, vascular endothelial growth factor

Table 4.8 Summary of studies quantifying receptor-binding capacity of dieldrin

Model	Concentration	Results	Reference
Recombinant yeast assay	0.1 nM–10 mM	^{3}H-E_2 was displaced by dieldrin concentrations above 1.0 μM	Graumann et al. (1999)
Displacement of ^{3}H-E_2 binding to estrogen receptor fusion proteins from human (ERα), mouse (ERα), chicken, green anole (ERdef), and rainbow trout (rtERdef)	0.1 nM–100 μM	Dieldrin, at a concentration of 100 μM, was considered a weak binder of the ER across all species tested	Matthews et al. (2000)
Displacement of ^{3}H-E_2	2.5, 15, 60 μmol/kg	Alone or in combination with equimolar concentration of toxaphene did not bind with mouse uterine ER	Ramamoorthy et al. (1997)
MCF-7 cells and immature female SD rats. Displacement of ^{3}H-E_2	10 nM–10 μM	Micromolar concentrations inhibited ^{3}H-E_2 binding	Wade et al. (1997)
Displacement of ^{3}H-E_2 from alligator & human ER	630 nM	Dieldrin alone failed to bind appreciably with either cytosolic aER or hER. However, in combination with other chemical contaminants additive to synergistic displacement of ^{3}H-E_2 from the ER was detected	Arnold et al. (1997)
Displacement of ^{3}H-DHT from rat ventral prostate	10 μM	Dieldrin non-competitively inhibited the binding of ^{3}H-DHT to androgen receptors in the rat prostate in vitro	Wakeling & Visek (1973)
Displacement of ^{3}H-E_2 from CN & CGC in vitro	0.06–3 μM	Dieldrin displaced ^{3}H-E_2 in the competitive binding assay with the LOEC of between 1 and 3 μM for CGC and CN cells, respectively	Briz et al. (2011)
Displacement of ^{3}H- E_2 from Atlantic salmon and rainbow trout estrogen receptors	10 μM/L to 1 mM/L	Dieldrin failed to show any evidence of binding with either the salmon or rainbow trout ER	Tollefsen et al. (2002)
Displacement of ^{3}H-E_2 from recombinant catfish ERα and ERβ	6–20 μM	Dieldrin demonstrated little competition for binding with either ER	Gale et al. (2004)
Competitive radioreceptor binding assay in two nematode species	25 nM	Significant inhibition of estrogen binding in nematode homogenates; however, binary mixtures with other chlorinated contaminants failed to reveal any evidence of additive or synergistic effects	Hood et al. (2000)

CGC, cerebellar granule cells; CN, cortical neuron; DHT, dihydrotestosterone; E_2, 17β estradiol; ER, estrogen receptor; LOEC, lowest observed effect concentration

Table 4.9 Summary of dieldrin effects on receptor expression from animal and tissue culture studies

Test system	Concentration	Results	Reference
CN and CGC in vitro	0.03–1.0 μM	ERα expression was downregulated in both CGC and CN but not ERβ	Briz et al. (2011)
FVB-MMTV/*neu* mice	0.45–4.5 μg/g bw	Treatments induced a significant dose-dependent increase in Ntrk2 expression	Cameron & Foster (2009)
Largemouth bass	0.4–0.81 ppm	Dieldrin exposure had no effect on AR and ERα expression but downregulated expression of ERβ in the gonad of both sexes. Exposure upregulated AR in the liver of males only	Garcia-Reyero et al. (2006a)
Largemouth bass	0.4–0.81 μg/g feed	Exposure had no effect on ERα expression in the liver of both sexes but induced decreased ERα expression of ERβ in the liver and gonad of females whereas the highest dose increased its expression in the liver of both sexes. Effects of dietary dieldrin exposure on AR expression varied by dose, sex, and target tissue	Garcia-Reyero et al. (2006b)
Immature female Sprague-Dawley rats	3 mg/kg per day	Treatments had no effect on nuclear or cytosolic ER expression	Wade et al. (1997)
PC12 cells (rat adrenal gland pheochromocytoma)	30 μM	Upregulation of Fgfr1, Ntrk1, and Ntrk3 expression after 72 h in culture	Slotkin et al. (2010)
Differentiating PC12 cells (rat adrenal gland pheochromocytoma)	30 μM	Treatment increased Avpr1b, Cckbr, and Smstr28 expression	Slotkin & Seidler (2010b)
Embryonic d14 brainstem cell cultures	10 μM	Treatments upregulate GABA(β3) expression while expression of GABA(γ2S) and GABA(γ2L) expression was downregulated. GABA1 subunit expression was unaffected	Liu et al. (1997b)
In utero exposure, embryonic d12–17 brainstem cells		Decreased expression of GABA(α1), GABA(β3) and GABA(γ1) but did not affect expression of GABA(γ2S) and GABA(γ2L)	Liu et al. (1998)
CN cultures	60 and 200 nM	200 nM of dieldrin decreased the expression of NR2A	Briz et al. (2012)
Testis explants	1 pM–1 nM	Both concentrations of dieldrin increased LHR expression	Fowler et al. (2007)

AR, androgen receptor; Avpr, arginine vasopressin receptor; bw, body weight; Cckbr, cholecystokinin B receptor; CGC, cerebellar granule cells; CN, cortical neuron; d, day of gestation; ER, estrogen receptor; Fgfr, fibroblast growth factor receptor; GABA, α-aminobutyric acid receptor; h, hour; LHR, luteinizing hormone receptor; NR2A, glutamate (NMDA) receptor subunit 2A; Ntrk, neutrophin receptor kinase; Smstr, somatostatin receptor

of Atlantic salmon and rainbow trout (Tollefsen et al., 2002) and weakly bound ERα and ERβ in catfish (Gale et al., 2004). Dieldrin also inhibited binding of [^{3}H]estradiol (E_2) to the ER in a nematode species (*Panagrellus redivivus*) (Hood et al., 2000).

Androgen uptake by prostate cells in culture was adversely affected by dieldrin treatment (Blend, 1975), and adverse effects of dieldrin on rat thymocytes in culture have also been reported (Hallegue et al., 2002).

Using cultures of the rat ventral prostate, dieldrin inhibited binding of 5α[^{3}H]dihydrotestosterone to the androgen receptor (Wakeling & Visek, 1973; Wakeling et al., 1973). However, other investigators were unable to demonstrate any interference of dieldrin with 5α[^{3}H]dihydrotestosterone binding in the anterior prostate, seminal vesicle, kidney, and liver of mice (Schein et al., 1979).

Dieldrin has been shown to induce non-genomic effects in a rat prolactinoma cell line (GH3/B6/F10) as shown by an increase in calcium influx and prolactin release (Watson et al., 2007a). β-Hexosaminadase release from cultures of a human mast cell line were significantly increased after treatment with dieldrin at concentrations as low as 1.0 pM, an effect that was abolished in ERα knockout mouse primary mast cell cultures (Narita et al., 2007). Similar non-genomic effects have also been documented in rat GH3/BH6 cells, a pituitary tumour cell line (Wozniak et al., 2005).

Regarding other receptors, several studies have demonstrated that dieldrin affects gamma-aminobutyric acid (GABA)- and *N*-methyl-D-aspartate (NMDA)-mediated signalling (Lawrence & Casida, 1984; Briz et al., 2012; Martyniuk et al., 2013). The expression of other neurotrophin receptors, including neurotrophin receptor kinase 1 (Ntrk) and Ntrk 2, Ntrk 3, was significantly affected by dieldrin treatment in PC12 cells after 72 hours in culture (Slotkin et al., 2010). Dieldrin was also a ligand for PXR and CAR receptors (Wei et al., 2002; Zhang et al., 2004).

4.2.3 Inflammation and immunosuppression

(a) Humans

(ii) Exposed humans

Aldrin

A cross-sectional study of agricultural workers suggested an association between pesticide exposure and immune dysfunction (Rosenberg et al., 1999). Aldrin residue in the plasma and adipose tissue of pre- and postmenopausal obese women was infrequently detected in this study population, and thus links with inflammation and cardiometabolic risk could not be established (Teixeira et al., 2015). However, maternal exposure to pesticides including aldrin and dieldrin has been associated with inflammation and dysregulation of coagulation mechanisms in infants (Schaalan et al., 2012).

Dieldrin

In a study on Inuit infants exposed perinatally to organochlorines, dieldrin exposure was associated with an increased relative risk (RR, 1.75; 95% CI, 1.05–2.91) of otitis media only in the age group 4–7 months for the highest tertile versus the lowest (Dewailly et al., 2000). Of note, similar effects were not elicited in infants aged 0–3 or 8–12 months.

(ii) Human cells in vitro

For aldrin, no data were available to the Working Group.

Dieldrin induced reactive oxygen species (ROS) in human neutrophils in culture (Pelletier et al., 2001), and lead to a calcium-dependent induction of arachidonic acid and eicosanoid production by human monocytes in culture (Mangum et al., 2015).

(b) Experimental system

No studies on aldrin and immune function or inflammation were available to the Working Group.

Dieldrin treatment is pro-inflammatory and drives the generation of ROS in rat neutrophils, as well as calcium-dependent induction of arachidonic acid and eicosanoid production (Hewett & Roth, 1988; Tithof et al., 2000; Mangum et al., 2015).

4.2.4 Oxidative stress

(a) Humans

(i) Exposed humans

Significantly higher levels of aldrin, but not dieldrin, were observed in patients with chronic kidney disease than in healthy controls. Plasma levels of malondialdehyde (MDA) and advanced oxidation protein production were positively associated with plasma levels of total organochlorine pesticides, including aldrin and dieldrin, indicating augmentation of oxidative stress with increased accumulation of organochlorine pesticides in patients with chronic kidney disease (Siddharth et al., 2012).

(ii) Human cells in vitro

No data on aldrin were available to the Working Group.

For dieldrin, several studies demonstrated ROS production in various types of human cells in vitro, reporting increased levels of oxidative markers, cell-cycle progression, and apoptosis. In human THP-1 monocyte cultures, dieldrin (10 μM) elevated levels of intracellular ROS, as shown by dichlorofluorescence-derived fluorescence by flow cytometry (Mangum et al., 2015). Dieldrin also induced human neutrophil superoxide dismutase (SOD) production (Pelletier et al., 2001), although dieldrin did not induce P4501A and 1B nor deplete GSH in human HepG2 cells (Dehn et al., 2005). ROS generated by dieldrin activated the ERK pathway in human HaCaT cells (Ledirac et al., 2005), and induced caspase-3 activation leading to apoptosis via alteration of mitochondrial transmembrane permeability in human peripheral blood lymphocytes (Michałowicz et al., 2013).

(b) Experimental systems

(i) Non-human mammals in vivo

No data on aldrin were available to the Working Group.

For dieldrin, the potential to induce oxidative stress in experimental animals has been investigated in rats and mice. Hfaiedh et al. (2012) reported perturbations of oxidative stress in hepatic and renal tissues induced by dieldrin (50 mg/kg bw by gavage for 4 consecutive days), as shown by increased lipid peroxidation levels associated with increased SOD activity and decreases in glutathione peroxidase and catalase activities. Increased urinary MDA was observed in B6C3F$_1$ mice fed diets containing dieldrin at 0.1, 1.0, or 10 mg/kg for 7, 14, 28, or 90 days. In rats, while dieldrin had no effects on urinary MDA levels after 7, 14, or 28 days of treatment, a dose-dependent increase in urinary MDA was observed at 90 days. Only in mice fed dieldrin was there a temporal association of increases in hepatic MDA and hepatic DNA synthesis (Bachowski et al., 1998; see also Section 4.2.1). In short-term studies in mice and rats exposed to dieldrin, hepatic vitamin E was decreased in correlation with dieldrin dose. Because of normally lower levels of vitamin E in the mouse, MDA formation in the liver was found only in this species (not in the rat). Also, dieldrin produced a dose-dependent increase in DNA synthesis only in the mouse (Klaunig et al., 1995). Dieldrin (10 mg/kg) increased the liver focal lesion volume, focal lesion number, and focal lesion labelling index in B6C3F$_1$ mouse liver induced by diethylnitrosamine (DEN). Supplementation with vitamin E at 50 mg/kg

blocked this effect (Kolaja et al., 1998). Vitamin E inhibited hepatic DNA synthesis in B6C3F$_1$ mice fed diet containing dieldrin at 1, 3, and 10 mg/kg for 7 or 28 days, but not liver enlargement, hypertrophy of centrilobular hepatocytes, or induction of hepatic ethoxyresorufin O-deethylase activity (Stevenson et al., 1995).

In studies in the brain, dieldrin caused global oxidative stress as shown by increased levels of lipid peroxidation in all brain regions in the mouse. Dieldrin also elicited increases in SOD activity and oxyguanosine glycosylase activity (Sava et al., 2007) and decreases in total glutathione (Hatcher et al., 2007) in the mouse brain.

(ii) Non-human mammalian cells in vitro

Aldrin did not generate oxygen-free radicals in rat cerebellar granule cells (Rosa et al., 1996).

Dieldrin increased concentrations of 8-OHdG (see Section 4.2.1), ROS, and MDA, and decreased cellular antioxidants in cultured mouse hepatocytes (Klaunig et al., 1995).

Neuronal cells, such as PC12, SN4741, and microglial cells, were used in many studies in vitro. After treatment of PC12 cells with dieldrin, ROS generation (analysed by flow cytometric analysis) was evident within 5 minutes, and lipid peroxidation was increased within 1 hour (Kitazawa et al., 2001). ROS generation was inhibited by SOD (Kitazawa et al., 2001), and lipid peroxidation increase was inhibited by ascorbate or vitamin E (Slotkin & Seidler, 2010a). Dieldrin also increased the frequency of 8-OHdG in PC12 cells (Stedeford et al., 2001), induced haem oxygenase-1 (Kim et al., 2005), and generated ROS (Chun et al., 2001) in SN4741 cells, and increased ROS in microglia cells (Mao et al., 2007).

(c) Non-mammalian experimental systems

The effects of aldrin on amphibian neuronal, hepatic and muscular tissue were reported to be attributable to changes in oxidative enzymes (Joseph & Rao, 1990), and ascorbic acid (vitamin C) was able to prevent aldrin toxicity in an air-breathing fish (Agrawal et al., 1978).

Dieldrin induced thiobarbituric acid reactive substances and 8-OHdG in *Sparus aurata* (Pedrajas et al., 1995, 1998; Rodríguez-Ariza et al., 1999).

4.2.5 Altered cell proliferation, cell death, or nutrient supply

(a) Apoptosis

(i) Humans

No data on aldrin were available to the Working Group.

Schroeder et al. (2001) (described in Section 2.1.2) reported an association of dieldrin with t(14;18)-positive, but not t(14;18)-negative, NHL. The *BCL2* gene is overexpressed in t(14;18), prolonging survival through the inhibition of apoptosis (Schroeder et al., 2001).

Dieldrin increased resistance to anoikis (apoptosis triggered by inappropriate anchorage) in the human breast cancer cell line MDA-MB-231 (Cameron & Foster, 2008). An increase in the expression of tyrosine kinase B (TrkB), a suppressor of anoikis, by dieldrin was also demonstrated.

(ii) Experimental systems

No data on aldrin were available to the Working Group.

Dose-dependent thymic atrophy [an effect associated with apoptosis], apparently mediated by endogenous corticosteroids, was induced in rats after exposure to dieldrin in vivo (Hallegue et al., 2002). However, apoptosis was not decreased in foci by dieldrin at any concentration (0.1, 1.0, or 10.0 mg/kg diet) in rat or mouse liver (Kolaja et al., 1996). Kamendulis et al. (2001) also found no effect of dieldrin (0, 1, 3, or 10 mg/kg diet) on hepatocyte apoptosis in male F344 rats or B6C3F$_1$ mice after 7, 14, 28, or 90 days.

Incubation of rat thymocytes for 6 hours with dieldrin in vitro resulted in a dose-dependent decrease in cell viability comparable to that of dexamethasone (Hallegue et al., 2002). DNA fragmentation was induced by dieldrin, demonstrating apoptosis, whereas higher concentrations stimulated necrosis. Apoptosis, downregulated gap junction intracellular communication, and interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α) expression were induced in mouse CID-9 mammary cells exposed to dieldrin (5 or 25 µM, up to 9 hours) (Tarraf et al., 2003).

Dieldrin treatment promoted apoptosis in a dopaminergic neuronal cell model, inducing caspase-3 activation and apoptosis in PC12 cells by generating oxidative stress (Buchmann et al., 1999; Kitazawa et al., 2001, 2003; Slotkin et al., 2007). Overexpression of human Bcl-2 in PC12 cells completely suppressed dieldrin-induced caspase-3 activation and DNA fragmentation (Kanthasamy et al., 2003; Kitazawa et al., 2004).

(b) Proliferation

(i) Humans

Exposed humans

In a representative sample of the general population of the Canary Islands, Spain, levels of insulin-like growth factor-1 (IGF-I) were significantly lower in women and men with detectable levels of aldrin (Boada et al., 2007).

No data on dieldrin were available to the Working Group.

Human cells in vitro

No data on aldrin were available to the Working Group.

In a study on the effects of dieldrin on mitogen-activated protein kinase (MAPK) cascades in human HaCaT cells, it was reported that dieldrin strongly activates the ERK1/2 pathway (Ledirac et al., 2005).

(ii) Experimental systems

Büsser & Lutz (1987) investigated stimulation of liver DNA synthesis after a single gavage dose of aldrin in rats and mice. Aldrin gave positive results only in male mice, doubling thymidine incorporation at 0.007 mmol/kg, but not in male rats or female mice.

In swine IB-RS-2 cells, aldrin (0.1–100 µg/mL medium for 48 hours) decreased cell growth, and also decreased cellular protein, RNA, and DNA levels (Rodrigues & Puga, 1979).

Bulayeva & Watson (2004) demonstrated that dieldrin (10^{-10} to 10^{-8} M) can rapidly activate the phosphorylation of extracellular signal-regulated kinases (ERKs) in the rat pituitary tumour cell line GH_3/B6/F10.

(c) Cell–cell communication

(i) Humans

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

In human teratocarcinoma cells, dieldrin inhibited gap junctional intercellular communication at non-cytotoxic doses (Lin et al., 1986).

(ii) Experimental systems

Trosko et al. (1987) reported that aldrin inhibits gap junctional communication using Chinese hamster cells. Similarly, aldrin and dieldrin were shown to affect metabolic cooperation in V79 cells (Kurata et al., 1982).

Dieldrin (1–10 µg/mL) inhibited intercellular communication between primary cultured hepatocytes from four different strains of male mice ($B_6C_3F_1$, C3H, C57BL and Balb/c strains), but not from male F344 rats (Klaunig & Ruch, 1987).

4.3 Data relevant to comparisons across agents and end-points

For the results of high-throughput screening assays carried out by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast™) programmes of the government of the USA, see Section 4.3 of the *Monograph* on pentachlorophenol in the present volume.

4.4 Cancer susceptibility

Koutros et al. (2013a) examined single nucleotide polymorphism–environment interactions for prostate cancer susceptibility loci and pesticide exposures. For aldrin, a statistically significant increased risk (corrected for multiple comparisons) of prostate cancer was observed among men carrying two A alleles at rs7679673 in *TET2*. Høyer et al. (2002) examined the interaction between dieldrin exposure and *TP53* status on risk of breast cancer. No statistically significant change in risk was observed on the basis of *TP53* status, but cases with "wild-type" *TP53* had a significant increased risk of dying associated with dieldrin exposure.

4.5 Other adverse effects

Several case reports of liver toxicity and haemolytic anaemia after oral exposure to aldrin or dieldrin have been published (ATSDR, 2002). No additional studies in humans were available to the Working Group.

In experimental systems, liver toxicity was observed in multiple studies on aldrin or dieldrin administered orally in mice, rats, and dogs; effects observed included elevated serum enzyme levels, decreased serum proteins, hyperplasia, bile-duct proliferation, focal degeneration, and necrosis (ATSDR, 2002).

5. Summary of Data Reported

5.1 Exposure data

Aldrin and dieldrin are synthetic organochlorine pesticides that act as effective contact and ingested poisons for insects. They have been used to control infestations of pests such as ants and termites, and to control several insect vectors of disease. Commercial formulations of aldrin contain 90.3% (1R,4S,4aS,5S,8R,8aR)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene and 4.7% other insecticidally active related compounds. Commercial formulations of dieldrin contain 85% 1*R*,4*S*,4a*S*,5*R*,6*R*,7*S*,8*S*,8a*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene and 15% other insecticidally active, related compounds.

Both aldrin and dieldrin have been classified as persistent organic pollutants under the Stockholm Convention, which requires parties to take measures to eliminate their production and use. Since the early 1970s, use of these two compounds have been banned or severely restricted in several countries, especially in agriculture. Use for specific purposes, including as a termiticide and for vector control, continued up to the 1980s and 1990s, when many countries implemented complete bans. Some continued use has been reported, primarily for malaria vector control.

Aldrin rapidly converts to dieldrin in the human body and in soil. Measurements of dieldrin in the body and the soil represent exposure to dieldrin, aldrin, or both. Occupational exposure to aldrin and dieldrin has been measured in aldrin- and dieldrin-manufacturing workers, agricultural workers, and pesticide-treatment workers. The highest concentrations of dieldrin were observed in insecticide-plant workers in the USA, with mean serum concentrations in aldrin formulators of aldrin, 29.5 µg/L, and dieldrin, 182.5 µg/L. Pesticide-treatment workers had

median dieldrin serum concentrations ranging from < 1 to16 µg/L in several studies. The general population can be exposed to dieldrin and aldrin directly from residues on food, from living near areas where dieldrin or aldrin was sprayed, or from (past) use of aldrin or dieldrin for insecticide treatments in and around the home. The 95th percentile of dieldrin serum concentrations in the general population in the USA has decreased by 10 times between 1976–1980 and 2001–2004. In measurements from the 1980s until the 2010s in various countries, mean dieldrin concentrations were ~0.5–2 µg/L in blood, 2–5 ng/g lipid in breast milk, and 17–40 ng/g lipid in adipose tissue.

5.2 Human carcinogenicity data

An important consideration in the interpretation of the studies on aldrin and dieldrin that were available to the Working Group was the type of exposure assessment used. In studies that used questionnaires, it was possible to differentiate between dieldrin and aldrin use, while in studies based on measurements in serum or adipose tissue, the dieldrin measurements may reflect exposure to aldrin and/or dieldrin.

5.2.1 Aldrin

Data were available from two cohort studies: the AHS, in which dieldrin use was assessed using questionnaires; and a cohort study of male workers at a Dutch manufacturing plant, in which combined exposure to dieldrin and/or aldrin was assessed. In the most recent update of the Dutch cohort, there was no increase in overall cancer mortality or mortality from cancer of the lung associated with total intake of aldrin and dieldrin. The AHS reported a decrease in risk of non-Hodgkin lymphoma (NHL) associated with aldrin use.

Three population-based case–control studies in the USA and Canada have investigated the association between NHL and exposure to aldrin, and reported conflicting results. The only statistically significant positive finding was based on results for 10 cases who had ever handled aldrin in a study in Canada.

A study of cancer of the breast among wives of pesticide applicators in the AHS showed increased risk associated with use of aldrin by the husband, but not by the wife, although the latter finding was based on results for only four cases. A case–control study on cancer of the breast that was nested within the Janus cohort in Norway found only three serum samples that contained aldrin at above the detection limit, with an odds ratio of 0.5. A case–control study on cancer of the breast and pesticide exposures in Spain reported increased risk associated with adipose tissue levels of aldrin at greater than the limit of detection, but this result was difficult to interpret because of the unexpected finding that aldrin was detected more frequently than dieldrin.

One case–control study investigated the association between soft tissue sarcoma and exposure to aldrin, and another study reported on the association between leukaemia and exposure to aldrin.

Because of the inconsistent results reported in studies on NHL and cancer of the breast, the different study designs used, different countries in which the studies were set, and the small number of studies available for other cancer sites, together with the small number of cases exposed to aldrin in most studies, the Working Group concluded that there were insufficient data to draw a conclusion regarding carcinogenicity associated with exposure to aldrin.

5.2.2 Dieldrin

Data were available from two cohort studies: the AHS, in which dieldrin use was assessed using questionnaires; and a cohort study of male workers at a Dutch manufacturing plant in which

combined exposure to dieldrin and/or aldrin was assessed. There were also several case–control studies nested within large population cohorts, and most of these reported levels of serum dieldrin that had been measured at baseline. Other case–control studies either used questionnaires or measured serum dieldrin concentrations at the time of recruitment (after diagnosis for cases).

Two or more studies considered other cancers including NHL, leukaemia, and cancers of the breast, prostate, or lung; the results of these studies are discussed below.

(a) Cancer of the breast

Two nested case–control studies with very similar methods assessed serum dieldrin concentrations in samples taken at baseline. The Danish study found a doubling in risk of cancer of the breast for the highest quartile of exposure, with a strong dose–response relationship limited to subjects with estrogen-receptor-negative (ER–) tumours. The Norwegian study found no increase in risk (but had fewer cases). The case–control study of cancer of the breast in Long Island, USA, found risk of breast cancer to be increased for the highest quintile of serum dieldrin concentration measured at diagnosis, but this was not statistically significant. In the AHS, risk of breast cancer in wives of pesticide licensees was statistically significantly doubled if the husband had ever used dieldrin. The number of wives who had used dieldrin themselves was too small to provide meaningful results. The Working Group considered that there was evidence for an association between dieldrin and cancer of the breast, but that chance, bias, and confounding could not be ruled out.

(b) Non-Hodgkin lymphoma

In two studies in the USA that measured biomarkers, no increase in risk of NHL was seen with serum dieldrin concentration measured at time of diagnosis in the case–control study, nor at enrolment in the cohort study. In a study in the USA that used stored adipose tissue mainly from cadavers, the highest quartile of dieldrin concentration at time of death was significantly associated with an increased risk of NHL. In questionnaire studies, the AHS cohort study reported that ever use of dieldrin was not associated with an increase in NHL or in any NHL subtype, including multiple myeloma. The case–control study in the midwest USA (De Roos et al., 2003) found an elevated risk of NHL associated with dieldrin use, although the effect estimate was not statistically significant.

(c) Other cancers

For leukaemia, the AHS found a non-statistically significant increase in risk for ever use of dieldrin, while an older case–control study found no increase in risk among subjects who had ever used dieldrin. Dieldrin exposure was not associated with cancer of the prostate in two studies, nor was it associated with cancer of the colorectum in the two cohort studies. Lung cancer risk was increased with dieldrin use in the AHS, but not in the Dutch cohort study. Only one study was available for cancer of the bladder, melanoma, or for cancer of the pancreas, and no associations with dieldrin were reported.

5.3 Animal carcinogenicity data

5.3.1 Aldrin

Three studies in mice fed diets containing aldrin were available to the Working Group: two studies in males and females combined, and one study in males and females considered separately. Aldrin increased the incidence of hepatocellular carcinoma in both studies in males and females combined, and in males only in the study in males and females considered separately.

Five studies in rats fed diets containing aldrin were available to the Working Group: one study in males and females combined, and four studies in males and females considered

separately. In one study in males and females considered separately, there was an increase in the incidence of tumours of the thyroid in males and females, and in the incidence of tumours of the pancreas in males and of the adrenal gland in females. These increases were not considered to be treatment-related, because they were significant only for groups at the lower dose, and only when compared with pooled controls. No significant increase in the incidence of neoplasms was observed in three other studies, and an additional study in males and females separately was judged inadequate for the evaluation.

5.3.2 Dieldrin

Sixteen studies in mice fed diets containing dieldrin were available to the Working Group: two studies in males and females combined, six studies in males only (one was judged inadequate for the evaluation), and eight studies (including one co-carcinogenicity study) in males and females considered separately. Dieldrin increased the incidence of hepatocellular carcinoma and/or hepatocellular adenoma or carcinoma (combined) in males and females in most of these studies. In one additional study in female transgenic offspring mice treated with dieldrin by gavage in addition to transplacental exposure and exposure throughout lactation, there was an increase in the multiplicity of tumours of the thoracic mammary gland (mainly adenocarcinomas). In another study, in male mice exposed to dieldrin by gavage and/or in the diet, there was an increase in the incidence of hepatocellular tumours when mice were exposed to dieldrin by gavage and in the diet.

Six studies in rats fed diets containing dieldrin were available to the Working Group: one study in males and females combined and five studies (one was judged inadequate for the evaluation) in males and females considered separately. In one study in males and females separately, there was an increase in the incidence of tumours of the adrenal gland in females. This increase was not considered to be treatment-related, because it was significant only for the group at the lower dose, and only when compared with pooled controls. No significantly increased incidence of neoplasms was observed in the other studies.

One study in male and female hamsters fed diets containing dieldrin gave negative results. One study in male rhesus monkeys fed diets containing dieldrin gave negative results. One study in dogs fed diets containing dieldrin was judged inadequate for the evaluation.

5.4 Mechanistic and other relevant data

Absorption of aldrin and dieldrin in humans has been documented after occupational and non-occupational exposures. Both compounds are detected in the blood and in adipose tissue biopsies. Gastrointestinal and percutaneous absorption have been reported in studies in human volunteers. In studies in experimental animals, absorption occurs readily via oral and dermal routes. In all species, aldrin and dieldrin are rapidly distributed by blood circulation to systemic tissues, with adipose tissue being an important storage depot. Metabolism of aldrin involves its rapid conversion to the epoxide-containing dieldrin, but there are no data to suggest that dieldrin forms protein or DNA adducts. Subsequently, dieldrin is very slowly metabolized to polar glucuronide metabolites that are excreted in the bile and, to a lesser degree, in the urine. The blood half-life of dieldrin in humans is about 1 year. The slow excretion of dieldrin is attributed to inefficient metabolism and to sequestration in adipose tissue.

With respect to the key characteristics of carcinogens, adequate data were available to evaluate whether dieldrin is genotoxic, modulates receptor-mediated effects, induces inflammation, is immunosuppressive, induces oxidative

stress, and alters cell proliferation, cell death, or nutrient supply. For aldrin, the available data were sparse or inconsistent.

There is *weak* evidence that aldrin is genotoxic. No effect was seen in human lymphocytes from exposed populations, on end-points such as DNA damage and strand breaks. Aldrin also gave negative results in human lymphocytes treated in vitro, and in other experimental systems (animals in vivo, bacteria, and plants).

There is *moderate* evidence that dieldrin is genotoxic. The frequency of chromosomal aberrations was not increased in exposed workers, and two studies in human cell lines were not informative. Chromosomal aberrations (at toxic exposures) and micronucleus formation were induced in the bone marrow of male mice, but not in Chinese hamsters. Levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) were elevated in the urine, but not in the liver, of male mice fed diets containing dieldrin for up to 90 days. In vitro, dieldrin increased the formation of 8-OHdG in mouse hepatocytes and PC12 cells, but not in rat hepatocytes. Findings of mutations and micronucleus formation in mammalian cells may have been compromised by excessive toxicity.

There is *weak* evidence that aldrin modulates receptor-mediated effects. Aldrin did not bind the estrogen receptor or activate estrogen receptor-mediated signalling pathways. Results were conflicting in two studies on activation of the human retinoic acid receptor.

There is *moderate* evidence that dieldrin modulates receptor-mediated effects, on the basis of anti-estrogenic effects in complementary assay systems in vitro. Dieldrin is a ligand for the xenobiotic receptors constitutive androstane receptor (CAR) and pregnane X receptor (PXR), resulting in increased transcription of cytochrome P450 2B and 3A genes.

There is *weak* evidence that aldrin induces oxidative stress, based on sparse data; the evidence is *moderate* for dieldrin. No studies in exposed humans or human primary cells in vitro were available, but dieldrin induced production of reactive oxygen species in several studies in human cell lines. In rodents fed dieldrin, levels of various markers of oxidative stress were increased. Supplementation with vitamin E blocked mouse liver focal-lesion enhancement by dieldrin after initiation with diethylnitrosamine.

There is *weak* evidence that aldrin induces chronic inflammation and is immunosuppressive; the evidence is *moderate* for dieldrin. Maternal exposure to multiple chlorinated pesticides, including aldrin and dieldrin, was associated with inflammation and dysregulation of coagulation mechanisms in infants. Dieldrin stimulated an oxidative burst in human THP-1 monocytes and in rat neutrophils.

No studies on aldrin were available, and there is *moderate* evidence that dieldrin alters cell proliferation, cell death, or nutrient supply. Although no studies in exposed humans were available, dieldrin increased resistance to anoikis (apoptosis triggered by inappropriate anchorage) in a human breast-cancer cell line, MDA-MB-231. Dieldrin induced dose-dependent thymic atrophy (an effect associated with apoptosis) in rats. Dieldrin strongly activated the ERK1/2 pathway in human HaCaT cells.

In high-throughput testing in the Toxicity Testing in the 21st Century and Toxicity Forecaster research programmes of the USA government, aldrin and dieldrin were active for multiple assay end-points measuring markers of oxidative stress. Aldrin and dieldrin were cytotoxic in cell lines and primary cells, and were also active for many assay end-points related to modulation of receptor-mediated effects that may be related to cytotoxicity.

Few data were available concerning cancer susceptibility. The liver was consistently identified as a target organ of toxicity and carcinogenicity.

6. Evaluation

6.1 Cancer in humans

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

There is *limited evidence* in humans for the carcinogenicity of dieldrin. A positive association has been observed between dieldrin and cancer of the breast.

6.2 Cancer in experimental animals

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

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

6.3 Overall evaluation

Dieldrin, and aldrin metabolized to dieldrin, is *probably carcinogenic to humans* (*Group 2A*).

6.4 Rationale

Because aldrin is rapidly metabolized to dieldrin in humans and experimental animals, exposure to aldrin always leads to internal exposure to dieldrin. Therefore, for the evaluation of aldrin, the evidence on the carcinogenicity of dieldrin was taken into account.

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