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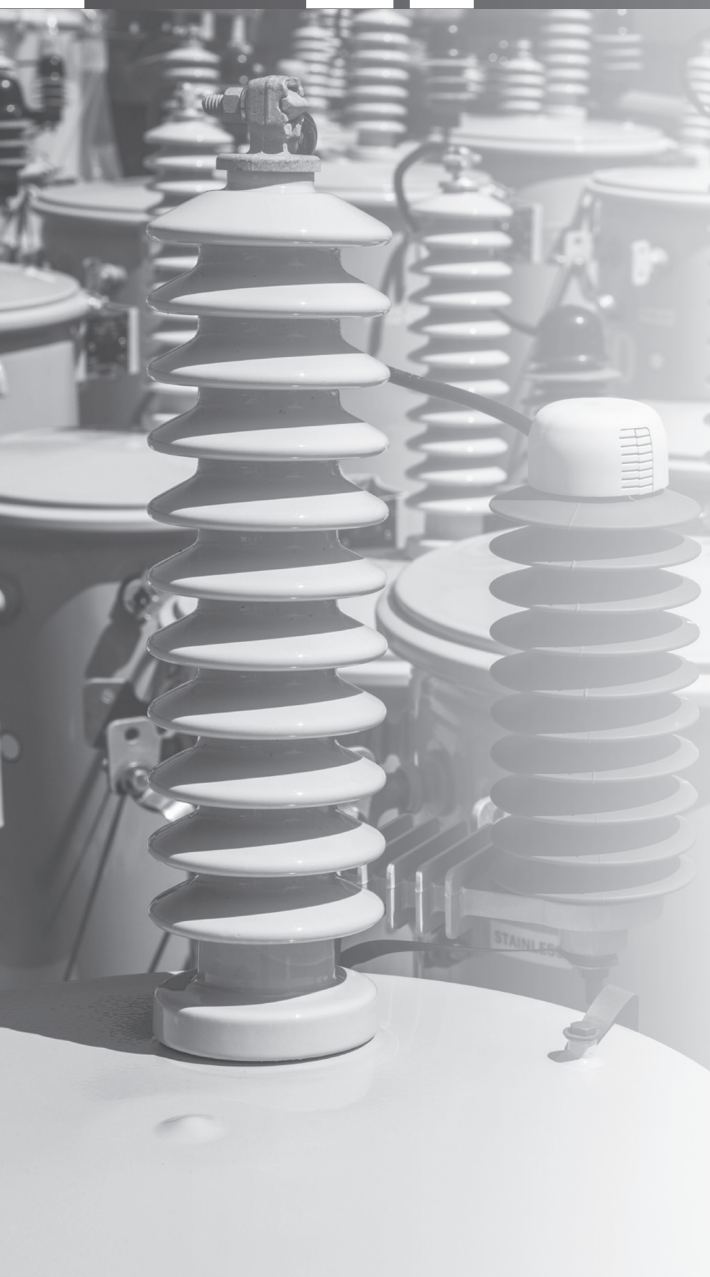

POLYCHLORINATED BIPHENYLS AND POLYBROMINATED BIPHENYLS

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2. CANCER IN HUMANS

2.1 Cohort studies of occupational exposure

Commercial mixtures of congeners of polychlorinated biphenyls (PCBs) were manufactured starting in the 1920s in Austria, France, Germany, Italy, Japan, Spain, Poland, the Russian Federation, the United Kingdom, and the USA. No published epidemiological studies of cancer among PCB-production workers were available to the Working Group.

2.1.1 Capacitor manufacture

Studies of cancer mortality and incidence among workers exposed to PCBs in the manufacture of capacitors have been conducted in Italy (Bertazzi *et al.*, 1982, 1987; Tironi *et al.*, 1996; Pesatori *et al.*, 2013), Sweden (Gustavsson *et al.*, 1986; Gustavsson & Hogstedt, 1997), and the USA (Brown & Jones, 1981; Brown, 1987; Sinks *et al.*, 1992; Kimbrough *et al.*, 1999, 2003; Mallin *et al.*, 2004; Prince *et al.*, 2006a, b; Ruder *et al.*, 2006; Silver *et al.*, 2009). The details of cohort studies among capacitor-manufacturing workers are presented in Table 2.1.

Bertazzi *et al.* (1982, 1987) studied 544 male and 1556 female former capacitor-production workers exposed between 1946 and 1980 at one capacitor-manufacturing plant in Monza, Italy. Cancer mortality until 1991 was non-statistically significantly increased among men (standardized mortality ratio, SMR, 1.1; 95% CI, 0.7–1.7; 20 deaths) and women (SMR, 1.2; 95% CI, 0.7–1.8; 19 deaths) (Tironi *et al.*, 1996). The most recent update also included 373 male and 97 female workers at a second plant that operated from 1950 to 1982 (Pesatori *et al.*, 2013). There was no excess overall cancer mortality; however, mortality due to cancers of the digestive tract, not otherwise specified, was statistically significantly increased (SMR, 2.5; 95% CI, 1.2–5.3; seven deaths). Deaths due to cancer of the brain (SMR, 1.8; 95% CI, 0.9–3.6; eight deaths) and lymphoma (SMR, 1.9; 95% CI, 1.0–3.3; twelve deaths) were in excess, especially for Hodgkin disease (SMR, 4.0; 95% CI, 1.3–12; three deaths) among women. Men were at increased risk of mortality from cancer of the biliary tract (SMR, 3.9; 95% CI, 1.5–10.4; four deaths) and cancer of the prostate (SMR, 1.7; [95% CI, 0.8–3.5]; seven deaths). [This cohort was notable for the high proportion of women.]

Gustavsson & Hogstedt (1997) studied cancer incidence and mortality until 1991 among 242 male capacitor-manufacturing workers employed for at least 6 months between 1965 and 1978 at a plant in Sweden. Individuals were classified as "high-exposed" if they had ever worked in the impregnation or repair departments. Cancer mortality was not significantly elevated among highly exposed workers (SMR, 1.9; 95% CI, 0.8–3.9; seven deaths). Two cases of cancer of the liver and bile duct were diagnosed (SMR, 6.7; 95% CI, 0.0–37 for highly exposed workers). Mortality from non-Hodgkin lymphoma (NHL) was increased among highly exposed workers based on one case (SMR, 9.1; 95% CI, 0.2–51).

Table 2.1 Cohort studies in capacitor-manufacturing workers

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Tironi *et al.* (1996), Italy, 1954–1982	1556 women, 544 men	Employment, 1 wk, 1946–82	All cancers (140–209)	All women	19	SMR, 1.2 (0.7–1.8)	Update of cohort studied by Bertazzi *et al.* (1982, 1987)
				All men	20	SMR, 1.1 (0.7–1.7)	
			Digestive organs (150–159)	All women	2	SMR, 0.9 (0.1–3.3)	
				All men	10	SMR, 2.0 (0.9–3.6)	
			Lymphatic & haematopoietic (200–209)	All women	5	SMR, 1.4 (0.5–3.3)	
				All men	3	SMR, 2.0 (0.4–5.9)	
			Lymphoma (200–202)	Women	4	SMR, 1.8 (0.5–4.5)	
Pesatori *et al.* (2013), Italy, 1946–1978 (plant 1)	1551 women and 544 men (plant 1); 97 women and 373 men (plant 2)	Employment > 1 wk 1946–1978 (plant 1), all workers employed 1950–1982 (plant 2); PCBs used until 1980	All cancers	All workers	183	SMR, 1.0 (0.9–1.0)	
			Lymphoma (200–202)		12	SMR, 1.9 (1.1–1.3)	
			Digestive NOS (159)		7	SMR, 2.5 (1.2–5.3)	
			Brain		8	SMR, 1.8 (0.9–3.6)	
			Breast	All women	16	SMR, 0.8 (0.5–1.3)	
			Prostate	All men	7	SMR, 1.7 (0.8–3.5)	
Gustavsson & Hogstedt (1997); Gustavsson *et al.* (1986), Sweden, 1965–1991	242 men	Employed > 6 mo, 1965–1978; low, medium, or high exposure to PCBs	All cancers (140–209)	High-exposed	7	SMR, 1.9 (0.8–3.9)	Age, calendar period, country of origin
			Liver (155)	High-exposed	1	SMR, 6.7 (0.02–37)	
			Lung (162)	High-exposed	2	SMR, 2.2 (0.3–8.0)	
			Prostate (185)	High-exposed	1	SMR, 2.2 (0.1–12)	
			Lymphatic & haematopoietic (200–209)	High-exposed	1	SMR, 3.3 (0.1–19)	
			Lymphoma (200–202)	High-exposed	1	SMR, 9.1 (0.2–51)	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Mallin *et al.* (2004), Illinois, USA, 1944–2000	2885 white (25 non-white workers excluded)		All cancers (140–208)	All	347	[SMR, 1.1 (1.0–1.2)]	Sex, age, race, calendar period
			Stomach (151)	All	17	[SMR, 1.9 (1.1–3.1)]	Workers also exposed to trichloroethylene, 1,1,1-trichloroethane, lead solder, mineral oil, lacquer, paint thinner, epoxies, methyl ethyl ketone
			Intestine excluding rectum (152–153)	All	39	[SMR, 1.3 (0.9–1.7)]	
			Biliary passages, liver, & gallbladder (155–156)	All	14	[SMR, 2.4 (1.3–4.1)]	
			Thyroid (193)	Men	3	SMR, 15.2 (3.1–45)	No deaths from thyroid cancer among women
			Rectum (154)	All	7	[SMR, 1.1 (0.5–2.4)]	
			Prostate (185)	Men	9	SMR, 1.1 (0.5–2.0)	
			Breast (174–175)	Men	49	SMR, 1.2 (0.9–1.6)	
			NHL (200, 202)	Women:			No NHL deaths among those who worked 5–9 years. Data not reported for men
				Worked < 1 yr	7	SMR, 2.1 (0.8–4.3)	
				Worked 1–4 yr	4	SMR, 1.6 (0.4–4.1)	
				Worked ≥ 10 yr	2	SMR, 1.9 (0.2–6.8)	
			Oral cavity & pharyn (140–149)	Men only	3	SMR, 1.1 (0.2–3.3)	No deaths among women
Ruder *et al.* (2006), Indiana, USA, 1957–1998	3569	JEM based on department, job, tasks, monitored exposure levels, estimated cumulative exposure for each worker		*Cumulative exposure*			Sex, age, race, calendar period
			All cancers	Lowest tertile (< 11 000 unit-days)	56	SMR, 0.9 (0.7–1.2)	
				Middle tertile (11 000–89 999 unit days)	62	SMR, 0.9 (0.7–1.2)	
				Highest tertile (≥ 90 000 unit-days)	52	SMR, 0.8 (0.6–1.1)	*P* for trend = 0.48
			Melanoma	Lowest tertile	5	SMR, 3.7 (1.2–8.7)	
				Middle tertile	2	SMR, 1.5 (0.2–5.4)	
				Highest tertile	9	SMR, 2.4 (1.1–4.6)	*P* for trend = 0.72
			Brain	Lowest tertile	3	SMR, 1.4 (0.3–4.0)	
				Middle tertile	4	SMR, 1.8 (0.5–4.6)	
				Highest tertile	5	SMR, 2.7 (0.9–6.3)	*P* for trend = 0.016

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Ruder et al. (2006), Indiana, USA, 1957–1998 (cont.)			Breast	Lowest tertile	4	SMR, 1.0 (0.3–2.7)	
				Middle tertile	3	SMR, 0.9 (0.2–2.7)	
				Highest tertile	0	–	
			Prostate	Lowest tertile	1	SMR, 0.5 (0.0–2.7)	
				Middle tertile	2	SMR, 0.8 (0.1–2.7)	
				Highest tertile	1	SMR, 0.3 (0.0–1.8)	
			NHL (200, 202)	Lowest tertile	1	SMR, 0.4 (0.0–2.3)	
				Middle tertile	5	SMR, 1.9 (0.6–4.5)	
				Highest tertile	3	SMR, 1.3 (0.3–3.8)	
			Oral cavity & pharyn	Lowest tertile	2	SMR, 2.0 (0.2–7.1)	
				Middle tertile	0	–	
				Highest tertile	1	SMR, 0.9 (0.0–4.9)	
Prince *et al.* (2006b), Hopf *et al.* (2010), Massachusetts & New York, USA, 1939–1998	14 458	JEM for each plant based on department, job, tasks, monitored exposure levels, estimated cumulative exposure for each worker		Cumulative exposure: referent category < 150 unit-yr			Sex, age, race, calendar period The New York plant was also studied by Kimbrough *et al.* (1999, 2003). Results for 0-yr lag
			All cancers	150 to < 620 unit-yr	229	RR, 1.1 (0.9–1.3)	*P* for trend = 0.03
				620 to < 2300 unit-yr	238	RR, 1.3 (1.1–1.5)	
				≥ 2300 unit-yr	240	RR, 1.3 (1.1–1.5)	
			Melanoma	150 to < 620 unit-yr	2	RR, 0.3 (0.1–1.3)	*P* for trend = 0.83
				≥ 620 unit-yr	6	RR, 0.7 (0.2–1.9)	
			Brain	150 to < 620 unit-yr	5	RR, 0.6 (0.2–1.8)	*P* for trend = 0.32
				620 to < 2300 unit-yr	3	RR, 0.4 (0.1–1.6)	
				≥ 2300 unit-yr	3	RR, 0.5 (0.1–1.7)	
			Stomach	150 to < 620 unit-yr	6	RR, 1.5 (0.5–4.9)	
				620 to < 2300 unit-yr	10	RR, 3.2 (1.1–9.3)	
				≥ 2300 unit-yr	8	RR, 2.9 (0.9–9.2)	*P* for trend = 0.12
			Intestine excluding rectum	150 to < 620 unit-yr	26	RR, 1.5 (0.8–2.6)	*P* for trend = 0.55
				620 to < 2300 unit-yr	26	RR, 1.5 (0.8–2.6)	
				≥ 2300 unit-yr	27	RR, 1.4 (0.8–2.6)	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Prince et al. (2006b), Hopf et al. (2010), Massachusetts & New York, USA, 1939–1998 (cont.)			Rectum	150 to < 620 unit-yr	5	RR, 1.1 (0.3–3.9)	
				620 to < 2300 unit-yr	1	RR, 0.2 (0.0–1.8)	
				≥ 2300 unit-yr	8	RR, 1,4 (0.4–4.3)	*P* for trend = 0.36
			Biliary passages, liver, & gallbladder	150 to < 620 unit-yr	3	RR, 1.7 (0.3–10.0)	
				620 to < 2300 unit-yr	6	RR, 3.1 (0.6–15)	
				≥ 2300 unit-yr	9	RR, 4.2 (0.9–20)	*P* for trend = 0.07
			Breast	150 to < 620 unit-yr	26	RR, 1.1 (0.6–1.9)	
				620 to < 2300 unit-yr	19	RR, 0.8 (0.4–1.4)	
				≥ 2300 unit-yr	27	RR, 1.3 (0.8–2.3)	*P* for trend = 0.26
			Prostate	150 to < 620 unit-yr	5	RR, 1.5 (0.4–5.6)	
				620 to < 2300 unit-yr	7	RR, 2.8 (0.8–9.6)	
				≥ 2300 unit-yr	18	RR, 6.1 (2.0–18)	*P* for trend < 0.01
			NHL (200, 202)	150 to < 620 unit-yr	13	RR, 1.6 (0.7–3.6)	
				620 to < 2300 unit-yr	3	RR, 0.5 (0.1–1.7)	
				≥ 2300 unit-yr	7	RR, 1.2 (0.4–3.3)	*P* for trend = 0.99
			Myeloma (203)	150 to < 620 unit-yr	6	RR, 1.5 (0.5–4.9)	
				620 to < 2300 unit-yr	9	RR, 2.4 (0.8–7.3)	
				≥ 2300 unit-yr	8	RR, 1.9 (0.6–5.9)	*P* for trend = 0.48
Kimbrough *et al.* (2003), New York, USA, 1946–1998	7075	Duration of employment, whether hourly or salaried	All cancers (140–208)	Hourly workers	381	[SMR, 1.0 (0.9–1.2)]	Sex, age, race, calendar period The plant was also studied by Prince *et al.* (2006b) and Silver *et al.* (2009)
				Salaried workers	111	[SMR, 0.8 (0.7–1.0)]	
			Prostate	Hourly workers	17	SMR, 1.3 (0.7–1.8)	
				Salaried workers	4	SMR, 0.5 (0.1–1.4)	
			Brain	Hourly workers	5	[SMR, 0.5 (0.2–1.2)]	
				Salaried workers	6	[SMR, 1.5 (0.6–3.4)]	
			Breast	Hourly workers	32	SMR, 0.9 (0.6–1.3)	
				Salaried workers	6	SMR, 0.9 (0.3–1.9)	
			Skin, including melanoma	Hourly workers	9	[SMR, 1.2 (0.6–2.4)]	
				Salaried workers	6	[SMR, 2.1 (0.8–4.7)]	
			Biliary passages, liver, & gallbladder	Hourly workers	6	[SMR, 0.97 (0.4–2.1)]	
				Salaried workers	1	[SMR, 0.3 (0.0–2.6)]	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Kimbrough et al. (2003), New York, USA, 1946–1998 (cont.)			Intestine excluding rectum	Hourly workers	41	[SMR, 1.3 (0.9–1.7)]	
				Salaried workers	11	[SMR, 0.9 (0.5–1.7)]	
			Rectum	Hourly workers	8	[SMR, 1.2 (0.5–2.4)]	
				Salaried workers	4	[SMR, 1.6 (0.4–4.5)]	
			Oral cavity	Hourly workers	4	[SMR, 2.0 (0.6–5.2)]	
				Salaried workers	1	[SMR, 1.1 (2.9–6.4)]	
Silver *et al.* (2009), Indiana, Massachusetts & New York, USA, 1940–1998	5752 women	JEMs (see Ruder *et al.*, 2006 and Prince *et al.*, 2006b for description) Questionnaire for non-occupational risk factors	Breast	All	257	SIR, 0.8 (0.7–0.9)	Sex, age, race, calendar period. Results for subcohort with questionnaire data (n = 3141). Exposure lagged 10 yr
				Cumulative exposure per 1000 unit-yr:			Age, race, calendar period, ever smoking, parity, age at first live birth, breast cancer in first-degree female relative, age began hormone use
				All women	145	HR, 1.0 (1.0–1.1)	
				White women	131	HR, 1.0 (1.0–1.0)	
				Non-white women	14	HR, 1.3 (1.1–1.6)	

HR, hazard ratio; JEM, job-exposure matrix; mo, month; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; wk, week; yr, year

[Findings based on this small cohort were difficult to interpret because of limited precision.]

A cohort of 2885 white workers employed between 1944 and 1977 at a capacitor-manufacturing facility in Illinois, USA, who were exposed to PCBs (1952–1977), chlorinated naphthalenes (1944–1981), and other chemicals, was followed until 2000 (Mallin *et al.*, 2004). Plant records were incomplete and short-term workers (less than 1 year employment) were least likely (83%) to have been traced. There was excess mortality from cancers of the stomach [SMR, 1.9; 95% CI, 1.1–3.1], liver and biliary tract [SMR, 2.4; 95% CI, 1.3–4.1] and breast [SMR, 1.2; 95% CI, 0.9–1.6]. Women with 5 or more years employment during the period of PCB use had significantly elevated mortality from cancers of the liver and biliary tract (SMR, 5.6; 95% CI, 1.5–14; four deaths) and intestine (SMR, 2.3; 95% CI, 1.0–4.3; nine deaths). Men had excess mortality from cancer of the thyroid (SMR, 15.2; 95% CI, 3.1–45; three deaths), while women had excess mortality from NHL, which was not related to the duration of employment (SMRs, 1.6–2.1). Data on NHL were not reported for men. [Exposure assessment was limited and workers were exposed to multiple chemicals, which hampered attribution of cancer outcomes to PCB exposure.]

The United States National Institute for Occupational Safety and Health (NIOSH) cohort (Ruder *et al.*, 2014) included 25 000 workers at facilities in three states, originally studied separately, in Indiana (Sinks *et al.*, 1992; Ruder *et al.*, 2006) and Massachusetts and New York (Brown & Jones, 1981; Brown, 1987; Prince *et al.*, 2006a, b), and combined for an analysis of cancer of the breast (Silver *et al.*, 2009). Separate job-exposure matrices were developed for each of the plants, based on department, job title, era, company records, information about job tasks, and sampling data (Nilsen *et al.*, 2004; Hopf *et al.*, 2009, 2010), with each worker receiving an estimated cumulative exposure score, so that cancer outcomes could be analysed by level of relative exposure.

Updating vital status until 1998 for the Indiana subcohort (which comprised 3569 workers exposed to PCBs between 1957 and 1977) confirmed the earlier findings of excess melanoma and cancer of the brain (Sinks *et al.*, 1992). Melanoma remained in excess (SMR, 2.4; 95% CI, 1.1–4.6), particularly in the lowest tertile of estimated cumulative exposure (SMR, 3.7; 95% CI, 1.2–8.7; five deaths). Mortality from cancer of the brain (SMR, 1.9; 95% CI, 1.0–3.3) increased with exposure, with a standardized mortality ratio of 2.7 (95% CI, 0.9–6.3; five deaths) in the highest quartile and a significant exposure–response trend in the standardized rate ratio (SRR) ($P = 0.02$). Among those having worked ≥ 90 days, both melanoma (SMR, 2.7; 95% CI, 1.1–5.2) and cancer of the brain (SMR, 2.1; 95% CI, 1.1–3.8) were elevated, especially for women (melanoma: SMR, 6.0; 95% CI, 1.2–17.5; three deaths; cancer of the brain: SMR, 2.9; 95% CI, 0.6–8.4; three deaths). The standardized mortality ratio for mortality from NHL was 1.2 (95% CI, 0.6–2.3) (Ruder *et al.*, 2006).

The original studies in the Massachusetts-New York subcohorts (Brown & Jones, 1981; Brown, 1987) included only 2567 workers considered to be highly exposed to PCBs during 1938–1977 (Massachusetts) or 1946–1977 (New York). The update until 1998 expanded the study population to include 14 458 workers with at least 90 days of potential exposure to PCBs (Prince *et al.*, 2006b). Cancer of the liver, leukaemia and aleukaemia [aplastic anaemia], and NHL were not in excess overall, but mortality from multiple myeloma was (SMR, 1.85; 95% CI, 1.23–2.67). In the New York subcohort, mortality from melanoma was elevated (SMR, 1.79; 95% CI, 0.98–3.0). Mortality from cancer of the stomach was elevated among men (SMR, 1.53; 95% CI, 0.98–2.28) and increased with cumulative exposure (trend, $P = 0.039$). Mortality from cancer of the prostate was not elevated overall (SMR, 1.0; 95% CI, 0.72–1.45),

but increased with cumulative exposure (trend, $P < 0.001$). Mortality from intestinal cancer was elevated among women (SMR, 1.31; 95% CI, 1.02–1.66), especially in categories with higher cumulative exposure, but did not show a clear trend.

[The NIOSH studies were originally reported in multiple, overlapping publications based on several plants, but were subsequently merged into a single cohort. The Working Group regarded the quality of the NIOSH studies as high, and noted that they represented considerable effort to enumerate, expand and update the cohorts and assess exposure using objective job-exposure matrices.]

In addition to the NIOSH studies, separate analyses were conducted independently for the New York plant (Kimbrough *et al.*, 1999, 2003). These studies, which used duration of employment and whether hourly or salaried as surrogates for exposure, reported on virtually the same workers as in the NIOSH New York subcohort (mortality until 1998, employed at least 90 days, 7075 workers versus the 6941 studied by NIOSH), but found no significant excess mortality for any cancers (Kimbrough *et al.*, 1999, 2003). [The Working Group noted that the analyses by Kimbrough included 134 more workers than did Prince et al. but was not able to determine the reason for the discrepancy. In addition, Kimbrough et al. presented results only in subgroups defined by sex and pay grade, limiting the power of the analyses.]

The NIOSH study of cancer of the breast (Silver *et al.*, 2009) included 5752 women employed for at least 1 year in any one of the three capacitor-manufacturing facilities studied previously by NIOSH. Exposure to PCBs was estimated semiquantitatively using job-exposure matrices and information about incident cancer of the breast, parity, age at first live birth, breast cancer in a first-degree female relative, hormone use, and smoking was used in analyses for 3952 women who completed questionnaires. Cancer registries and death certificates up to 1998 were used to identify 281 incident cases. The overall standardized incidence ratio (SIR) for cancer of the breast was 0.8 (95% CI, 0.7–0.9), with little effect of employment duration or cumulative exposure. However, for the 282 women of race identified by questionnaire as "other than white," there was a positive, statistically significant association with cumulative exposure, with a hazard ratio for cancer of the breast of 1.3 (95% CI, 1.1–1.6) per 1000 unit-years of estimated cumulative exposure, while no association was observed in "white" women.

2.1.2 Transformer manufacture and repair

Studies of cancer mortality and incidence among workers exposed to PCBs in the manufacture or repair of transformers have been conducted in Canada (Yassi *et al.*, 1994, 2003), Italy (Caironi *et al.*, 2005), and the USA (Greenland *et al.*, 1994; Table 2.2).

Cancer mortality among a subset of deceased former workers at a transformer-manufacturing plant in Massachusetts, USA, was evaluated for (ever having had) exposure to PCBs (Pyranol) (Greenland *et al.*, 1994). There were positive associations with cancer of the liver and biliary tract (odds ratio, OR, 2.4; 95% CI, 0.6–9.7) and lymphoma (OR, 3.3; 95% CI, 1.1–9.3). In an analysis adjusted for age at death, year of death, and year of hire, the adjusted odds ratio was 2.2 (95% CI, 0.8–6.5) for cancer of the liver and biliary tract and 1.5 (95% CI, 0.55–4.3) for lymphoma. [The Working Group noted that numbers of deaths by site associated with exposure to PCBs were not reported, and job histories were unavailable for 34% of the study population.]

Cancer incidence and mortality until 1995 were studied in a cohort of 2222 men working between 1946 and 1975 at a transformer-manufacturing plant in Manitoba, Canada, where PCBs (Askarels) were used from 1956 to fill large transformers (mineral oils were used in other

Table 2.2 Cohort studies in transformer-manufacturing and transformer-repair workers

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Greenland *et al.* (1994), Massachusetts, USA, 1969–1984	1821 deceased white male workers, aged 21–90 yr, vested in company pension plan	Expert assessment	Oral cavity, larynx, pharynx	Pyranol exposure, ever	NR	OR, 1.1 (0.4–3.4)	Age at death, yr of hire, yr of death. Job history unavailable for 34% of deceased former workers; non-white men and women excluded; workers with > 50% work history unrated for PCBs excluded; deceased < 1969 or not vested (10–15 yr work) excluded. No. of exposed deaths, NR. Pyranol contained about 50% PCB. Other exposures included solvents, machining fluids, asbestos, resins
			Oesophagus		NR	OR, 0.9 (0.2–4.1)	
			Stomach		NR	OR, 0.9 (0.3–3.1)	
			Colon excluding rectum		NR	OR, 0.6 (0.3–1.4)	
			Rectum		NR	OR, 0.9 (0.3–2.3)	
			Pancreas		NR	OR, 1.1 (0.4–2.6)	
			Biliary passages, liver, and gallbladder		NR	OR, 2.4 (0.6–9.7)	
				Pyranol exposure at 97th percentile of control exposure	NR	OR, 2.2 (0.8–6.5)	
			Trachea, bronchus, & lung	Pyranol exposure, ever	NR	OR, 1.0 (0.6–1.6)	
			Prostate		NR	OR, 0.8 (0.4–1.7)	
			Bladder		NR	OR, 0.5 (0.1–2.3)	
			Kidney		NR	OR, 0.4 (0.1–3.4)	
			Lymphoma (200–203)	Pyranol exposure at 97th percentile of control exposure	NR	OR, 3.3 (1.1–9.3)	
					NR	OR, 1.5 (0.6–4.3)	
			Leukaemia (204–208)	Pyranol exposure, ever	NR	OR, 0.5 (0.1–2.1)	
			Brain		NR	OR, 1.1 (0.3–3.9)	

Table 2.2 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Yassi *et al.*(1994, 2003), Manitoba, Canada, 1946–1995; 1950–1995 (mortality); 1969–1995 (cancer incidence)	2222 men			Employment:			
			All cancers	> 1 mo	NR	SMR, 1.2 (1.0–1.5)	13% excluded from original mortality study because of missing identifiers. Total of 261 deaths in cohort until 1995
				> 6 mo	NR	SMR, 1.2 (0.9–1.6)	Total of 104 deaths in subcohort until 1995
				Transformer assembly	NR	SMR, 1.6 (0.9–2.8)	Total of 31 deaths in transformer-assembly department until 1995
			Digestive organs (150–159)	> 1 mo	NR	SMR, 1.3 (0.9–1.9)	
				> 6 mo	NR	SMR, 1.3 (0.6–2.3)	
				Transformer assembly	NR	SMR, 2.7 (1.0–5.9)	
			Stomach	> 1 mo	NR	SMR, 0.8 (0.2–2.3)	
				> 6 mo	NR	SMR, 1.8 (0.4–5.2)	
				Transformer assembly	NR	SMR, 5.1 (9.6–18)	
			Pancreas	> 1 mo	NR	SMR, 3.6 (1.9–6.1)	
				> 6 mo	NR	SMR, 4.8 (2.1–9.5)	
				Transformer assembly	NR	SMR, 7.5 (1.5–2.2)	
			Melanoma	> 6 mo	8	SMR, 1.8 (0.2–6.4)	
			All cancers	> 1 mo	NR	SIR, 1.2 (1.0–1.4)	Total diagnoses, 168
				> 6 mo	NR	SIR, 1.0 (0.8–1.3)	Total diagnoses, 65
				Transformer assembly	NR	SIR, 1.1 (0.6–1.7)	Total diagnoses, 18
			Digestive organs (150–159)	> 1 mo	NR	SIR, 1.4 (1.1–1.9)	
				> 6 mo	NR	SIR, 1.1 (0.6–1.8)	
				Transformer assembly	NR	SIR, 1.6 (0.6–3.4)	
			Stomach	> 1 mo	NR	SIR, 1.3 (0.5–2.7)	
				> 6 mo	NR	SIR, 0.4 (0.0–2.4)	
				Transformer assembly	NR	SIR, 1.7 (0.0–9.5)	

Table 2.2 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Yassi et al.(1994, 2003), (cont.)			Pancreas	> 1 mo	NR	SIR, 2.7 (1.3–4.9)	
				> 6 mo	NR	SIR, 4.3 (1.7–8.8)	
				Transformer assembly	NR	SIR, 7.2 (1.5–21.1)	
			Gall bladder	> 1 mo	NR	SIR, 5.1 (1.4–13)	
				> 6 mo	NR	SIR, 2.9 (0.0–16)	
				Transformer assembly	NR	0	
			Melanoma	> 1 mo	10	SIR, 2.2 (1.1–4.0)	
Caironi *et al.* (2005), Bergamo, Italy, 1950–early 1990s; 1950–2002	471 (372 men, 99 women)		Stomach	All exposed	7	SMR, 1.6 (0.6–2.5)	No. of deaths, but not SMRs reported for other cancers (oral cavity, 4; oesophagus, 1; pancreas, 1; larynx, 2; lung, 18; breast, 3; prostate, 3; bladder, 2; lymphoma, 3; other cancers, 4)
			Intestine excluding rectum (153–4, 159)	All exposed	11	SMR, 2.6 (1.6–3.5)	
			Liver	All exposed	3	SMR, 0.3 (0.0–1.1)	
			Leukaemia (204–208)	All exposed	2	SMR, 1.8 (0.0–3.6)	

HR, hazard ratio; JEM, job-exposure matrix; mo, month; NHL, non-Hodgkin lymphoma; NR, not reported; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio

transformers) (Yassi *et al.*, 2003). The mortality study showed an increased risk of mortality for cancer of the digestive tract, particularly cancers of the stomach and pancreas, among workers in the transformer-assembly department. The incidence study included ten cases of malignant melanoma in the full cohort (SIR, 2.2; 95% CI, 1.1–4.0). Increased risk of cancers of the gall bladder and pancreas was also observed among all workers, and an excess of cancer of the pancreas was reported among workers in the transformer-assembly department (SIR, 7.2; 95% CI, 1.5–21.1) (Yassi *et al.*, 2003). [The Working Group noted that the authors did not assess individual exposure to PCBs, which makes it difficult to attribute effects specifically to PCBs.]

In a study in Bergamo, Italy, among 471 workers who built transformers between 1950 and 1988, using PCBs until 1980 and mineral oils thereafter, and who repaired transformers from 1988 until the early 1990s, mortality from cancer of the intestine was significantly elevated (SMR, 2.6; 95% CI, 1.6–3.5; 11 deaths), but mortality from cancer of the stomach or liver, or leukaemia, was not (Caironi *et al.*, 2005). [This was a small study, but it focused on transformer-repair workers who would have had substantial dermal exposure to PCBs.]

2.1.3 Electric power and telecommunications

Studies of cancer mortality and incidence among workers exposed to PCBs in the electric-power and telecommunications industries have been conducted in Canada (De Guire *et al.*, 1988; Hay & Tarrel, 1997), Italy (Cammarano *et al.*, 1984, 1986), Norway (Tynes *et al.*, 1994), and the USA (Savitz & Loomis, 1995; Loomis *et al.*, 1997; Charles *et al.*, 2003; Table 2.3).

De Guire and coworkers found increased incidence of and mortality from malignant melanoma among 9590 employees of a telecommunications company in Montreal, Canada, who had been employed for 6 months or more between 1976 and 1983 (De Guire *et al.*, 1988, 1992). Three deaths were identified among men (SMR, 3.0; 95% CI, 0.6–8.8), with a stronger association for those with < 20 years latency (SMR, 9.4; 95% CI, 1.1–34; two deaths) than for those with ≥ 20 years latency (one death; SMR, 1.3; 95% CI, 0.0–7.1). Only one case occurred among women (SMR, 4.8; 95% CI, 0.1–27). [This was a reasonably large cohort, but the number of incident cases was small. Exposure to PCBs may have occurred, but was not assessed.]

Cancer incidence among 5088 workers in the hydroelectric-power industry in Norway employed for at least 1 year between 1920 and 1991 was examined in relation to magnetic fields or electric sparks, and to exposure to PCBs (Tynes *et al.*, 1994). Workers were classified as ever or never exposed to PCBs, based on work histories. The incidence of malignant melanoma was increased in the full cohort (SIR, 1.1; 95% CI, 0.7–1.8) and among power-supply electricians (SIR, 2.1; [95% CI, 1.0–3.7]). Significantly increased incidence was also reported among workers ever exposed to PCBs and to > 15 μT-years of magnetic fields (SIR, 2.7; [95% CI, 1.2–5.2]). [This study investigated exposure to PCBs and to electric and magnetic fields. Exposures to PCBs and to electric and magnetic fields may be correlated through associations with certain jobs, but exposure is unlikely to confound the association with PCBs, as such exposure is not known to be associated with melanoma.]

Loomis and colleagues assessed risk of cancer in relation to PCB exposure among 138 905 male employees of five utility companies in California, North Carolina, Pennsylvania, Tennessee, and Virginia, USA, who were employed for at least 6 months between 1950 and 1986 (Savitz & Loomis, 1995; Loomis *et al.*, 1997). Exposures were assessed jointly by representatives of employees and management and by industrial hygienists. Mortality from melanoma increased with increasing exposure to PCBs, from 1.2 (95% CI, 0.6–2.5) for those with < 2000 hours cumulative

Table 2.3 Cohort studies in electric-power and telecommunications workers

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
De Guire *et al.* (1988, 1992), Montreal, Canada, 1976–1983	9590	Working on 1 January 1976 or up to 31 December 1963, ≥ 6 mo employment. Exposed to polyvinyl chloride, soldering fumes, and PCBs	All cancers	Men	67	SMR, 0.6 (0.5–0.7)	
			Oral cavity, larynx, pharynx	Men	1	SMR, 0.2 (0.0–1.0)	
				Women	17	SMR, 0.9 (0.5–1.4)	
			Digestive organs (150–159)	Men	22	SMR, 0.7 (0.4–1-1)	
				Women	5	SMR, 1.2 (0.4–2.9)	
			Trachea, bronchus, lung	Men	26	SMR, 0.6 (0.4–0.8)	
				Women	4	SMR, 1.5 (0.4–4.0)	
			Melanoma	Men	3	SMR, 3.0 (0.6–8.8)	
				Women	1	SMR, 4.8 (0.1–27)	
				Men, < 20 yr latency	2	SMR, 9.4 (1.1–34)	
				Men, ≥ 20 yr latency	1	SMR, 1.3 (0.0–7.1)	
				Women, < 20 yr latency	1	SMR, 12.1 (0.0–67)	
			Eye, brain	Men	2	SMR, 0.5 (0.1–1.7)	
			Lymphatic and haematopoietic (200–208)	Men	7	SMR, 0.7 (0.3–1.5)	
			Bone, breast (170–171, 173–178)	Women	5	SMR, 0.9 (0.3–2.0)	
Tynes *et al.* (1994), Norway, 1920–1991; 1953–1991	5088 men	Worked ≥ 1 yr at any of eight hydroelectric-power companies	Rectum	Employment ≥ 1 yr	27	SIR, 1.1 (0.7–1.6)	
			Lung		68	SIR, 1.1 (0.9–1.4)	
			Breast		1	SIR, 1.1 (0.0–76)	
			Prostate		90	SIR, 1.1 (0.9–1.3)	
			Bladder		27	SIR, 0.8 (0.5–1.2)	
			Melanoma		19	SIR, 1.1 (0.7–1.8)	
			Brain		13	SIR, 0.9 (0.5–1.5)	
			Lymphoma		12	SIR, 0.7 (0.4–1.2)	
			Leukaemia		11	SIR, 0.9 (0.5–1.6)	
			Melanoma	Ever exposed to PCBs	9	SIR, 1.8 [0.8–3.4]	Incidence of other cancers not analysed in association with PCB exposure
				Ever exposed to PCBs, 0–15 μT-yr	0		
				Ever exposed to PCBs, > 15 μT-yr	9	SIR, 2.7 [1.2–5.2]	

Table 2.3 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Loomis *et al.* (1997), California, North Carolina, Pennsylvania, Tennessee, Virginia, USA, 1950–1988	138 905 men	Employed > 6 mo, 1950–1986, exposures assessed by panels of workers, hygienists, managers; calculated cumulative exposure to insulating fluids containing PCBs	All cancers	Potential PCB exposure:			Age, calendar time, race, social class, active work status.
				> 0 to < 5 year	916	RR, 2.2 (0.9–1.2)	
				5 to < 10 year	454	RR, 1.0 (0.9–1.2)	
				10 to < 20 year	601	RR, 1.1 (1.0–1.2)	
				≥ 20 year	656	RR, 1.1 (1.0–1.2)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0–2000	2605	RR, 1.0 (1.0–1.1)	
				> 2000–10 000	331	RR, 1.2 (1.1–1.3)	
				> 10 000	81	RR, 1.0 (0.8–1.3)	
			Brain	Potential PCB exposure:			Age, calendar time, race, social class, active work status, magnetic fields, solvents
				0 to < 5 yr	32	RR, 1.3 (0.8–2.2)	
				5 to < 10 yr	15	RR, 1.4 (0.7–2.6)	
				10 to < 20 yr	17	RR, 1.3 (0.7–2.4)	
				≥ 20 yr	12	RR, 1.1 (0.6–2.2)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0–2000	66	RR, 1.0 (0.7–1.6)	
				> 2000–10 000	5	RR, 0.7 (0.3–1.9)	
				> 10 000	0	RR, 0.0 (0.0–2.6)	
			Liver (155)	Potential PCB exposure:			Age, calendar time, race, social class, active work status, solvents
				0 to < 5 yr	13	RR, 1.1 (0.5–2.3)	
				5 to < 10 yr	5	RR, 0.8 (0.3–2.2)	
				10 to < 20 yr	13	RR, 1.8 (0.9–3.6)	
				≥ 20 yr	5	RR, 0.7 (0.3–1.9)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0 to 2000	29	RR, 0.5 (0.3–0.5)	
				> 2000–10 000	3	RR, 0.4 (0.1–1.4)	
				> 10 000	1	RR, 0.4 (0.1–3.0)	

Table 2.3 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Loomis et al. (1997), (cont.)			Melanoma	Potential PCB exposure:			Age, calendar time, race, social class, active work status, occupational sunlight, wood preservatives
				0 to < 5 yr	25	RR, 1.3 (0.6–2.6)	
				5 to < 10 yr	9	RR, 1.1 (0.5–2.7)	
				10 to < 20 yr	11	RR, 1.4 (0.6–3.3)	
				≥ 20 yr	8	RR, 1.6 (0.6–4.2)	
				Cumulative PCB exposure (h), 0-yr lag:			
				> 0–2000	73	RR, 1.2 (0.6–2.5)	
				> 2000–10 000	12	RR, 1.7 (0.7–7.1)	
				> 10 000	3	RR, 1.9 (0.5–7.1)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0 to 2000	42	RR, 1.3 (0.8–2.2)	
				> 2000–10 000	8	RR, 2.6 (1.1–6.0)	
				> 10 000	1	RR, 4.8 (1.5–15)	
				RR per 2000 h cumulative PCB exposure (continuous variable):			
				0-yr lag	-	RR, 1.02 (0.99–1.05)	
				20-yr lag	-	RR, 1.05 (1.01–1.09)	
Charles et al. (2003), California, North Carolina, Pennsylvania, Tennessee, Virginia, USA, 1950–1988	387 cases of prostate cancer and 1935 controls matched on age at risk	See Loomis et al. (1997)	Prostate (185)	Cumulative PCB exposure (h):			Age-matched and adjusted for race Same cohort studied by Loomis et al. (1997)
				< 1.9	94	OR, 1.0	
				1.9 to < 12.6	85	OR, 0.9 (0.6–1.2)	
				12.6 to < 620.1	105	OR, 1.1 (0.8–1.5)	
				620.1 to < 2821.4	55	OR, 0.8 (0.6–1.2)	
				≥ 2821.4	48	OR, 1.2 (0.8–1.7)	

Table 2.3 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Charles et al. (2003) (cont.)				Cumulative PCB exposure (h), 5-yr lag:			
				< 1.6	91	OR, 1.0	
				1.6 to < 12.1	87	OR, 0.9 (0.6–1.2)	
				12.1 to < 597.9	104	OR, 1.1 (0.8–1.5)	
				597.9 to < 2763.2	58	OR, 0.9 (0.6–1.3)	
				≥ 2763.2	47	OR, 1.1 (0.8–1.7)	
				Cumulative PCB exposure ≥ 2763.2 h and EMF ≥ 4.4 μT-yr	35	OR, 1.5 (1.0–2.2)	Equivalent results for total cumulative exposure
Hay & Tarrel (1997), New Brunswick, Canada, 1950–1966; 1950–1992	225 men		All cancers	First sprayed 1950–1958	18	SMR, 1.5 (0.9–2.3)	Sprayed vegetation under power lines with 2,4-D and 2,4,5-T; 1958–66, waste transformer oil with PCBs added to herbicides
				First sprayed 1959–1966	3	SMR, 1.1 (0.2–3.2)	
Cammarano *et al.* (1984, 1986), Milano, Italy, 1960–1969; 1969–1985	270 men	Working on 1 January 1960 or up to 31 December 1969, ≥ 6 mo employment		Exposure:			Exposed to PAHs, asbestos, hydrazine, chromium, nickel, beryllium, and PCBs SMRs from Cammarano *et al.* (1986) All other cancer sites had one or zero death
			All cancers	≥ 10 yr	18	[SMR, 2.2 (1.3–3.4)]	
			Stomach	≥ 10 yr	3	[SMR, 3.0 (0.6–8.7)]	
			Trachea, bronchus, lung	≥ 10 yr	5	[SMR, 1.8 (0.6–4.1)]	
			Bladder	≥ 10 yr	2	[SMR, 7.4 (0.9–26)]	

EMF, electromagnetic fields; mo, month; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; wk, week; yr, year

exposure to PCBs, to 1.7 (95% CI, 0.7–7.1) among those with 2000–10 000 hours cumulative exposure, to 1.9 (95% CI, 0.5–7.1) for those with > 10 000 hours of cumulative exposure over their career. When exposure was lagged by 20 years, the respective relative risks were 1.3 (95% CI, 0.8–2.2), 2.6 (95% CI, 1.1–6.0), and 4.8 (95% CI, 1.5–15.0). When the risk of melanoma was modelled with a continuous variable for cumulative exposure to PCBs, the relative risk per 2000 hours of exposure was 1.05 (95% CI, 1.01–1.09) with a 20-year lag. There was no association with cancer of the liver, and the association with cancer of the brain was less strong: the relative risk was 1.6 (95% CI, 0.9–3.0) among those with < 2000 hours cumulative exposure and 1.8 (95% CI, 0.8–4.0) among those with 2000–10 000 hours cumulative exposure, but there were no deaths from cancer of the brain among those with > 10 000 hours cumulative exposure (Loomis *et al.*, 1997).

A nested case–control study within this utility-worker cohort investigated mortality from cancer of the prostate relative to exposure to electromagnetic fields and PCBs (Charles *et al.*, 2003). Cases were 387 prostate-cancer decedents; 1935 controls (5 per case) were randomly selected from the risk sets of the cases. The odds ratio for cumulative exposure to PCBs for ≥ 2821.4 hours and mortality from cancer of the prostate, adjusted for age and race, was 1.2 (95% CI, 0.8–1.7). For workers with ≥ 2763.2 hours of exposure to PCBs and ≥ 4.4 μT years of exposure to magnetic fields, the adjusted odds ratio was 1.5 (95% CI, 1.0–2.2).

[The Working Group considered that, because of the size of the cohort and the efforts to assess exposure, the Loomis–Charles studies were the strongest in this group, especially the results showing an exposure–response effect. The lagged analysis of melanoma mortality was informative about exposure-time windows.]

Some information about cancer risk among electrical workers with exposure to PCBs was reported in two smaller studies. Hay & Tarrel (1997) investigated mortality in 1958–1991 among power-company workers in Canada who applied mixtures of the pesticides 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and waste transformer oil that contained up to 10% PCBs. All-cancer mortality was increased among workers who first sprayed in 1958 or earlier (SMR, 1.5; 95% CI, 0.9–2.3; 18 deaths), but not among those first exposed in 1959 or later, when used transformer oil was added to the pesticide mix (SMR, 1.1; 95% CI, 0.2–3.2; three deaths). [The Working Group noted that the results were not presented by cancer site and concluded that exposures to PCBs were likely to have been negligible.]

Mortality until 1985 was investigated among 270 men who had worked for at least 6 months in a thermoelectric power plant in Italy and who were exposed to PCBs, chromium, nickel, beryllium, polycyclic aromatic hydrocarbons (PAHs), asbestos, and hydrazine (Cammarano *et al.*, 1984, 1986). Among workers with > 10 years exposure, 18 cancer deaths occurred [SMR, 2.2; 95% CI, 1.3–3.4] (Cammarano *et al.*, 1986). [The Working Group noted that workers were exposed to several human carcinogens and that the study was very small, with only one death for most cancer sites, making it difficult to interpret site-specific mortality.]

2.1.4 Miscellaneous industries

As PCBs have been used in many applications, workers in many industries have been exposed, and as structures and equipment that contain PCBs are repaired, demolished, or replaced, workers involved in these operations and/or in waste recycling and disposal may be exposed. There have been many reports of PCB exposure levels and existing or potential health effects associated with exposure to materials containing PCBs, but studies of cancer are very limited.

Robinson *et al.* (1999) conducted a proportionate mortality study of 31 068 deceased,

unionized, electrical workers employed in the construction industry, who might have been exposed to PCBs (and other agents) during their working lives. Excess mortality occurred for melanoma (proportionate mortality ratio, PMR, 1.23; 95% CI, 1.02–1.47) and cancer of the prostate (PMR, 1.07; 95% CI, 1.00–1.14). [Although this very large death-certificate study found an excess risk for cancers that have been associated with exposure to PCBs in other PCB-exposed cohorts, exposure in this cohort could not be confirmed.]

Unspecified industrial uses of PCBs have been associated with an increased risk of cancer. Bahn and colleagues reported two cases of malignant melanoma among 31 workers in research and development and refinery industries in New Jersey, USA, who were exposed to PCB mixtures, where 0.04 cases would be expected [SIR, 50.0; 95% CI, 5.6–217] (Bahn *et al.*, 1976).

2.2 Cohort studies of environmental exposure

2.2.1 Accidental exposure to PCBs

(a) Cancer mortality in Yusho patients, Japan

The first evaluation by IARC of the possible carcinogenic risk of human exposure to PCBs reported the accidental exposure to PCBs through ingestion of rice oil contaminated by Kanechlor 400 in 1968 in western Japan (see Section 1). In an early analysis of deaths occurring up to 5.5 years after exposure among 1200 Yusho patients, nine deaths from malignant neoplasms were reported, including three tumours of the stomach, two tumours of the lung, one cancer of the liver, one of the breast, and two lymphomas (Urabe, 1974; Kuratsune, 1976). A first update considered mortality among 1761 Yusho patients followed up until 1983 (Kuratsune *et al.*, 1988). Among men, there was a statistically significant increase in mortality from all neoplasms (SMR, 2.13; 95% CI, 1.5–3.0), and particularly cancer of the liver (SMR, 5.6; 95% CI, 2.6–10.7), and lung (SMR, 3.2; 95% CI, 1.4–6.3). No statistically significant increase in tumours was reported among the women.

After these early reports, two other mortality analyses of this cohort have been published with follow-up periods up to 1990 and up to 2007 respectively (see Table 2.4). The first report (Ikeda & Yoshimura, 1996) analysed the mortality of 1815 patients (916 men and 899 women), with an average follow-up of 17 years. In the 40-year follow-up of the total of 1918 patients registered as of 31 December 2007 (Onozuka *et al.*, 2009), 254 cases who had not been diagnosed as Yusho from the beginning of the incident were excluded, leaving 1664 cases for analysis (860 men and 804 women). Of the 269 deaths among men, there was a significant excess mortality from all cancers (SMR, 1.37; 95% CI, 1.11–1.66), and from cancers of the lung (SMR, 1.75; 95% CI, 1.14–2.57) and liver (SMR, 1.82; 95% CI, 1.06–2.91). For women, mortality for cancer of the liver was in excess, although not significantly so (SMR, 1.95; 95% CI, 0.78–4.01). Analysis of different periods since the incident showed that the increased risk for all malignancies, and for cancers of the lung and liver tended to decrease over time.

A more recent analysis that did not exclude the 254 patients diagnosed after 1977 (Yoshimura, 2012) reported essentially the same pattern of mortality, with slightly weaker standardized mortality ratios for cancers of the lung and liver (Table 2.4).

Finally, another analysis of mortality of Yusho patients followed up until 2007 was restricted to the area of Tamamoura in the Goto Archipelago (Nagasaki prefecture), because it was the most severely affected (Kashima *et al.*, 2011). Standardized mortality ratios for all cancers, lung cancer, and liver cancer were estimated using the rates of Nagasaki prefecture as the reference and compared for the years 1968–77 and 1978–2002. A slight excess cancer of the

Table 2.4 Cohort studies of cancer associated with poisoning from rice oil contaminated with PCBs in Japan and Taiwan, China

Reference, location follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases/ deaths	SMR (95% CI)	Covariates Comments
Yusho patients							
Onozuka *et al.* (2009) Fukuoka and Nagasaki, Japan 1968–2007	1664 Yusho patients	Mass poisoning by contaminated rice oil		Overall, compared with national death rates	100 men, 33 women		Age, sex Total number of Yusho patients was 1918, but 254 subjects registered after 1977 (not diagnosed as Yusho from the beginning of the incident) were excluded in this analysis
		Men	All cancers		100	1.37 (1.11–1.66)	
			Liver		17	1.82 (1.06–2.91)	
			Lung		26	1.75 (1.14–2.57)	
			Stomach		20	1.17 (0.72–1.81)	
			Rectum		2	0.65 (0.08–2.36)	
			Pancreas		6	1.49 (0.55–3.24)	
			Leukaemia		2	1.19 (0.14–4.29)	
		Women	All cancers		33	0.75 (0.51–1.05)	
			Liver		7	1.95 (0.78–4.01)	
			Lung		4	0.82 (0.22–2.11)	
			Stomach		2	0.22 (0.03–0.81)	
			Rectum		1	0.56 (0.01–3.10)	
			Pancreas		3	1.02 (0.21–2.98)	
			Leukaemia (204–206)		0	0.00 (0.00–3.25)	
			Breast		3	0.93 (0.19–2.72)	
			Uterus		3	1.14 (0.24–3.33)	
Yoshimura (2012) Fukuoka and Nagasaki, Japan 1968–2007	1918 Yusho patients	Mass poisoning by contaminated rice oil		Overall, compared with national death rates			Age, sex As for Onozuka *et al.* (2009), including the 254 subjects registered after 1977
		Men	All cancers		106	1.26 (1.03–1.53)	
			Liver		18	1.67 (0.99–2.63)	
			Lung		27	1.56 (1.03–2.27)	
			Stomach		21	1.09 (0.68–1.67)	
		Women	All cancers		46	0.89 (0.65–1.17)	
			Liver		8	1.87 (0.81–3.69)	
			Lung		5	0.86 (0.28–2.01)	
			Stomach		4	0.39 (0.11–0.99)	

Table 2.4 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases/ deaths	SMR (95% CI)	Covariates Comments
Kashima *et al.* (2011) Fukuoka and Nagasaki, Japan 1968–2002	533 Yusho patients from Tamamoura area	Mass poisoning by contaminated rice oil		Rates from Tamamoura, compared with Nagasaki prefecture	329 (total)		Age, sex As for Onozuka *et al.* (2009) for both sexes combined, using different reference population; Tamanoura was the most affected area Liver cancer was not mentioned in the analysis of the period 1968–77
		1968–77	All cancers		86	1.13 (0.92–1.40)	
			Lung		11	1.37 (0.76–2.48)	
		1978–2002	All cancers		243	1.03 (0.91–1.17)	
			Liver		21	0.77 (0.50–1.18)	
			Lung		37	0.87 (0.63–1.20)	
Yucheng patients							
Tsai *et al.* (2007) Three counties in central Taiwan, China 1980–2003	1823 Yucheng patients	Mass poisoning by contaminated rice oil		Overall, compared with national death rates	215 deaths (129 men, 86 women)		Age, sex There was also a significant association for mortality by chronic liver disease and cirrhosis (ICD-9 571)
		Men (n = 841)	All cancers		29	0.9 (0.6–1.3)	
			Nasopharynx		3	2.3 (0.5–6.8)	
			Liver & intrahepatic bile ducts		4	0.5 (0.1–1.2)	
			Lung		7	1.1 (0.4–2.2)	
			Lymphatic & haematopoietic (200–208)		4	2.3 (0.6–6.0)	
		Women (n = 987)	All cancers		12	0.7 (0.3–1.1)	
			Nasopharynx		0	–	
			Liver & intrahepatic bile ducts		4	1.6 (0.4–4.1)	
			Lung		1	0.3 (0.0–1.9)	
			Lymphatic & haematopoietic		0	–	
		Both sexes	All cancers		41	0.8 (0.6–1.1)	
			Nasopharynx		3	1.6 (0.3–4.7)	
			Liver & intrahepatic bile ducts		8	0.7 (0.3–1.4)	
			Lung		8	0.8 (0.4–1.6)	
			Lymphatic & haematopoietic (200–208)		4	1.3 (0.4–3.4)	

Table 2.4 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases/ deaths	SMR (95% CI)	Covariates Comments
Li *et al.* (2013) Three counties in central Taiwan, China 1980–2008	1803 Yucheng patients and 5170 referents (neighbours)	Mass poisoning by contaminated rice oil		Overall, compared with neighbourhood referents	295 deaths (178 men, 117 women)		Age, sex, community Significant association for mortality from chronic liver disease and cirrhosis (ICD-9 571)
		Men (n = 830)	All neoplasms (148–239)		46	1.3 (0.9–1.7)	
			Liver & intrahepatic bile ducts (155)		4	0.4 (0.1–1.1)	
			Trachea, bronchus & lung (162)		10	1.5 (0.8–2.7)	
			Stomach (151)		7	3.5 (1.5–7.0)	
			Lymphatic & haematopoietic (200–208)		5	3.0 (1.1–6.6)	
			Thyroid gland (193)		0	–	
		Women (n = 973)	All neoplasms (148–239)		21	0.8 (0.5–1.2)	
			Liver & intrahepatic bile ducts (155)		6	2.1 (0.9–4.5)	
			Trachea, bronchus & lung (162)		1	0.4 (0.0–1.7)	
			Stomach (151)		1	0.5 (0.0–2.5)	
			Lymphatic & haematopoietic (200–208)		0	–	
			Thyroid gland (193)		2	2.0 (0.3–6.7)	
			Breast, female (174)		4	1.1 (0.4–2.7)	
		Both sexes	All neoplasms (148–239)		67	1.1 (0.8–1.4)	
			Liver & intrahepatic bile ducts (155)		10	0.9 (0.4–1.5)	
			Trachea, bronchus & lung (162)		11	1.1 (0.6–1.9)	
			Stomach (151)		8	2.0 (0.9–3.8)	
			Lymphatic & haematopoietic (200–208)		5	1.5 (0.6–3.4)	
			Thyroid gland (193)		2	2.2 (0.4–7.2)	

PCB, polychlorinated biphenyl; SMR, standardized mortality ratio

lung was observed in Tamamoura in 1968–77 (SMR, 1.37; 95% CI, 0.76–2.48) [data for cancer of the liver not reported for that period] and no increase in mortality was seen during the later period (Table 2.4). However, significant excess mortality for all cancers, and for cancers of the lung or liver, were observed for the rest of the Goto Archipelago (excluding Tamamoura) in 1978–2002.

[The Working Group noted that excess cancer mortality was largely restricted to men. In addition the excesses of cancers of the lung and liver were observed in the full population of Yusho patients in analyses using national references rates, but not in the subset from the Tamamoura area analysed using local reference rates. Important confounders such as tobacco smoking for cancer of the lung, or viral hepatitis for cancer of the liver could not be taken into account directly, although they may have been partially controlled for by using local reference rates, if the distribution of such confounders in the local reference population were similar to that of the study population. Yusho patients were also exposed to PCDFs. The possibility of confounding by other exposures therefore could not be completely ruled out.]

(b) Cancer mortality in Yucheng patients, Taiwan, China

In 1979, about 10 years after the incident in western Japan, a similar food poisoning incident occurred in three counties (Taichung, Changhua, and Miaoli) of central Taiwan, China (see Section 1). About 2000 residents from these counties had ingested rice oil contaminated with PCBs, and showed clinical manifestations similar to those described for Yusho (skin eruptions and pigmentation, ocular hypersecretion, and peripheral neuropathy); the syndrome was named 'Yucheng' ('oil disease' in Chinese) (see Section 4). Two mortality analyses have been carried out on this exposed cohort, after 12 and 24 years of follow-up, and are summarized in Table 2.4. The first study cohort was based upon 2038 cases registered until 1979; after excluding 99 cases for which vital status could not be assessed, 1940 [sic] Yucheng patients (929 men, 1011 women) remained for analysis of mortality (Hsieh *et al.*, 1996). During 1980–91, 11 deaths from malignancies were observed (8 men, 3 women); overall and sex-specific mortality was non-significantly lower than among the general population, using either local or national reference rates. Data for specific tumour sites were sparse, and included one death from Hodgkin lymphoma and two deaths from cancer of the liver (one man and one woman). Another analysis of the same study population was conducted with the same follow-up (1980–91), but further exclusions, leaving 1837 patients for analysis and 10 observed deaths from cancer (Yu *et al.*, 1997). Although the standardized mortality ratio for all cancers differed substantially from that in the previous analysis, it was not significantly different from that expected based on national rates (SMR, 1.2; 95% CI, 0.6–2.3). Data for specific cancer sites were not reported. [The Working Group noticed the discrepancy between estimates of standardized mortality ratio based upon apparently very similar data sets.]

Data for updated analyses of Yucheng patients are shown in Table 2.4. Tsai *et al.* (2007) extended the follow-up to 2003. From a list of 2061 registered patients, 70 exposed in utero and 168 who could not be traced were excluded, leaving 1823 patients. Forty-one deaths by cancer were observed between 1980 and 2003. Mortality from all neoplasms was not statistically different from that in the population in Taiwan, China, overall or by sex; mortality from cancers at several sites, including liver, lung, and the lymphatic and haematopoietic system, was also similar to that of the national population. As in a previous study, mortality from chronic liver disease and cirrhosis was significantly increased. [The Working Group noted that chronic liver disease and cirrhosis are important risk factors for cancer of the liver,

together with infection with hepatitis B and C viruses, and tobacco smoking.]

A second updated analysis of Yucheng patients extended the follow-up to 2008 (Li *et al.*, 2013). As referents for comparison, the authors used subjects from the registry set up in 1979, residents of the same community, of the same sex and age (within 3 years) as the Yucheng patients, but who did not meet the criteria to be considered as Yucheng patients. After exclusions because of missing or inconsistent data, a total of 1803 Yucheng subjects and 5170 neighbourhood referents were considered for analysis; a total of 67 Yucheng patients died from cancer during 1980–2008. No significant association with all cancer mortality was found overall or among women. Among men, increased mortality was reported for cancer of the stomach (SMR, 3.5; 95% CI, 1.5–7.0, seven deaths) and neoplasms of lymphatic and haematopoietic tissue (SMR, 3.0; 95% CI, 1.1–6.6, five deaths). Mortality from cancer of the liver was elevated among women (SMR, 2.1; 95% CI, 0.9–4.5, six deaths), but not among men (SMR, 0.4; 95% CI, 0.1–1.1, four deaths). [The neighbourhood referent population used in this study may also have been exposed, which would lead to underestimation of relative risks.]

[The Working Group noted that the excess mortality from all cancers and tumours of the liver observed in Yusho patients was not present in Yucheng patients. The composition of PCDF isomers differed markedly between the two incidents: the main PCDF isomer in Yusho patients was 2,3,4,7,8-pentachlorinated dibenzofuran, which has a higher toxic equivalency factor than the main isomer affecting Yucheng patients, 1,2,3,4,7,8-hexachlorinated dibenzofuran (Onozuka *et al.*, 2009). On the other hand, no excess mortality for cancers of the stomach or lymphatic and haematopoietic tissue was observed in the Yusho patients. The same other limitations mentioned for the Yusho cohort applied to the Yucheng studies: residual confounding, or chance due to multiple comparison made in these analyses could not be discounted.]

2.2.2 Dietary exposure to PCBs

See Table 2.5

Apart from incidental contamination, chronic exposure to PCBs may occur through a diet rich in foods with a high content of PCBs; such exposure has been observed in northern Europe in populations with a high consumption of fish.

Cohorts of fishermen from the east coast and west coasts of Sweden were established in 1968 and 1965 respectively (Rylander & Hagmar, 1995; Svensson *et al.*, 1995). Women who were, or had been, married to these fishermen were identified from national and local population registries. After exclusion because of death, divorce, or emigration, the respective cohorts of fishermen's wives included 1986 women on the east coast and 6605 women on the west coast (Rylander & Hagmar, 1995). Information on vital status and cancer incidence up to 1989 was gathered from Swedish statistics and the Swedish cancer registry. Cancer incidence was compared directly between the cohorts on the east coast (contaminated) and west coast (control), with adjustment for age and calendar year. The incidence rate ratio (IRR) for all cancers was 1.19 (95% CI, 1.00–1.41). Among specific cancer sites, risk was increased for cancer of the breast (IRR, 1.35; 95% CI, 0.98–1.86), cervix (IRR, 1.93; 95% CI, 0.83–4.50) and corpus uteri (IRR, 1.16; 95% CI, 0.61–2.20). All cancer mortality was also significantly more elevated in the east-coast cohort when compared with the regional rates (SIR, 1.17; 95% CI, 1.00–1.36). Dietary information showed modest differences in consumption of fatty fish between the east and west coasts. In a recent update extending the follow-up until 2002 (Mikoczy & Rylander, 2009) expected mortality and cancer incidence were based on national

Table 2.5 Cohort studies of risk of cancer associated with high dietary intake of PCBs

Reference, location, follow-up period	Total subjects	Exposure assessment/ population	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Mikoczy & Rylander (2009) Sweden 1968–2002 (east coast) 1965–2002 (west coast)	2042 (east coast) and 6674 (west coast) fishermen's wives	Dietary intake of fatty fish from Baltic Sea (east coast)		Comparison with national rates		*SIR (95% CI)*	Age Possible coexposure to PCDDs and PCDFs
		West coast	All sites		1201	0.92 (0.87–0.98)	
			Stomach		39	0.86 (0.61–1.18)	
			Colon		103	0.97 (0.79–1.18)	
			Rectum		52	1.00 (0.75–1.31)	
			Liver, bile ducts		39	0.99 (0.70–1.36)	
			Lung		33	0.61 (0.42–0.86)	
			Breast		305	0.90 (0.81–1.01)	
			Melanoma		38	1.03 (0.73–1.41)	
			Skin		60	1.43 (1.09–1.84)	
			Brain		41	1.05 (0.75–1.42)	
			Soft tissue sarcoma		3	0.38 (0.08–1.10)	
			Lymphohaematopoietic (200–207)		75	0.92 (0.73–1.16)	
			Hodgkin lymphoma (201)		3	0.63 (0.13–1.83)	
			Multiple myeloma (203)		19	1.12 (0.68–1.76)	
			NHL (200, 202)		35	1.03 (0.71–1.43)	
		East coast	All sites (140–209)		345	1.09 (0.98–1.21)	
			Stomach		12	1.39 (0.72–2.43)	
			Colon		38	1.61 (1.14–2.21)	
			Rectum		13	1.09 (0.58–1.86)	
			Liver, bile ducts		11	1.35 (0.67–2.42)	
			Lung		12	0.83 (0.43–1.46)	
			Breast		92	1.03 (0.83–1.27)	
			Melanoma		8	0.76 (0.33–1.49)	
			Skin		9	0.95 (0.43–1.80)	
			Brain		14	1.37 (0.75–2.30)	
			Soft tissue sarcoma		1	0.51 (0.01–2.84)	
			Lymphohaematopoietic (200–207)		18	0.94 (0.56–1.48)	
			Hodgkin lymphoma (201)		1	0.93 (0.02–5.19)	
			Multiple myeloma (203)		6	1.58 (0.58–3.43)	
			NHL (200, 202)		6	0.71 (0.26–1.55)	

Table 2.5 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment/ population	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Turunen *et al.* (2008) Finland 1980–2005	4260 fishermen's wives	Dietary intake of fatty fish from Baltic Sea		Overall, compared with national death rates		*SMR (95% CI)*	Age
			All malignant neoplasms		115	0.97 (0.80–1.15)	
			Colon		10	1.30 (0.62–2.39)	
			Rectum & anus		8	2.13 (0.92–4.19)	
			Stomach		2	0.30 (0.04–1.08)	
			Breast		18	0.80 (0.47–1.25)	
			Larynx, trachea & lung		8	0.70 (0.30–1.38)	
			Lymphoid, haematopoietic, & related tissue		10	0.83 (0.40–1.53)	
Helmfrid *et al.* (2012) Gusum, Sweden 1960–2003	Residents in contaminated area (number not given)	Consumption of foods with high PCB content from contaminated local river	(ICD-7)	Overall, compared with national death rates		*SIR (95% CI)*	Age, time period Possible coexposure to metals because of industrial activities
		Men	All sites		346	0.91 (0.78–1.05)	
			Stomach		25	1.00 (0.65–1.83)	
			Colon		21	0.76 (0.46–1.16)	
			Rectum		10	0.54 (0.25–0.99)	
			Liver/bile ducts		8	0.88 (0.37–1.73)	
			Pancreas		14	1.17 (0.63–1.97)	
			Bronchus & lung		22	0.64 (0.40–0.97)	
			Breast		1	NR	
			Prostate		100	1.06 (0.86–1.29)	
			Testis		7	2.46 (0.99–5.08)	
			Malignant melanoma of skin		15	1.56 (0.87–3.94)	
			Other skin		15	0.81 (0.45–1.34)	
			Brain		3	0.31 (0.06–0.91)	
			Lymphoma (200–202)		22	1.60 (1.00–2.42)	
			Multiple myeloma (203)		7	1.25 (0.50–2.42)	
			Leukaemia (204)		5	0.88 (0.28–3.57)	
			Lymphatic & haematopoietic tissues (200–207)		38	1.20 (0.84–1.65)	

Table 2.5 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment/ population	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Helmfrid et al. (2012) Gusum, Sweden 1960–2003 (cont.)		Women	All sites		295	0.91 (0.77–1.07)	
			Stomach		15	1.11 (0.62–1.88)	
			Colon		17	0.65 (0.37–1.04)	
			Rectum		12	0.95 (0.49–1.66)	
			Liver/bile ducts		9	0.91 (0.41–1.73)	
			Pancreas		6	0.62 (0.22–1.34)	
			Bronchus & lung		6	0.49 (0.18–1.08)	
			Breast		80	0.97 (0.77–1.21)	
			Malignant melanoma of skin		11	1.22 (0.60–2.19)	
			Other skin		7	0.70 (0.28–1.44)	
			Brain		13	1.37 (0.72–2.34)	
			Lymphoma (200–202)		8	0.82 (0.35–1.63)	
			Multiple myeloma (203)		2	0.49 (0.05–1.77)	
			Leukaemia (204)		4	1.25 (0.34–3.21)	
			Lymphatic & haematopoietic tissues (200–207)				
Tomasallo *et al.* (2010) Great Lakes area, USA 1995–2006	3757 subjects (2275 fish consumers, 1482 non-consumers)	Dietary intake of Great Lakes sport fish				*SMR (95% CI)*	
			All cancers	Fish consumers	83	0.92 (0.74–1.13)	
			Pancreas		6	1.24 (0.45–2.44)	
			Brain		5	1.91 (0.60–3.96)	
			Breast, ovary, & uterus		6	1.47 (0.46–3.04)	
			All cancers	Non-consumers	47	0.87 (0.64–1.13)	
			Pancreas		2	0.72 (0.07–2.07)	
			Brain		1	0.70 (0.0–2.76)	
			Breast, ovary, & uterus		1	0.44 (0.0–1.73)	

NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; SIR, standardized incidence ratio; SMR, standardized mortality ratio

rates, and no direct comparison between east- and west-coast cohorts were reported. Standardized mortality ratios for all cancers combined were 0.98 (0.91–1.06) for the west-coast cohort and 1.15 (95% CI, 0.98–1.34) for the east-coast cohort. Statistically significant excess incidence was reported for cancer of the colon in the east-coast cohort (SIR, 1.61; 95% CI, 1.14–2.21) and non-melanoma cancer of the skin in the west-coast cohort (SIR, 1.43; 95% CI, 1.09–1.84). [The Working Group noted that the excess of cancer incidence observed using regional rates as reference became nonsignificant when national rates were used. Because of the lack of specific exposure information, the possibility of confounding cannot be ruled out.]

In Finland, a cohort of Baltic Sea fishermen was identified from the Professional Fishermen Register, and their wives were identified from the Population Register (Turunen *et al.*, 2008). A cohort of 4260 women was linked with Statistics Finland's national cause-of-death data from 1980 to 2005, and expected deaths were calculated according to national rates. Furthermore, a cross-sectional substudy was conducted among 94 cohort participants who undertook a health examination in 2004–2005, including a food-frequency questionnaire and fasting-blood collection; data from a population-based survey were used for comparison. No statistically significant standardized mortality ratios were found for all cancers, or for any specific tumour site.

After an accidental spill of oil contaminated with PCBs from the brass works industry in Gusum, Sweden, in 1972, elevated levels of PCBs were measured in local fish in 2006. Among the population of the contaminated area, 641 cases of cancer were identified in 1960–2003, which was not above the expected number based on national rates for the same period (Helmfrid *et al.*, 2012). Among men, 22 lymphomas were observed, with a statistically significant increased standardized incidence ratio (SIR) of 1.60 (95% CI, 1.00–2.42). There was also an increased risk of cancer of the testis (SIR, 2.46; 95% CI, 0.99–5.08; seven cases) and malignant melanoma of the skin (SIR, 1.56; 95% CI, 0.87–3.94) in the contaminated area when compared with the general population, while the risk for cancer of the prostate was near unity (SIR, 1.06; 95% CI, 0.86–1.29). In addition to the cohort analysis, a case–control study based upon a dietary questionnaire was carried out on 67 cases of cancer, including cancers of the colorectum, skin (including melanoma), cervix, breast, prostate, and lymphoma, and 326 controls resident in the same area. The case–control analysis reported an increased risk of cancer of the female breast associated with consumption of fish more than twice per month, but with only two cases. Excess risks of lymphoma (five cases, including men and women) were also observed with consumption of fish more than twice per month. Consumption of locally produced foods was also analysed, but no other statistically significant increased risks associated with potential sources of exposure to PCBs were reported in the case–control analysis. [The Working Group noted that subjects from this area could have also been exposed to other contaminants, such as metals. The case–control analysis was based upon a very small number of subjects, and there was poor assessment of dietary exposure and control for potential confounders.]

Regular consumption of predatory fish constitutes a large source of exposure to several persistent pollutants, including PCBs, for residents of the Great Lakes Basin (Falk *et al.*, 1999). A cohort of regular consumers of sport fish from the Great Lakes, and residents in the same communities who consumed no sport fish from the Great Lakes (referents), were recruited in 1993–94 (Tomasallo *et al.*, 2010). A total of 3757 subjects (2275 fish consumers and 1482 referents) were followed from 1995 to 2006, and mortality was compared with national death rates. Information about fish consumption and other lifestyle characteristics was obtained by telephone interview, and a blood sample for measurement of PCBs

was collected for a subgroup of 610 individuals. During the 12-year follow-up period, 342 deaths were recorded, including 134 deaths from cancer. Cancer mortality rates did not differ from those of the general population for fish consumers or referents: SMRs for all cancers were 0.92 (95% CI, 0.74–1.13) and 0.87 (95% CI, 0.64–1.13), respectively. However, fish consumers had non-statistically significant excesses of cancers of the pancreas, brain and combined breast, uterus and ovary. Although blood PCB levels were positively associated with fish consumption among fish consumers ($P < 0.001$ for comparison of mean PCB concentrations according to three levels of fish consumption), there was no association between fish consumption and cancer mortality. [The Working Group regarded this study as informative because it included information about PCB exposures, as well as fish consumption. However, the possibility of confounding from concurrent exposure to other contaminants could not be ruled out.]

[Compared with cohorts of Yusho or Yucheng patients, who consumed food contaminated with a high level of PCBs for a short period, potential exposure to PCBs through diet is a long-term, low-level exposure. Fish or local vegetables contaminated by PCBs are often also contaminated by other compounds such as DDT, PCDFs, PCDDs, or heavy metals. Furthermore, as detailed information on other risk factors for the tumours analysed (i.e. lymphoma, breast, colon, skin) was lacking, residual confounding could not be ruled out as a potential explanation for the associations found in these studies.]

2.2.3 Nested case–control studies of PCB concentrations in blood or adipose tissue

Since the 1980s, several cohort studies have addressed the potential relationship between risk of cancer and internal measurements of exposure to PCBs. The most commonly used marker of past exposure to PCBs is the serum or plasma concentration of a set of PCB congeners, although a few studies have measured PCB concentrations in adipose tissue. Most studies used a case–control design nested within a cohort as an efficient method for analysis: PCB concentrations were measured in all incident cases diagnosed within a defined follow-up period, and in a sample of at-risk subjects (controls) selected within the same cohort. A few studies have used a case–cohort approach, in which the referent group is formed by a random sample of the whole cohort selected at baseline. Various sets of PCB congeners were measured; PCB-118, PCB-138, PCB-153, and PCB-180 were reported more often because they were frequently analysed and prevalent in human biological samples (see Section 1.2 for more information on analytical methods). In some instances results for individual congeners were provided but, unless otherwise specified, the summary estimate refers to the sum of all measured PCBs.

(a) Cancer of the breast

See Table 2.6

(i) USA

The New York University Women's Health Study (NYUWHS) enrolled 14 290 women from New York City between 1985 and 1991; these women donated a 30 mL blood sample while attending a mammography screening clinic (Wolff *et al.*, 1993). During this period, women who were diagnosed with cancer of the breast 1–6 months after entry into the study were defined as cases. Controls were selected at random from all cohort members who were alive and free of cancer at the time of the cancer diagnosis in a case patient, matched on menopausal status, age at entry and day of menstrual cycle at the time of blood collection. Concentrations of PCBs were measured without correction for serum lipids. [Since cases were diagnosed only 1–6 months subsequent to entry, the disease

Table 2.6 Nested case-control studies on risk of cancer of the breast and measured serum or adipose concentrations of PCBs

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
USA							
Wolff *et al.* (2000a) New York, USA 1985–1991 until 1994	14 275 women; 148 cases and 295 controls	Serum, GC, lipid-corrected concentrations (Akins method)		Quartiles of PCB concentration (ng/g lipid)			Age, menopausal status, date of blood collection (matching), age at menarche, number of pregnancies, age at first pregnancy, family history of breast cancer, lactation, height, BMI No. and list of PCB congeners not provided; LOD, < 1 ng/mL
				478–638	30	1.55 (0.59–4.12)	
				639–876	26	1.23 (0.49–5.08)	
				> 876	33	2.02 (0.76–5.37)	
						P for trend = 0.23	
Krieger *et al.* (1994) Northern California, USA 1964–1969 until 1990	57 040 women; 150 case–control pairs (50 each white, black, Asian)	Serum, GC/ECD, no lipid adjustment		Tertiles of PCB concentration (ng/mL)			Race, age, date of entry, duration of follow-up (matching), BMI, age at menarche, menopausal status, ever pregnant No. and list of PCB congeners not provided; LOD, 2 ng/mL
			All women	3.5–5.0		1.17 (0.66–2.10)	
				5.1–20.6		0.94 (0.48–1.84)	*P* for trend = 0.88
			White	2.94–3.96		0 21 (0.05–0.88)	
				3.97–10.01		0 17 (0.03–0.89)	*P* for trend = 0.039
			Black	3.51–4.98		1.74 (0.56–5.43)	
				4.99–20.55		2 13 (0.70–6.50)	*P* for trend = 0.18
			Asian	4.16–5.76		1.56 (0.47–5.17)	
				5.77–14.62		1.06 (0.32–3.52)	*P* for trend = 0.93
Hunter *et al.* (1997), Laden *et al.* (2001a) 11 states, USA (Nurses' Health Study cohort) 1989–1994	32 826 women; 370 case–control pairs	Serum PCB levels measured by GC/ECD, no lipid adjustment		Quintiles of PCB concentration (µg/g lipid)			Age, menopausal status, month of blood collection, fasting status at blood sampling (matching), BMI, breast cancer in first-degree relatives, history of benign breast disease, age at menarche, first full term pregnancy, parity, lactation LOD, < 1 ng/mL; sum of 16 penta-, hexa-, and heptachlorobiphenyls; congeners 118, 138, 153 and 180 accounted for 64% of total
			Sum of PCBs	0.406–0.491	65	0.73 (0.44–1.21)	Continuous (log-concentration) *P* = 0.56
				0.491–0.596	65	0.75 (0.44–1.28)	
				0.602–0.763	80	0.85 (0.49–1.47)	
				0.766–1.986	74	0.84 (0.47–1.52)	

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Hunter et al. (1997), Laden et al. (2001a) (cont.)			PCB-118	0.045–0.060	62	0.68 (0.39–1.17)	Continuous (log-concentration) $P = 0.67$
				0.061–0.074	61	0.62 (0.36–1.06)	
				0.074–0.101	90	1.02 (0.59–1.77)	
				0.101–0.313	69	0.69 (0.39–1.22)	
			PCB-138	0.066–0.087	69	0.82 (0.49–1.37)	Continuous (log-concentration) $P = 0.21$
				0.087–0.108	75	0.90 (0.53–1.50)	
				0.109–0.142	65	0.71 (0.41–1.20)	
				0.143–0.402	78	0.87 (0.50–1.50)	
			PCB-153	0.078–0.094	58	0.67 (0.39–1.14)	Continuous (log-concentration) $P = 0.26$
				0.095–0.121	75	0.69 (0.41–1.15)	
				0.121–0.159	69	0.77 (0.45–1.31)	
				0.159–0.447	79	0.83 (0.47–1.48)	
			PCB-180	0.055–0.068	65	0.70 (0.41–1.20)	Continuous (log-concentration) $P = 0.67$
				0.069–0.082	62	0.65 (0.37–1.11)	
				0.082–0.103	63	0.70 (0.41–1.19)	
				0.103–0.467	91	0.98 (0.55–1.75)	
				Tertiles of PCB concentration			
			BMI ≥ 30	Tertile 2	19/21	0.40 (0.15–1.05)	Continuous (log-concentration) $P = 0.02$
				Tertile 3	11/19	0.26 (0.09–0.76)	
			Nulliparous	Tertile 2	5/14	0.81 (0.18–3.68)	Continuous (log-concentration) $P = 0.02$
				Tertile 3	12/6	5.30 (1.06–26.6)	
Laden *et al.* (2002) 1989–1994	367 pairs	Serum PCB levels measured by GC/ECD, no lipid adjustment	*CYP1A1* exon 7 genotype	Tertiles of PCB concentration			Same data set as study by Hunter *et al.* (1997), Laden *et al.* (2001a)
			Wildtype	0.13–0.46	113	1.00	
			Variant	0.13–0.46	12	0.54 (0.24–1.22)	
				0.46–0.65	18	0.76 (0.35–1.63)	
				0.65–1.99	21	1.36 (0.60–3.12)	Interaction ($P = 0.19$)
			Postmenopausal women				
			Wildtype	0.13–0.47	84	1.00	
			Variant	0.13–0.47	16	0.52 (0.20–1.36)	
				0.47–0.67	12	1.29 (0.51–3.21)	
				0.67–1.99	7	2.78 (0.99–7.82)	Interaction ($P = 0.05$)

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Dorgan *et al.* (1999) Missouri, USA 1977–1987 until 1989	7224 women; 105 cases and 208 matched controls	Serum, GC/ECD, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)			Age, benign breast disease, mo/year blood collection (matching), height, weight, BMI, parity, age at menarche, menopause, estrogen use, history of breast cancer in first-degree relatives, smoking, education 70% lost to follow-up after 1983; LOD, 0.25–0.97ng/g; 27 PCB congeners measured[a]
			Sum of PCBs	258–369	21	0.7 (0.3–1.4)	Continuous (log-concentration) $P = 0.79$
				370–563	33	1.1 (0.6–2.2)	
				564–2682	21	0.7 (0.3–1.5)	
			PCB-118	50–74	25	1.1 (0.6–2.3)	Continuous (log-concentration) $P = 0.77$
				75–109	34	1.6 (0.8–3.2)	
				110–533	23	1.0 (0.5–2.2)	
			PCB-138	70–93	29	1.3 (0.6–2.5)	Continuous (log-concentration) $P = 0.82$
				94–124	26	1.2 (0.6–2.3)	
				125–359	26	1.2 (0.6–2.4	
Helzlsouer *et al.* (1999) Maryland, USA 1974–1994 or 1989–1994	20 305 recruited in 1974; 25 080 recruited in 1989; 340 cases and matched controls	Serum, GC/ECD, lipid-corrected concentrations		Sum of PCBs (ng/g lipid)			Age, race, menopausal status, date of blood collection
			Recruited in 1974	< 394.47	42	1.00	Approx. 70% participation; no association for specific congeners (data not reported); no effect modification by menopausal status, ER status, polymorphisms in *GSTM1*, *GSTT1*, *GSTP1*, *COMT* and *CYP17*; LOD, NR; 27 PCB congeners measured
				394.48–558.72	59	1.41 (0.79–2.50)	
				558.73–669.46	41	0.94 (0.49–1.77)	
				669.47–852.22	45	1.08 (0.59–2.01)	
				852.23–6460.04	48	1.12 (0.59–2.15)	P for trend = 0.44
			Recruited in 1989	13.6–191.8	40	1.00	
				191.9–333.5	32	0.78 (0.41–1.47)	
				333.6–2007.9	33	0.76 (0.38–1.51)	P for trend = 0.60

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cohn *et al.* (2012) Oakland, California, USA 1959–1967 until 1998 (average follow-up, 17 years)	Women in the CHDS who gave birth in 1959–1967 [number of participants not given]; 112 case–control pairs (cases all aged < 50 yr)	Serum samples collected during early post-partum, GC/ECD		Quartiles of PCB concentration (mmol/L)			Age (matching), blood lipids (total cholesterol, total triglycerides), parity, year of blood draw, BMI, breast-feeding after current pregnancy 10 congeners measured[b] No associations with total PCBs or with Wolff's groups (data not shown)
			PCB-167	Quartile 2	NR	1.09 (0.48–2.47)	*P* for trend < 0.04
				Quartile 3	NR	0.70 (0.27–1.78)	
				Quartile 4	NR	0.24 (0.07–0.79)	
			PCB-187	Quartile 2	NR	0.94 (0.41–2.17)	*P* for trend < 0.02
				Quartile 3	NR	0.92 (0.36–2.38)	
				Quartile 4	NR	0.35 (0.11–1.14)	
			PCB-203	Quartile 2	NR	1.21 (0.46–3.18)	*P* for trend < 0.001
				Quartile 3	NR	2.89 (0.98–8.55)	
				Quartile 4	NR	6.34 (1.85–21.7)	
Northern Europe							
Høyer *et al.* (1998, 2000) Copenhagen, Denmark (CCHS cohort) 1979–1993	5838 women with two examinations (1976–78 and 1981–83); 155 cases, 274 controls	Serum, GC/ECD, lipid-corrected concentrations		Quartiles of PCB concentration [unit not given]			Age, date of examination, weight changes between two examinations, parity, HRT Response rate 75% (first exam), 78% (second exam); LOD, 0.66–0.20 ng/mL; No. and list of PCB congeners not provided
			Sum of PCBs	Quartile 2	NR	0.8 (0.4–1.9)	
				Quartile 3	NR	0.8 (0.4–1.7)	
				Quartile 4	NR	1.6 (0.8–3.3)	*P* for trend = 0.17
			PCB-118	Quartile 2	NR	0.8 (0.4–1.9)	
				Quartile 3	NR	1.1 (0.5–2.4)	
				Quartile 4	NR	1.9 (0.9–3.9)	*P* for trend = 0.07

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Høyer et al. (1998, 2000) (cont.)			PCB-138	Quartile 2	NR	0.9 (0.4–1.9)	
				Quartile 3	NR	1.0 (0.5–2.1)	
				Quartile 4	NR	2.1 (1.0–4.4)	*P* for trend = 0.04
			PCB-153	Quartile 2	NR	0.7 (0.3–1.4)	
				Quartile 3	NR	0.8 (0.4–1.8)	
				Quartile 4	NR	1.3 (0.2–2.6)	
			PCB-180	Quartile 2	NR	1.2 (0.6–2.5)	
				Quartile 3	NR	1.1 (0.5–2.2)	
				Quartile 4	NR	0.9 (0.4–2.2)	
Høyer *et al.* (2001)	161 cases, 318 controls		ER status	Quartiles of PCB concentration [unit not given]			Age, weight, parity, HRT See Høyer *et al.* (2000) for details
			ER+	811–1076.04	24/56	1.1 (0.6–1.7)	
				1076.04–1405.73	20/57	0.7 (0.4–1.2)	
				< 1405.73	36/56	1.3 (0.8–2.2)	
			ER–	811–1076.04	11/23	1.0 (0.4–2.7)	
				1076.04–1405.73	11/23	1.3 (0.4–3.9)	
				< 1405.73	8/23	0.8 (0.3–2.6)	
Høyer *et al.* (2002)	162 cases, 316 controls		*p53* mutations in tumour	Quartiles of PCB concentration [unit not given]			Age, weight, parity, HRT See Høyer *et al.* (2000) for details
			Wildtype	Quartile 2	24	0.53 (0.28–1.04)	
				Quartile 3	20	0.52 (0.26–1.05)	
				Quartile 4	34	0.96 (0.50–1.83)	
			≥ 1 p53 mutations	Quartile 2	9	1.78 (0.43–7.41)	
				Quartile 3	11	3.82 (0.85–17.4)	
				Quartile 4	10	3.00 (0.66–13.6)	

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Ward *et al.* (2000) Norway (Janus cohort) 1973–1991	25 431 women working outside home and resident on a farm; 150 case–control pairs	Serum, HRGC/ID-HRMS, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)		[95% CI not given]	Age (matching), occupation, age at first birth, parity, residence All cases ≥ 2 years from blood collection to diagnosis; sum of 36 congeners: 26 with > 90% samples > LOD Groups according to Wolff's classification (Wolff *et al.*, 1997)
			Sum of PCBs	Quartile 2		0.6	*P* = 0.47 (paired t-test)
				Quartile 3		0.8	
				Quartile 4		0.5	
			Group 1B	Quartile 2		0.6	*P* = 0.56 (paired t-test)
				Quartile 3		0.6	
				Quartile 4		0.5	
			Group 2A	Quartile 2		0.8	*P* = 0.50 (paired t-test)
				Quartile 3		0.6	
				Quartile 4		0.6	
			Group 2B	Quartile 2		0.4	*P* = 0.32 (paired t-test)
				Quartile 3		1.0	
				Quartile 4		0.5	
			Group 3	Quartile 2		0.7	
				Quartile 3		0.8	
				Quartile 4		0.6	*P* = 0.18 (paired t-test)
Raaschou-Nielsen *et al.* (2005) Copenhagen and Aarhus, Denmark (DCH cohort) 1993–1997 until 2000	29 875 women; 220–365 pairs, depending on congener	Adipose tissue, GC/MS, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)			Age, use of HRT (matching), benign breast tumour, BMI, alcohol, parity, age at delivery, years of HRT, lactation Response rate, 37%; all cases were postmenopausal women; LOD, 2.8–28.4 ng/g lipids; 18 PCB congeners[c] measured
			All cases (*n* = 365)	671–852	NR	0.9 (0.6–1.4)	
				852–1.024	NR	0.7 (0.5–1.1)	
				1024–4357	NR	1.1 (0.7–1.7)	
				Continuous (log ng/g lipid)	NR	*P* = 0.44	

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Raaschou-Nielsen et al. (2005) (cont.)			ER+ (n = 261)	671–852	NR	1.1 (0.6–1.8)	
				852–1.024	NR	0.8–0.5–1.4)	
				1024–4357	NR	1.4 (0.8–2.5)	
				Continuous (log ng/g lipid)	NR	P = 0.50	
			ER– (n = 75)	671–852	NR	0.4 (0.1–1.3)	
				852–1.024	NR	0.3 (0.1–0.9)	
				1024–4357	NR	0.3 (0.1–0.9)	
				Continuous (log ng/g lipid)	NR	P = 0.007	

[a] Congeners measured: 28, 52, 56, 66, 74, 90, 101, 105, 110, 118, 138, 146, 153, 156, 170, 172, 178, 180, 183, 187, 189, 193, 194, 195, 201, 203, 206

[b] Congeners measured: 101, 187, 201, 138, 170, 99, 153, 180, 183, 203

[c] Congeners measured: 28, 52, 54, 99, 101, 104, 105, 118, 128, 138, 153, 155, 156, 170, 180, 183, 187, 201

BMI, body mass index; CHDS, Child Health and Development Studies; DCH, Diet, Cancer, and Health; ECD, electron capture detection; ER, estrogen receptor; FTP, full-term pregnancy; GC, gas chromatography; HRGC, high-resolution gas chromatography; HRT, hormone-replacement therapy; ID-HRMS, isotope dilution high-resolution mass spectrometry; LOD, limit of detection; mo, month; NR, not reported; PCB, polychlorinated biphenyl

could have been present when the blood sample was collected, despite negative mammography findings, and could therefore have affected the measured concentration of PCBs.] Additional cases and controls were included in an extended follow-up of this cohort to 1994, giving totals of 148 cases and 295 controls (Wolff *et al.*, 2000a). In this update, only incident cases were considered (thus excluding those with a lag time of 6 months or less). Serum lipids were measured and PCB concentrations were calculated on a lipid basis. The risk estimates were further adjusted for family history of cancer of the breast, reproductive risk factors, height, and body mass index (BMI). Odds ratios increased across quartiles of serum PCB concentrations, reaching 2.02 (95% CI, 0.76–5.37) in the highest quartile; the trend was not statistically significant. [The Working Group noted that this was a well-designed study; however, the follow-up was relatively short and the analysis thus had limited power.]

Krieger *et al.* (1994) performed a nested case–control study among women in Northern California, USA, who were members of the Kaiser Permanente Medical Care Program and who underwent a health examination, including giving a sample of blood, between 1964 and 1969, and were followed up until 1990. Among the 2072 patients identified with cancer of the breast, 150 cases were randomly selected (50 white, 50 black, and 50 Asian) and matched to 150 controls by race, age, date of entry, and date of follow-up. After adjustment for reproductive factors, menopausal status and BMI, no association was seen between risk of cancer of the breast and serum PCB concentrations for all subjects (OR, 0.93; 95% CI, 0.83–1.05 per ppb). In subgroup analyses by ethnic group, there was an inverse association for white women (OR, 0.21; 95% CI, 0.05–0.88; and OR, 0.17; 95% CI, 0.03–0.89 for the second and third tertiles respectively, *P* for trend = 0.04) and a positive association for black women (OR, 1.74; 95% CI, 0.56–5.43 and OR, 2.13; 95% CI, 0.70–6.50, respectively, *P* for trend = 0.18). [This was a well-designed study with adjustment for relevant confounders, with more than 2000 cases of cancer of the breast identified during the follow-up; however, only 150 were selected for measurement of PCBs and thus power was limited, especially for subgroup analyses.]

The Nurses' Health Study was established in 1976 and included more than 120 000 registered nurses in the USA, who were subsequently followed by questionnaire every 2 years and 32 826 women from the cohort provided a blood sample between 1989 to 1990. Results were reported from follow-ups until 1992 (Hunter *et al.*, 1997) and 1994 (Laden *et al.*, 2001a). In the first follow-up, no association was found between cancer of the breast and PCB concentrations after adjustment for family history of cancer of the breast, reproductive factors, BMI, and cholesterol (Hunter *et al.*, 1997). The extended follow-up to 1994 included 370 case–control pairs, and provided results for individual congeners (Laden *et al.*, 2001a). The pattern of risk by quintile did not change and no association was found for PCB-118, PCB-138, PCB-153, or PCB-180. In subgroup analyses, a significant increase in risk was reported for exposure to the sum of 16 PCBs in nulliparous women (OR, 5.30; 95% CI, 1.06–26.6 for the third tertile of PCB serum concentrations when compared with the first tertile, but the overall trend was not significant; $P = 0.11$). An inverse association was found for women with BMI ≥ 30; the odds ratio for the highest versus lowest tertile was 0.26 (95% CI, 0.09–0.76; *P* for trend = 0.01), while elevated odds ratios were found for women in the highest tertile of PCB exposure with BMI of 25–29.9 and < 25. Since PCB exposure induces activity of cytochrome P450 1A1 (CYP1A1), and PCBs themselves can be metabolized to carcinogenic intermediates by this enzyme, it was explored whether the potential effect of PCBs was modified by the CYP1A1 polymorphism using the same data set (Laden *et al.*, 2002). In 367 case–control pairs, *CYP1A1* exon 7 and *MspI* polymorphisms

were determined. The relative risk increased across tertiles of PCB exposure among those with the variant exon 7 genotype, but not among those with the wild-type genotype. When the analysis was restricted to postmenopausal women, the odds ratio was 2.78 (95% CI, 0.99–7.82) for the highest tertile of PCB exposure, with a *P* value for interaction of 0.05. No gene–environment interaction was seen for *MspI* polymorphism. [The Working Group noted that this was a well-designed study with good controls for most relevant confounders, including reproductive factors and family history of cancer of the breast. The sample size was reasonable when compared with previous studies, and estimates for specific PCB congeners were reported. The only statistically significant associations were limited to specific subgroups after several subgroup analyses and multiple comparisons.]

In another study in the USA, 7224 female volunteers were identified through the Breast Cancer Detection and Demonstration Project (BCDDP) and donated blood to the Columbia Missouri Breast Cancer Serum Bank; active follow-up continued until 1989 (Dorgan *et al.*, 1999). Among these women, 105 were diagnosed with histologically confirmed cancer of the breast, and two controls for each were selected, matched on year of age, date of blood sampling, and history of benign breast disease at the time of enrolment. No association was reported between risk of cancer of the breast and lipid-corrected concentrations of total PCBs (sum of 27 PCB congeners measured), or serum concentrations of PCB-118 and PCB-138, after adjustment for the main risk factors for cancer of the breast. [This study had a relatively small number of cases and was therefore of limited power].

A case–control study was conducted among residents of Washington County, Maryland, USA, who had participated in one of two studies conducted in 1974 and 1989 to obtain blood samples for a serum bank (Helzlsouer *et al.*, 1999). Participants were followed up until 1994 by linkage with the Washington County Cancer Registry. Of the 346 cases of cancer of the breast diagnosed, valid measurements of PCBs were available for 340 cases, which were matched to 340 participating women without cancer of the breast by age, menopausal status and date of blood collection. Taking into account relevant confounders including family history of cancer of the breast, reproductive history and BMI, no association was found with total PCB serum concentration or with specific congeners. There were no statistically significant associations after stratifying for menopausal status, estrogen-receptor (ER) status or polymorphism in *GSTM1*, *GSTT1*, *GSTP1*, *COMT*, or *CYP17*. [The Working Group noted that this study, with an analysis adjusting for most relevant confounders, investigated the hormone-receptor status of tumours, and also considered possible effect modification by polymorphisms in several genes with a role in metabolism. Although the sample size was adequate for the main analysis, it was limited for subgroup analyses.]

A nested case–control study compared serum concentrations of 16 PCBs in archived early-postpartum serum samples collected between 1959 and 1967 from 112 cases of cancer of the breast and 112 age-matched controls (Cohn *et al.* 2012). Subjects were residents of Oakland, California, participating in the Child Health and Development Studies. Cases of cancer of the breast were identified by linkage to the California Cancer Registry, and the California Vital Status Records. The median time from blood draw to diagnosis was 17 years, and mean age of cases at diagnosis was 43 years. No associations were reported between risk of cancer of the breast and sum of total PCBs, or with PCB groups (Wolff *et al.*, 1997). [No odds ratios were reported for these analyses]. PCB-167 was associated with a lower risk (OR for highest versus lowest quartile, 0.2; 95% CI, 0.1–0.8), as was PCB-187 (OR for highest versus lowest quartile, 0.4; 95% CI, 0.1–1.1). In contrast, PCB-203 was associated

with an increased risk (OR for highest versus lowest quartile, 6.3; 95% CI, 1.9–21.7). [This was the only nested case–control study to include mostly premenopausal women. The study had limited power.]

(ii) Northern Europe

Serum samples were obtained in 1976 from a cohort of 7712 women aged 20 years or older who participated in the Copenhagen City Heart Study (Denmark) and provided information and a non-fasting blood sample (Høyer *et al.*, 1998). Case ascertainment was achieved by linkage to the Danish Cancer Registry up to 1993. For each case, two women free of breast cancer and alive at the time of diagnosis and matched for age and date of examination were selected from the rest of the cohort. After excluding subjects without a valid serum sample, 240 cases and 447 controls were included in the study. Concentrations of 28 PCB congeners were measured in serum. No association was reported between risk of cancer of the breast and lipid-adjusted concentrations of the sum of PCBs or specific congeners.

Participants in the same cohort study were invited for a second examination 5 years after recruitment; 155 cases and 274 controls from the previous study had a second serum sample available (Høyer *et al.*, 2000). Analyses were carried out in this group for four common PCB congeners. A statistically significant increased risk and trend was found for subjects in the highest quartile of PCB-138 concentration (average of two measurements; OR, 2.1; 95% CI, 1.0–4.4; *P* for trend = 0.04). Elevated odds ratios were reported for the highest quartile of exposure to total PCBs and congeners PCB-118 and PCB-153 (OR, 1.6, 1.9 and 1.3, respectively), but the association was not significant for these congeners or for PCB-180.

Within the same cohort, a total of 161 cases with ER status information and 318 matched controls who were free of breast cancer were included in an analysis according to ER status (Høyer *et al.*, 2001). No association was found between incidence of cancer of the breast and PCB concentrations regardless of ER status. Finally, paraffin embedded tumour-tissue specimens were retrieved for 162 cases and 316 controls and found to be suitable for *p53* analysis (Høyer *et al.*, 2002). A non-significant increased risk of cancer of the breast (OR, 3.00; 95% CI, 0.66–13.62) was observed in the highest level of exposure to PCBs among women with mutant *p53*. [Several analyses were carried out using data from this Danish study, but power was limited, particularly for subgroups.]

The JANUS Serum Bank contains serum samples collected between 1973 and 1991 from almost 300 000 individuals undergoing routine health examinations in Norway. Cases of cancer of the breast were identified among 25 431 women working outside home and resident on a farm who were followed until 1993 through linkage with the Norwegian Cancer Registry (Ward *et al.*, 2000). From the 272 cases diagnosed during this period, 150 women with a blood sample taken 2 or more years before diagnosis were randomly selected; an equal number of controls were matched to cases by date of sample collection and date of birth. The mean lipid-corrected concentration of serum PCBs (sum of 36 congeners) was similar for cases and controls (*P* value, 0.47 for paired *t*-test). No association was found for specific PCB congeners or for PCB groups as defined by Wolff *et al.* (1997). [The Working Group noted that this study was well designed and considered most relevant confounders for cancer of the breast but, similar to other nested case–control studies with serum PCB measurements, had limited power.]

Between 1993 and 1997, 29 875 Danish women aged 50 to 64 years were enrolled in a prospective study of diet and cancer and followed until December 2000 through linkage with Danish Cancer Registry (Raaschou-Nielsen *et al.*, 2005). During this period, 409 women were diagnosed with postmenopausal cancer of the breast; each case was matched to one control by age,

postmenopausal status (known/probable), and use of hormone replacement therapy, and measurements of 18 PCBs in adipose-tissue biopsies were obtained. No association was found between concentrations of PCBs and risk of cancer of the breast in the whole data set. However, an inverse association was observed when the analysis was restricted to the 75 ER-negative (ER–) cases (OR, 0.3; 95% CI, 0.1–0.9). This inverse association for ER– cases was also observed for the congeners PCB-138, PCB-153, PCB-170, PCB-180, PCB-183 and PCB-187. [The Working Group noted that this was the largest nested case–control study of cancer of the breast with PCB measurements, and the only one to measure PCBs in adipose tissue rather than serum. The inverse association of concentrations of total PCB and some PCB congeners among women with ER– tumours does not have a clear interpretation.]

(b) NHL

See Table 2.7

(i) USA

Seventy-four cases of NHL (ICD-8 200 or 202) identified during follow-up from 1975 to 1994 of the cohort from Washington County, Maryland, USA (described in the previous section) and 147 controls matched by race, sex, and age were included in a case–control study (Rothman *et al.*, 1997). PCB concentrations were measured in serum collected before diagnosis and corrected for lipids. There was a significant dose–response relationship between risk of NHL and quartiles of lipid-corrected serum concentrations of PCBs (sum of 28 measured congeners). The odds ratios for the third and fourth quartiles when compared with the first quartile were 2.8 (95% CI, 1.1–7.6) and 4.5 (95% CI, 1.7–12.0) respectively; these estimates were adjusted, in addition to matching variables, for education, cigarette smoking and occupational exposure to suspected risk factors for NHL. There was also an indication that seropositivity for the Epstein-Barr virus early antigen (EBV-EA) potentiated the effects of serum PCBs, with a statistically significant interaction (*P* value = 0.025).

An analysis of the same data set focusing on the effect of specific congeners reported a significant exposure–response relationship between risk of NHL and increasing concentrations of PCB-118, PCB-138, and PCB-153 (*P* for trend < 0.05) (Engel *et al.*, 2007). [The Working Group noted that this was the only nested case–control study on PCB concentrations and NHL that adjusted for occupational exposure to potential risk factors.]

An analysis of the association between NHL and exposure to PCBs conducted within the Nurses' Health Study cohort (described in the previous section) was reported in the same publication (Engel *et al.*, 2007). Thirty women with incident NHL diagnosed between the date of blood collection and May 1994 (median follow-up, 1 year) were included as cases and 78 cohort members selected previously as controls for a study of cancer of the breast served as controls. Plasma samples were analysed for PCB concentrations for cases and for controls at the same time. A statistically significant exposure–response relationship was observed between risk of NHL and increasing concentrations of lipid-corrected PCBs (sum of 21 congeners), with an odds ratio of 4.7 (95% CI, 1.2–18.9) for the third tertile, adjusted for age, BMI, and smoking status. A significant exposure–response relationship was also observed for PCB-118 and PCB-138 (*P* for trend < 0.05), but not for PCB-153.

An extended follow-up of the Nurses' Health Study cohort (median time to diagnosis, 5.8 years) included 145 cases of NHL and selected two controls for each case (n = 290) matched on age, race, month of blood draw, and fasting status (Laden *et al.*, 2010). Women with NHL were identified by annual follow-up questionnaires and confirmed by review of medical records and pathology reports. No association was observed between total serum concentrations of PCBs

Table 2.7 Nested case-control studies on risk of non-Hodgkin lymphoma and measured serum or adipose concentrations of PCBs

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
USA							
Rothman *et al.* (1997) Maryland, USA 1972–1990 until 1994	25 802 adults; 74 cases, 147 controls	Serum, GC/ECD, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)			Race, sex, age (matching), education, cigarette smoking, potential for occupational exposure
			Sum of PCBs	648–806	13	1.3 (0.5–3.3)	28 congeners measured[a]
				814–1060	21	2.7 (0.9–7.8)	
				1070–2070	30	4.1 (1.7–11.9)	*P* for trend = 0.0008
Engel *et al.* (2007) Maryland, USA				Median of quartiles of PCB concentration (ng/g lipid)			Same population studied by Rothman *et al.* (1997) and Helzlsouer *et al.* (1999)
			Total PCBs	726.0	13	1.6 (0.6–4.3)	
				911.5	21	3.0 (1.1–8.3)	
				1337.5	30	4.6 (1.7–12.7)	
			PCB-118	124.6	23	4.9 (1.6–15.3)	
				164.9	17	3.5 (1.0–11.8)	
				214.7	29	5.4 (1.7–17.1)	*P* for trend < 0.05
			PCB-138	129.1	20	2.5 (0.9–6.5)	
				164.5	19	2.7 (1.0–7.5)	
				242.4	27	4.4 (1.5–12.6)	*P* for trend < 0.05
			PCB-153	122.4	14	1.0 (0.4–2.3)	
				163.2	17	1.4 (0.5–3.5)	
				246.9	27	2.2 (0.9–5.2)	*P* for trend < 0.05

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Laden *et al.* (2010) 11 states, USA (Nurses' Health Study cohort)	145 cases and 290 controls	Serum, GC/ECD, lipid-corrected concentrations		Median of quartiles of PCB concentration (ng/g lipid)			Race, age, date of and fasting status at blood draw (matching), region, BMI, smoking, height, parity, breastfeeding 51 congeners measured[a]
			Total PCB	547.8	41/73	1.25 (0.68–2.28)	Continuous (log-concentration) $P = 0.76$
				678.0	41/73	1.32 (0.71–2.43)	
				945.4	30/72	1.02 (0.53–1.95)	
			PCB-118	42.9	49	1.39 (0.78–2.47)	Continuous (log-concentration) $P = 0.42$
				61.0	31	0.89 (0.48–1.64)	
				104.7	27	0.81 (0.42–1.56)	
			PCB-138	53.2	39	1.33 (0.73–2.40)	Continuous (log-concentration) $P = 0.59$
				75.7	48	1.61 (0.89–2.92)	
				113.3	27	0.95 (0.49–1.83)	
			PCB-153	91.2	33	0.85 (0.47–1.54)	Continuous (log-concentration) $P = 0.55$
				120.3	45	1.38 (0.76–2.51)	
				170.0	30	0.82 (0.43–1.56)	
			PCB-180	63.4	33	1.02 (0.54–1.93)	Continuous (log-concentration) $P = 0.82$
				80.5	44	1.24 (0.66–2.31)	
				109.4	32	1.03 (0.52–2.02)	
			Immunotoxic congeners[b]	111.5	56	1.83 (1.01–3.31)	Continuous (log-concentration) $P = 0.48$
				149.6	30	0.94 (0.51–1.76)	
				228.7	25	0.89 (0.45–1.77)	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bertrand *et al.* (2010) USA (Physicians' Health Study cohort) 1982–2003	14 916 men; 205 cases and 409 controls	Serum, GC/ECD, lipid-corrected concentrations		Quintiles of PCB concentration (ng/g lipid)			Age, race, time and fasting status at blood draw (matching), region, height, BMI, alcohol, smoking 51 congeners measured[c]
			Total PCB	163–617	33	1.0	Continuous (log-concentration) $P < 0.01$
				> 617–742	31	0.86 (0.47–1.6)	
				> 742–894	34	0.99 (0.55–1.8)	
				> 894–1121	46	1.3 (0.71–2.3)	
				> 1121–5322	61	1.6 (0.91–2.9)	
			PCB-118	> 42–56	29	0.80 (0.42–1.5)	Continuous (log-concentration) $P = 0.15$
				> 56–77	40	1.1 (0.59–2.0)	
				> 77–105	46	1.2 (0.63–2.2)	
				> 105–734	57	1.4 (0.76–2.5)	
			PCB-138	> 59–76	38	1.3 (0.68–2.3)	Continuous (log-concentration) $P = 0.02$
				> 76–97	38	1.2 (0.64–2.1)	
				> 97–122	37	1.2 (0.64–2.2)	
				> 122–541	63	1.8 (0.98–3.2)	
			PCB-153	> 95–122	37	1.2 (0.67–2.3)	Continuous (log-concentration) $P < 0.01$
				> 121–148	36	1.3 (0.68–2.4)	
				> 148–188	37	1.2 (0.62–2.2)	
				> 188–761	67	2.1 (1.1–3.8)	
			PCB-180	> 68–84	40	1.5 (0.82–2.7)	Continuous (log-concentration) $P < 0.01$
				> 84–102	35	1.4 (0.75–2.7)	
				> 102–126	44	1.8 (0.96–3.3)	
				> 126–528	61	2.4 (1.3–4.5)	
			Immunotoxic congeners[b]	> 113–145	35	0.98 (0.54–1.8)	Continuous (log-concentration) $P = 0.09$
				> 145–189	36	0.99 (0.55–1.8)	
				> 189–245	45	1.2 (0.64–2.1)	
				> 245–1813	57	1.4 (0.80–2.6)	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Northern Europe (Norway, Denmark)							
Engel *et al.* (2007) Norway (JANUS cohort) 1972–1978 until 1999	87 600; 190 case–control pairs	Serum, HRGC/ID-HRMS, lipid-corrected concentrations		Median of quartiles of PCB concentration (ng/g lipid)			Age, sex, county, date of examination (matching), BMI, smoking status All cases ≥ 2 years from blood collection to diagnosis; 36 congeners measured[d]
			Total PCB	1398.3	48	1.1 (0.7–2.0)	
				1674.9	38	1.0 (0.5–1.9)	
				2148.2	60	1.7 (0.8–3.4)	*P* for trend < 0.05
			PCB-118	80.6	43	1.0 (0.5–2.0)	
				100.0	47	1.2 (0.6–2.3)	
				138.7	58	1.7 (0.9–3.5)	*P* for trend < 0.05
			PCB-138	122.8	29	0.6 (0.3–1.2)	
				153.4	42	0.9 (0.5–1.7)	
				190.0	68	1.7 (0.8–3.2)	*P* for trend < 0.05
			PCB-153	268.1	44	1.2 (0.6–2.3)	
				330.2	43	1.2 (0.7–2.2)	
				417.3	63	2.0 (1.0–3.9)	*P* for trend < 0.05
Bräuner *et al.* (2012) Copenhagen and Aarhus, Denmark (DCH cohort) 1994–97 until 2008	57 053; 239 cases and 245 controls	Adipose tissue, GC/MS, lipid-corrected concentrations		Quintiles of PCB concentration (ng/g lipid)		*IRR (95% CI)*	Age, sex (stratified), adjusted for BMI Lipid content by gravimetric method; 10 PCB congeners measured.[e] Participants with PCB concentrations < LOD were excluded from the analysis Case-content analysis
			Total PCB	770–939	55	0.74 (0.44–1.24)	
				939–1143	57	0.81 (0.48–1.35)	
				1143–1351	42	1.15 (0.63–2.11)	
				1351–2157	23	0.71 (0.34–1.45)	
				Linear estimate per IQR	239	0.99 (0.79–1.25)	
			PCB-118	25–34	63	0.88 (0.50–1.56)	
				34–48	58	0.96 (0.55–1.65)	
				48–62	34	0.67 (0.34–1.31)	
				62–150	25	0.72 (0.36–1.44)	
				Linear estimate per IQR	233	0.88 (0.68–1.14	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bräuner et al. (2012) Copenhagen and Aarhus, Denmark (DCH cohort) 1994–97 until 2008 (cont.)			PCB-156	28–34	51	0.59 (0.34–1.02)	
				34–41	54	0.68 (0.40–1.16)	
				41–50	45	0.94 (0.51–1.75)	
				50–88	23	0.66 (0.31–1.37)	
				Linear estimate per IQR	171	1.01 (0.79–1.29)	
			PCB-99	20–27	42	1.60 (0.85–3.01)	
				27–37	53	1.56 (0.84–2.89)	
				37–47	24	1.20 (0.58–2.49)	
				47–110	20	1.42 (0.59–3.40)	
				Linear estimate per IQR	171	1.09 (0.83–1.43)	
			PCB-138	100–140	44	0.66 (0.38–1.14)	
				140–180	74	1.04 (0.62–1.74)	
				180–230	41	1.25 (0.67–2.33)	
				230–380	26	0.68 (0.34–1.36)	
				Linear estimate per IQR	238	0.99 (0.78–1.26)	
			PCB-153	240–300	57	0.88 (0.52–1.50)	
				300–370	56	0.67 (0.40–1.12)	
				370–430	42	1.50 (0.81–2.78)	
				430–730	28	0.85 (0.42–1.73)	
				Linear estimate per IQR	239	0.97 (0.77–1.23)	
			PCB-170	87–100	47	1.19 (0.68–2.09)	
				100–130	69	0.93 (0.54–1.59)	
				130–150	42	1.46 (0.75–2.83)	
				150–230	23	0.80 (0.38–1.69)	
				Linear estimate per IQR	238	0.98 (0.72–1.33)	
			PCB-180	170–200	55	1.03 (0.60–1.77)	
				200–240	61	1.19 (0.69–2.05)	
				240–290	49	1.09 (0.59–2.01)	
				290–480	21	0.69 (0.32–1.46)	
				Linear estimate per IQR	239	0.99 (0.77–1.27)	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bräuner et al. (2012) Copenhagen and Aarhus, Denmark (DCH cohort) 1994–97 until 2008 (cont.)			PCB-183	19–24	35	0.58 (0.32–1.03)	
				24–31	69	0.91 (0.54–1.51)	
				31–39	40	1.03 (0.56–1.90)	
				39–65	23	0.68 (0.34–1.37)	
				Linear estimate per IQR	226	0.88 (0.70–1.10)	
			PCB-187	17–46	61	1.00	
				46–56	49	0.69 (0.40–1.17)	
				56–68	62	0.97 (0.57–1.64)	
				68–84	44	1.30 (0.68–2.47)	
				84–140	22	0.69 (0.33–1.44)	
				Linear estimate per IQR	238	0.92 (0.73–1.15)	
			PCB-201	6–15	43	1.00	
				15–19	62	0.98 (0.56–1.73)	
				19–23	58	1.20 (0.66–2.21)	
				23–28	36	0.82 (0.41–1.67)	
				28–45	25	0.88 (0.38–2.03)	
				Linear estimate per IQR	224	0.93 (0.68–1.28)	

[a] Congeners measured: PCBs 28, 52, 56, 74, 99, 101, 105, 110, 118, 138, 146, 153, 156, 170, 172, 177, 178, 180, 183, 187, 189, 193, 194, 195, 201, 203, and 206

[b] Immunotoxic congeners: PCB-66, PCB-74, PCB-105, PCB-118, PCB-156, and PCB-167

[c] Ninety-nine percent of samples had concentrations greater than the limit of detection for PCB congeners 74, 118, 138, 146, 153, 156, 170, 180, 187, 194, 196, 199, 203, 206, and 209

[d] Congeners measured: PCBs 126, 169, 74, 99, 118, 105, 146, 153, 138, 158, 167, 156, 157, 178, 187, 183, 177, 172, 180, 170, 189, 201, 196, 203, 195, 194, 206, 209; 26 with > 90% samples having concentrations greater than the limit of detection

[e] Congeners measured: PCBs 99, 118, 138, 153, 156, 170, 180, 183, 187, and 201. LOD, 0.10–1.00 ng/g lipid; proportion of subjects with values greater than the limit of detection ranged from 72% (PCB-99) to 100% (PCB-153 and PCB-180)

BMI, body mass index; ECD, electron capture detection; ER, estrogen receptor; FTP, full-term pregnancy; GC, gas chromatography; HRGC, high-resolution gas chromatography; ID-HRMS, isotope dilution high-resolution mass spectrometry; IRR, incidence rate ratio; IQR, interquartile range; LOD, limit of detection; mo, month; NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl

(sum of 51 congeners measured as lipid-corrected concentrations) or for specific congeners (PCB-118, PCB-138, PCB-153, PCB-180) after adjustment for several confounders. The same pattern of no association was observed in the subgroup analysis by the main subtypes of NHL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukaemia/small lymphocytic lymphoma. [This was the only nested case–control study on non-Hodgkin lymphoma to include women only. The Working Group noted that it was a well-designed study. The positive association observed in the initial study was not confirmed in the second, larger study, after adjustment for additional relevant confounders. However, in the second study the time since blood draw was prolonged and different laboratories and laboratory methods were used for analysis.]

The Physicians' Health Study began in 1982 in the USA as a randomized trial for the primary prevention of cardiovascular disease and cancer in male physicians aged 40–84 years at enrolment. A total of 14 916 participants provided a blood sample in 1982–84 (before randomization) and were followed until 2003 using annual questionnaires confirmed by review of medical records to identify newly diagnosed NHL (Bertrand *et al.*, 2010). After excluding those with a diagnosis within 6 months after blood collection, prior diagnosis of cancer, NHL of uncommon subtypes (i.e. mantle cell lymphoma), or lacking sufficient information for subtype classification, 205 cases with available blood samples were included. For each case, two subjects who were at risk of NHL when the case occurred were randomly selected as controls matched by race, age, and date of blood collection. Lipid-corrected concentrations of 51 PCB congeners in serum were determined for cases and controls. The odds ratio for the highest versus lowest quintile of total PCBs adjusted for matching variables was 1.9 (95% CI, 1.1–3.2), which was reduced to 1.6 (95% CI, 0.91–2.9) after adjustment for region, BMI, smoking status, alcohol intake, and height, in addition to matching variables. However, using the natural log of lipid-corrected concentrations of PCBs, the association was statistically significant for the fully adjusted model (P value < 0.01, OR not reported). The association was also significant for the log-concentrations of PCB-138, PCB-153 and PCB-180, as well as for the sum of PCBs -118, -138, -153 and -180. [The Working Group noted that this was a well-designed study with reasonable sample size. The multivariable adjustment weakened the association with total PCBs, but did not substantially change the interpretation.]

(ii) Northern Europe

Within the JANUS cohort, described in the previous section, 194 histologically confirmed cases of NHL were ascertained with follow-up to 1999 (median time to diagnosis, 16.6 years) (Engel *et al.*, 2007). Information, including lipid-corrected concentrations of 36 PCB congeners, was available for 190 case–control pairs matched by age, sex, county, and date of examination. In the analysis further adjustments were made for BMI and smoking status. The odds ratio for the association of NHL with the sum of PCBs was 1.7 (95% CI, 0.8–3.4) when comparing the fourth quartile with the first. A statistically significant increase in risk was reported for the highest to the lowest quartile of PCB-153 concentrations (OR, 2.0; 95% CI, 1.0–3.9), with a significant upward dose–response trend (P < 0.05). Odds ratios of 1.7 in the fourth exposure quartile and significant trends were also reported for PCB-118 and PCB-138. [The Working Group noted that the sample size, and therefore the power of the study, was in the range of that of the remaining nested case–control studies. It was not clear, therefore, why significant associations were found for three congeners, namely PCB-118, PCB-138, and PCB-153, but not for all PCBs combined.]

The association between NHL and PCB concentrations in adipose tissue was also studied among participants in the Danish diet and cancer

study (Raaschou-Nielsen *et al.*, 2005) described in section 2.2.3(a)(ii) (Bräuner *et al.*, 2012). Up to July 2008 (mean follow-up, 9.6 years), 278 initially cancer free cohort members were diagnosed with NHL; a subcohort of 256 participants was randomly selected for analysis using a case–cohort approach. Valid measurements of concentrations of 10 PCB congeners in adipose tissue were available for 239 cases and 245 subcohort members. Age was used as the timescale for the analysis, stratified by sex and adjusted for BMI. No association was observed between lipid-corrected concentrations of total PCBs in adipose tissue and risk of NHL. There was also no consistent association and no significant trend with PCB congeners. However, odds ratios were greater than 1 for all concentrations of PCB-99. [The Working Group noted that this was the largest nested case–control study on NHL and PCB concentrations measured in adipose tissue; estimates were adjusted only for age, sex, and BMI. The study explored the potential effect of all PCBs and a list of 10 specific congeners, with a consistent pattern of no association for all of them.]

(c) Cancer of the male genital tract

See Table 2.8

A nested case–control study on the risk of testicular germ cell tumours was carried out within the Norwegian JANUS cohort, described in Section 2.2.3(a)(ii) (Purdue *et al.*, 2009). Cases and controls were selected from cohort members with baseline blood collection without prior history of cancer. One male control was matched to each case by region, age group (2 years), and year of blood draw. Lipid-corrected measurements of the concentrations of 34 PCBs were available for 49 cases and 51 controls; 34 of the 49 cases were seminomas, 8 were non-seminomas, 5 were of mixed histology, and 2 were of unknown histology. There was no statistically significant association between risk of testicular germ cell tumours and total PCB concentration (OR, 1.3; 95% CI, 0.5–3.8 for the third versus the first quartile); however, there was an increased risk of testicular germ cell tumours for the highest versus the lowest tertile of PCB-99 concentration (OR, 2.2; 95% CI, 0.8–5.9) and of PCB-167 (OR, 4.4; 95% CI, 1.0–19.8). Cases of seminoma had significantly lower concentrations of congeners PCB-44, PCB-49, and PCB-52 and significantly higher concentrations of congeners PCB-99, PCB-138, PCB-153, PCB-167, PCB-183, and PCB-195. Similar patterns of elevated odds ratios were seen for PCB-99 and PCB-167 in this subgroup of cases. [The Working Group noted that this was a well-designed study, but with small sample size and very limited power.]

McGlynn *et al.* (2009) analysed concentrations of 15 PCBs in pre-diagnostic serum samples of 736 incident cases of testicular germ cell tumours and 913 controls matched to the cases on age, race, and serum draw date in a cohort of men in the United States military. The sum of PCB concentrations was significantly associated with decreased risk of all testicular germ cell tumours, and with non-seminoma and seminoma. Statistically significantly decreased risks of all testicular germ cell tumours were also associated with eight specific congeners (PCB-118, PCB-138, PCB-153, PCB-156, PCB-163, PCB-170, PCB-180, and PCB-187). Similar decreases in risk were observed for non-seminoma with the same congeners, while decreased risk of seminoma was associated with PCB-138, PCB-153, PCB-156, PCB-163, and PCB-170. Other congeners and groups of congeners were not associated with testicular germ cell tumours. In another study using data from 568 cases and 698 controls enrolled in the same cohort, Chia *et al.* (2010) examined associations between testicular germ cell tumours and 11 PCB congeners in relation to polymorphisms in hormone-metabolizing genes. A statistically significant reduced risk of testicular germ cell tumour for PCB-118 and PCB-138 was found only among subjects with the major homozygous allele for *HSD17B4*. [These appear

Table 2.8 Nested case-control studies on risk of cancer of the male genital tract and measured serum concentrations of PCBs

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Purdue *et al.* (2009) Norway (JANUS cohort) 1972–1978 until 1999	87 647 men; 49 cases and 51 controls	Serum, HRGC/ID-HRMS, lipid-corrected concentrations	TGC tumour (186)	Tertiles of PCB concentration			Age, county, period of blood draw (matching) 34 congeners measured
				Tertile 1	14	1.0	
				Tertile 2	16	1.1 (0.5–2.7)	
				Tertile 3	19	1.3 (0.5–3.8)	
				Selected PCB congeners: tertile 3, tertile 1 as referent:			
				PCB-44	18	0.6 (0.1–3.8)	
				PCB-49	20	1.2 (0.2–7.6)	
				PCB-52	20	1.0 (0.3–3.5)	
				PCB-99	21	2.2 (0.8–5.9)	
				PCB-138	24	1.8 (0.6–5.1)	
				PCB-153	19	1.2 (0.4–3.4)	
				PCB-167	19	4.4 (1.0–20.0)	
				PCB-183	18	1.3 (0.5–3.5)	
				PCB-195	15	1.7 (0.6–4.6)	
			Seminoma (n = 34)	Selected PCB congeners: tertile 3, tertile 1 as referent			
				PCB-44	12	0.2 (0.01–2.0)	
				PCB-49	14	0.3 (0.02–4.7)	
				PCB-52	14	0.4 (0.07–2.3)	
				PCB-99	17	4.4 (1.0–21)	
				PCB-138	17	2.1 (0.6–7.2)	
				PCB-153	13	1.2 (0.4–4.3)	
				PCB-167	15	6.7 (1.1–43)	
				PCB-183	14	2.9 (0.6–14)	
				PCB-195	13	3.0 (0.8–12)	
				Total PCBs	14	1.2 (0.4–4.1)	

Table 2.8 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
McGlynn *et al.* (2009), USA (STEED Study) 2002–2005	Military men [number not reported]; 736 cases and 913 controls	Blood, GC-MS lipid-adjusted concentrations; questionnaire	TGC tumours	Quartiles of PCB concentration (ng/g lipid)			Age, race/ethnicity, date of serum sample collection, serum DDE level, age at serum draw, BMI, height Quartile 1 as reference
				Total PCBs			
			TGC tumours	(158–250)	171	0.88 (0.67–1.16)	*P* for trend = 0.006
				(251–390)	175	0.73 (0.54 –0.98)	
				(> 390)	162	0.61 (0.43–0.86)	
			Seminoma	(158–250)	60	0.90 (0.6–1.35)	*P* for trend = 0.05
				(251–390)	91	0.89 (0.59–1.34)	
				(> 390)	88	0.64 (0.41–1.02)	
			Non-seminoma	(158–250)	111	0.84 (0.61–1.15)	*P* for trend = 0.007
				(251–390)	84	0.62 (0.43–0.88)	
				(> 390)	73	0.55 (0.37–0.83)	
				PCB-118			
			All TGC tumours	(7.2–10.5)	171	0.71 (0.53–0.94)	
				(10.6–15.6)	151	0.60 (0.45–0.81)	
				(> 15.6)	148	0.55 (0.40–0.76)	*P* for trend = 0.0007
				PCB-138			
				(15.6–24.5)	168	0.65 (0.48–0.88)	
				(24.6–37.7)	162	0.54 (0.39–0.75)	
				(> 37.7)	164	0.46 (0.32–0.66)	*P* for trend = 0.0001
				PCB-153			
				(23.4–37.2)	158	0.61 (0.45–0.82)	
				(37.3–56.3)	166	0.53 (0.38–0.73)	
				(> 56.3)	169	0.45 (0.31–0.66)	*P* for trend = 0.0003
				PCB-156			
				(5.3–6.9)	98	0.66 (0.48–0.90)	
				(7.0–10.0)	120	0.77 (0.56–1.06)	
				(> 10.0)	96	0.57 (0.40–0.81)	*P* for trend = 0.002

Table 2.8 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
McGlynn et al. (2009), USA (STEED Study) 2002–2005 (cont.)				*PCB-163*			
				(5.9–8.1)	128	0.70 (0.52–0.93)	
				(8.2–11.5)	110	0.55 (0.40–0.76)	
				(> 115)	131	0.59 (0.42–0.83)	*P* for trend = 0.001
				PCB-170			
				(6.5–9.7)	145	0.73 (0.55–0.98)	
				(9.8–14.5)	136	0.61 (0.44–0.84)	
				(> 14.5)	144	0.56 (0.39–0.80)	*P* for trend = 0.002
				PCB-180			
				(15.8–25.9)	177	0.83 (0.62–1.12)	
				(26.0–41.8)	176	0.68 (0.49–0.95)	
				(> 41.8)	161	0.56 (0.38–0.82)	*P* for trend = 0.003
				PCB-187			
				(5.8–8.0)	133	0.70 (0.52–0.94)	
				(8.1–11.6)	120	0.58 (0.42–0.81)	
				(> 11.6)	133	0.60 (0.42–0.86)	*P* for trend = 0.004
Chia *et al.* (2010) USA 2002–2005	568 cases and 698 controls	Blood, GC-MS lipid-adjusted concentrations; questionnaire	TGC tumours (186)	*PCB-118*			Age, race, date of serum sample, cryptorchidism, family history of testicular cancer, BMI
				AA genotype			Same cohort studied by McGlynn *et al.* (2009)
				(7.01–10.40)	100	0.66 (0.46–0.96)	AA genotype: AA-homozygous major allele *HSD17B4;* AA/TT genotype: minor allele for *HSD17B4*
							Quartile 1 as reference
				(10.41–15.56)	92	0.59 (0.40–0.87)	
				(> 15.57)	74	0.46 (0.31–0.70)	*P* for trend ≤ 0.001
				AT/TT genotype			
				(7.01–10.40)	38	1.27 (0.66–2.41)	
				(10.41–15.56)	31	1.06 (0.54–2.08)	
				(> 15.57)	43	1.69 (0.85–3.38)	*P* for trend = 0.019

Table 2.8 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Chia et al. (2010) USA 2002–2005 (cont.)				*PCB-138*			
				AA genotype			
				(15.85–25.00)	95	0.72 (0.49–1.07)	
				(25.01–38.53)	96	0.57 (0.38–0.85)	
				(> 38.53)	79	0.46 (0.30–0.72)	*P* for trend < 0.001
				AA/TT genotype			
				(15.85–25.00)	27	0.61 (0.31–1.20)	
				(25.01–38.53)	36	1.10 (0.54–2.25)	
				(> 38.53)	43	1.61 (0.76–3.41)	*P* for trend = 0.287
Sawada *et al.* (2010) 10 areas of Japan 1990–1995 until 2005	14 203 men; 201 cases and 402 controls	Serum, HRGC/ID-HRMS; lipid-corrected concentrations	Prostate	Quartiles of PCB concentration (ng/g lipid)			Age, area, date, and fasting hours at blood draw (matching), BMI, smoking, alcohol, marital status, intake of green tea and miso soup Sum of 41 congeners; LOD, 2 pg/g wet weight
				319–447	49	1.06 (0.63–1.79)	
				448–668	41	0.84 (0.49–1.46)	
				≥ 669	44	0.97 (0.51–1.87)	
						P for trend = 0.9	

BMI, body mass index; DDE, dichlorodiphenyldichloroethylene; ECD, electron capture detection; GC, gas chromatography; HRGC, high-resolution gas chromatography; ID-HRMS, isotope dilution high-resolution mass spectrometry; IRR, incidence rate ratio; LOD, limit of detection; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; STEED, US Servicemen's Testicular Tumor Environmental and Endocrine Determinants Study; TGC, testicular germ cell

to have been large, well-designed and well-implemented studies, but the consistent inverse associations of cancer risk with exposure to PCBs could not be explained biologically.]

The Japan Public Health Center-based Prospective Study was initiated in 1990. After excluding subjects from Tokyo for whom cancer information was not available, the cohort consisted of 65 657 men, of whom 14 203 (28%) donated blood between 1990 and 1995 (Sawada *et al.*, 2010). Up to December 2005, 201 newly diagnosed cases of cancer of the prostate were identified using several information sources (97% pathologically confirmed). For each case, two controls were selected from among subjects with no history of cancer of the prostate when the case was diagnosed, matched by age (within 3 years), public health-centre area, residence, date and time of day of blood collection, and duration of fasting. Lipid-corrected plasma concentrations of 41 PCB congeners were measured. Apart from matching variables, comparisons between cases and controls were further adjusted for BMI, smoking, alcohol, marital status, and intakes of green tea and miso soup. No statistically significant association with all cancers of the prostate was seen for total PCBs, for individual PCBs, or for PCBs grouped according to Wolff *et al.* (1997). No statistically significant differences were found for total PCBs according to stage (localized or advanced) at diagnosis of cancer of the prostate. [The Working Group noted that this was a well-designed and -conducted study showing null results; although the sample size was limited, power was reasonable for the main analysis, but limited for subgroup analyses.]

2.3 Case–control studies of occupational and environmental exposure

2.3.1 NHL

See Table 2.9

In a case–control study in Australia (Fritschi *et al.*, 2005), including 694 histologically confirmed cases of NHL, and 694 controls, exposure to PCBs was coded by an expert industrial hygienist based on questionnaire information. After adjusting by age, sex, residence and ethnicity, ever exposure to PCBs was not notably related to increased risk of NHL (OR, 1.10; 95% CI, 0.49–2.44) or to the subgroup of B-cell NHL (OR, 1.18; 95% CI, 0.53–2.62); however, risk was elevated among the subjects probably exposed (OR, 4.54; 95% CI, 0.97–21). Indicators of frequency, intensity, and duration of exposure did not show clear trends in risk. Occupational exposure to PCBs was very rare in this study, with only 25 subjects (13 cases and 12 controls) possibly or probably exposed. [The Working Group noted that this general-population case–control study may have been underpowered to detect associations with PCBs, given the low prevalence of exposure.]

A case–control study was conducted in an area of northern Italy where environmental exposure had resulted from soil contamination, most likely generated by spills from an adjacent factory producing PCBs and organochlorine chemicals. PCB concentration in the soil was used to define four areas with increasing concentrations of exposure. Overall, 495 cases of NHL, including 208 prevalent cases and 287 incident cases, identified in the Cancer Registry of the Brescia Local Health Authority, and 1467 population controls, randomly selected from the resident population, frequency-matched to cases by age and sex, participated in the study. Exposure to PCBs was assigned according to residence in one of three contaminated zones or a control zone, using three metrics: main lifetime residence; residence for at least 10 years in a given area; and duration of residence. Risk of NHL was elevated for subjects having resided 10 or more years in any of the three contaminated areas (OR, 1.4; 95% CI, 1.1–1.8), and particularly in the most polluted (OR, 1.9; 95% CI, 0.9–3.9).

Table 2.9 Case–control studies on risk of non-Hodgkin lymphoma and exposure to PCBs

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Fritschi *et al.* (2005), Australia 2000–01	694 694	Population	NHL (200, 202)	Retrospective expert assessment of occupational exposure to PCBs	Unexposed	681	1.0	Age, sex, state of residence, ethnicity
					Any exposure	13	1.10 (0.12–1.31)	
					Possible exposure	NR	0.40 (0.12–1.31)	
					Probable exposure	NR	4.54 (0.97–21)	
					Low intensity level	NR	1.91 (0.75–4.85)	
					Medium intensity level	NR	0.78 (0.17–3.50)	
					Intensity level			
					≤ 4 days/yr	NR	1.44 (0.49–4.22)	
					> 4 days/yr	NR	1.15 (0.35–3.81)	
					< 5 yr duration	NR	1.04 (0.26–4.19)	
					> 5 yr duration	NR	1.13 (0.43–2.97)	
Maifredi *et al.* (2011), Italy	495 1467	Population	NHL (200, 202)	Residence in PCB contaminated areas in Brescia, Italy; median total PCB soil concentration, 0.55 mg/kg	*Residence 1–9* yr			Age, sex Subjects who changed area of residence were repeatedly considered in each area; substantial overlapping in contamination among the areas; incident and deceased cases were included
					Most polluted area	13	1.4 (0.7–2.8)	
					All contaminated areas	21	0.8 (0.5–1.3)	
					Residence ≥ 10 yr			
					Most polluted area	15	1.8 (0.9–3.9)	
					All contaminated areas	80	1.4 (1.1–1.8)	
					Residence 10–19 yr			
					Most polluted area	10	3.8 (1.5–9.8)	
					All contaminated areas	25	1.7 (1.0–2.8)	
					Residence ≥ 20 yr			
					Most polluted area	5	0.8 (0.3–2.3)	
					All contaminated areas	55	1.3 (0.9–1.8)	
Hardell *et al.* (1996, 1997), Sweden	27 17	Hospital	NHL, B-cell type	Total PCBs in adipose tissue	≤ 1300 ng/g lipid		1.0	Age, sex
					> 1300 ng/g lipid		1.8 (0.4–7.4)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Hardell *et al.* (2001), Sweden	82 83	Hospital	NHL (200, 202)	PCBs in adipose tissue or lipid-adjusted serum				Age, sex, BMI, sample (blood or adipose tissue)
				Total PCBs	> 1020 ng/g lipid	51	1.8 (0.9–3.9)	Interaction with EBV-EA immunity assessed; pooled analysis of studies conducted at different times with different specimens 36 congeners measured
				Immunotoxic PCBs	> 1020 ng/g lipid	57	3.2 (1.4–7.4)	
				Total PCBs, EBV EA ≤ 80	> 1018 ng/g lipid	17	1.6 (0.5–5.1)	
				Total PCBs, EBV EA > 80	> 1018 ng/g lipid	22	4.0 (1.2–14)	
				Immunotoxic PCBs, EBV EA ≤ 80	> 348 ng/g lipid	18	3.2 (1.7–11)	
				Immunotoxic PCBs, EBV EA > 80	> 348 ng/g lipid	25	6.4 (1.9–24)	
Hardell *et al.* (2009), Sweden	99 99	Population	NHL (200, 202)	Lipid-adjusted plasma PCB concentrations				Age, sex, BMI, time of sampling
				Total PCBs	> Median	59	2.0 (0.99–3.9)	Both sexes; interaction with EBV-EA immunity assessed.
				Moderately chlorinated		58	1.8 (0.9–3.6)	
				Higher-chlorinated		63	1.7 (0.8–3.4)	
				Immunotoxic		54	1.5 (0.8–3.0)	
			Follicular lymphoma	Total PCBs	> 646 ng/g lipid	15	5.9 (1.9–14)	
				Immunotoxic	> 226 ng/g lipid	13	3.0 (0.9–11)	
			Diffuse large B-cell lymphoma	Total PCBs	> 646 ng/g lipid	19	1.6 (0.6–4.0)	
				Immunotoxic	> 226 ng/g lipid	19	1.4 (0.6–3.3)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Nordström *et al.* (2000), Sweden	54 54	Population	Hairy cell leukaemia	Lipid-adjusted serum PCB concentrations, EBV EA antibody titre				Age, BMI Only men; OR for total PCB
				Total PCBs	> 831.6 ng/g lipid; EBV EA > 40	13	4.4 (1.2–18.5)	> 831.6 ng/g lipid = 0.8 (0.3–1.9)
				Immunotoxic PCBs	> 285.4 ng/g lipid; EBV EA > 40	15	11.3 (2.3–73.1)	
Spinelli *et al.* (2007), Canada	422 460	Population	NHL (200, 202)	Lipid-adjusted plasma PCB concentration	Quartiles of exposure (ng/g lipid)			Age, sex, region, ethnicity, education, family history of NHL, BMI and farming; sum of 14 congeners
				Sum of PCBs	101–155.6	103	1.41 (0.93–2.14)	
					155.7–220.0	77	1.11 (0.71–1.74)	
					> 220.0	142	2.14 (1.38–3.30)	*P* for trend < 0.001
				DL-PCBs (105, 118, 156)	10.13–15.35	96	1.41 (0.91–2.16)	
					15.36–23.72	82	1.57 (1.00–2.46)	
					> 23.72	143	2.40 (1.53–3.77)	*P* for trend < 0.001
				PCB-105	> 1.32	132	1.06 (0.93–1.42)	
				PCB-118	4.58–7.78	88	1.12 (0.74–1.69)	
					7.79–12.85	95	1.23 (0.81–1.88)	
					> 12.85	129	1.77 (1.15–2.72)	*P* for trend = 0.004
				PCB-156	3.66–5.51	85	1.10 (0.72–1.68)	
					5.52–8.32	105	1.43 (0.93–2.21)	
					> 8.32	128	1.77 (1.14–2.74)	*P* for trend = 0.004
				NDL-PCBs (28, 99 138, 153, 180, 183, 187)	88.58–136.2	96	1.30 (0.85–1.97)	
					136.21–196.4	93	1.19 (0.76–1.86)	
					> 196.4	148	2.18 (1.41–3.38)	*P* for trend < 0.001
				PCB-28	Undetected	348	1.0 (Ref)	
					> 1.38	74	0.95 (0.67–1.34)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Spinelli et al. (2007), Canada (cont.)				PCB-99	3.07–4.83	82	0.78 (0.52–1.15)	
					4.84–7.78	85	0.81 (0.54–1.21)	
					> 7.78	130	1.27 (0.86–1.87)	*P* for trend = 0.045
				PCB-138	11.62–19.28	90	0.93 (0.62–1.38)	
					19.29–29.72	94	0.99 (0.66–1.50)	
					> 29.72	138	1.46 (0.98–2.18)	*P* for trend = 0.02
				PCB-153	25.3–38.68	86	1.04 (0.68–1.57)	
					38.69–59.0	106	1.34 (0.87–2.04)	
					> 59.0	140	1.79 (1.17–2.72)	*P* for trend = 0.002
				PCB-170	7.17–11.17	93	1.17 (0.77–1.79)	
					11.18–17.23	107	1.41 (0.91–2.18)	
					> 17.24	134	1.80 (1.16–2.79)	*P* for trend = 0.005
				PCB-180	21.94–35.63	94	1.28 (0.82–2.00)	
					35.64–54.72	89	1.25 (0.78–2.00)	
					> 54.72	126	1.91 (1.19–3.07)	*P* for trend = 0.005
				PCB-183	1.87–3.95	107	0.83 (0.59–1.18)	
					> 3.95	153	1.22 (0.87–1.71)	*P* for trend = 0.113
				PCB-187	5.94–9.82	98	1.27 (0.83–1.95)	
					9.83–15.46	79	1.04 (0.66–1.63)	
					> 15.46	136	1.92 (1.23–2.98)	*P* for trend = 0.003
			Follicular lymphoma	Total PCBs	Largest vs smallest quartile		2.0 (1.1–3.7)	
				DL-PCBs			2.5 (1.3–4.7)	
				PCB-105			0.9 (0.6–1.4)	
				PCB-118			2.0 (1.1–3.7)	
				PCB-156			2.4 (1.2–4.5)	
				NDL-PCBs			2.1 (1.1–3.9)	
				PCB-28			0.7 (0.4–1.3)	
				PCB-99			1.3 (0.8–2.3)	
				PCB-138			1.5 (0.9–2.7)	
				PCB-153			2.0 (1.1–3.7)	
				PCB-170			1.5 (0.8–2.8)	
				PCB-180			1.6 (0.8–3.1)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Spinelli et al. (2007), Canada (cont.)			Diffuse large B-cell lymphoma	PCB-183			1.6 (1.0–2.7)	
				PCB-187			1.8 (1.0–3.3)	
				Total PCBs	Largest vs smallest quartile		1.8 (0.8–4.1)	
				DL-PCBs			2.1 (0.9–4.9)	
				PCB-105			0.8 (0.5–1.5)	
				PCB-118			2.0 (0.9–4.7)	
				PCB-156			1.3 (0.6–3.0)	
				NDL-PCBs			1.8 (0.8–4.1)	
				PCB-28			1.3 (0.7–2.4)	
				PCB-99			1.0 (0.5–2.0)	
				PCB-138			1.2 (0.6–2.6)	
				PCB-153			1.3 (0.6–2.7)	
				PCB-170			1.6 (0.7–3.6)	
				PCB-180			1.2 (0.5–2.9)	
				PCB-183			0.8 (0.4–1.6)	
				PCB-187			1.7 (0.7–4.0)	
Cocco et al. (2008), France, Spain, Germany	174 203	Hospital and population	NHL (200, 202)	Lipid-adjusted plasma PCB concentration (ng/g lipid) Total PCBs	200.43–387.79	50	1.2 (0.6–2.2)	Age, sex, education, centre Sum of 9 congeners LOD, 0.20–0.50 µg/L
					387.8–576.36	33	0.7 (0.3–1.4)	
					> 576.36	50	1.0 (0.5–2.0)	*P* for trend = 0.83
				PCB-28	10.51–31.70	25	0.9 (0.4–1.8)	
					31.71–67.94	21	0.7 (0.3–1.5)	
					> 67.94	45	1.6 (0.8–3.2)	*P* for trend = 0.23
				PCB-118	12.31–38.76	41	1.0 (0.5–2.0)	
					38.77–59.17	20	0.5 (0.2–2.0)	
					> 59.18	19	0.4 (0.2–0.8)	*P* for trend = 0.004
				PCB-138	45.74–72.41	37	1.1 (0.6–1.9)	
					72.42–116.12	42	1.1 (0.6–2.0)	
					> 116.12	44	1.1 (0.6–2.0)	*P* for trend = 0.88

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cocco et al. (2008), France, Spain, Germany (cont.)				PCB-153	62.57–100.66	51	1.5 (0.8–2.8)	
					100.67–142.43	28	0.8 (0.4–1.6)	
					> 142.43	52	1.3 (0.7–2.5)	*P* for trend = 0.70
				PCB-170	0.21–21.53	40	1.1 (0.5–2.2)	
					21.54–34.28	36	0.8 (0.4–1.7)	
					> 34.28	45	1.0 (0.5–1.8)	*P* for trend = 0.83
				PCB-180	0.31–51.22	40	1.2 (0.6–2.6)	
					51.23–85.93	50	1.4 (0.6–3.0)	
					> 85.93	61	1.5 (0.7–3.2)	*P* for trend = 0.31
			Chronic lymphocytic leukaemia	Total PCBs	200.43–387.79	15	1.4 (0.5–4.4)	
					387.8–576.36	10	0.8 (0.2–2.8)	
					> 576.36	18	1.4 (0.4–4.5)	*P* for trend = 0.71
				Immunotoxic PCBs	> median	NR	3.2 (0.9–12)	Subgroup analysis of combined French and German subjects
			Diffuse large B-cell lymphoma	Total PCBs	200.43–387.79	12	0.8 (0.3–2.1)	
					387.8–576.36	7	0.5 (0.1–1.6)	
					> 576.36	13	0.9 (0.3–2.5)	
De Roos et al. (2005), USA	100 100	Population	NHL (200, 202)	Lipid-adjusted plasma PCB concentration (ng/g lipid)	Quartiles of PCB concentration			Sex, study site, birth date, and date of blood draw
				PCB-74	7.8–13.3	28	1.12 (0.51–2.45)	
					13.4–19.3	16	0.73 (0.30–1.75)	
					> 19.4	31	1.26 (0.52–3.03)	*P* for trend = 0.66
				PCB-99	5.6–9.3	22	0.63 (0.24–1.68)	
					9.4–16.1	30	1.04 (0.45–2.39)	
					> 16.1	24	0.77 (0.28–2.10)	*P* for trend = 1.0
				PCB-118	8.1–11.8	14	0.36 (0.13–0.98)	
					11.9–25.8	30	0.91 (0.42–1.98)	
					> 25.8	24	0.73 (0.29–1.84)	*P* for trend = 0.88

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
De Roos et al. (2005), USA (cont.)				PCB-138–158	25.2–38.3	20	0.82 (0.38–1.78)	
					38.4–55.5	25	1.04 (0.47–2.33)	
					> 55.5	29	1.42 (0.49–3.05)	*P* for trend = 0.53
				PCB-146	4.4–6.0	24	1.06 (0.36–3.08)	
					6.1–8.7	24	1.37 (0.50–3.79)	
					> 8.7	32	1.81 (0.70–4.64)	*P* for trend = 0.17
				PCB-153	37–56.2	27	1.36 (0.54–3.25)	
					56.3–71.3	16	0.80 (0.32–2.03)	
					> 71.3	34	1.59 (0.63–4.00)	*P* for trend = 0.40
				PCB 156	5.6–7.8	27	1.70 (0.48–6.03)	
					7.9–9.8	16	1.02 (0.32–3.26)	
					> 9.8	40	2.70 (0.97–7.50)	*P* for trend = 0.03
				PCB-170	12.2–17.0	16	0.84 (0.36–1.92)	
					17.1–22.5	27	1.59 (0.63–4.02)	
					> 22.5	31	1.73 (0.73–4.14)	*P* for trend = 0.13
				PCB-180	28.7–41.2	21	1.72 (0.65–4.54)	
					41.3–54.4	22	1.82 (0.70–4.76)	
					> 54.4	41	3.50 (1.53–9.15)	*P* for trend = 0.01
				PCB-183	2.8–4.4	21	0.93 (0.16–5.46)	
					4.5–6.3	22	0.73 (0.26–2.06)	
					> 6.3	27	1.02 (0.36–2.93)	*P* for trend = 0.96
				PCB-187	8.9–12.0	13	0.59 (0.22–1.57)	
					12.1–18.0	33	1.34 (0.59–3.04)	
					> 18.0	30	1.22 (0.49–3.08)	*P* for trend = 0.18
				PCB-194	8.0–11.2	24	1.59 (0.62–4.04)	
					11.3–15.6	20	1.35 (0.53–3.48)	
					> 15.6	37	2.68 (1.04–6.90)	*P* for trend = 0.04
				PCB-126 (pg/g lipid)	19.0–30.3	20	0.65 (0.29–1.49)	
					30.4–52.7	21	0.73 (0.31–1.72)	
					> 52.7	30	1.09 (0.49–2.41)	*P* for trend = 0.54

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
De Roos et al. (2005), USA (cont.)				PCB-169 (pg/g lipid)	18.6–28.4	23	1.14 (0.49–2.66)	
					28.5–37.7	20	1.08 (0.41–2.82)	
					> 37.7	35	2.62 (0.88–7.80)	*P* for trend = 0.11
				Lower chlorinated PCBs (2–4) (mmol/g lipid)	0.028–0.046	28	1.12 (0.51–2.45)	
					0.047–0.066	16	0.73 (0.30–1.75)	
					> 0.067	31	1.26 (0.52–3.03)	*P* for trend = 0.66
				Moderately chlorinated PCBs (5–7) (mmol/g lipid)	0.386–0.599	25	1.52 (0.58–4.01)	
					0.600–0.785	20	1.43 (0.49–4.11)	
					> 0.785	29	1.88 (0.67–5.26)	*P* for trend = 0.29
				Highly chlorinated PCBs (8–10) (mmol/g lipid)	0.019–0.026	24	1.59 (0.62–4.04)	
					0.027–0.036	20	1.35 (0.53–3.48)	
					> 0.036	37	2.68 (1.04–6.90)	*P* for trend = 0.04
				PCB TEQ (summed pg/g lipid, weighted by TEF)	6.41–8.69	16	0.59 (0.25–1.40)	
					8.70–13.17	20	0.86 (0.38–1.98)	
					> 13.17	33	1.51 (0.62–3.67)	*P* for trend = 0.06
Colt *et al.* (2009), USA	685 646	Population	NHL (ICDO-3)	PCB-180 in carpet dust			*Risk increase in % per 10% increase in concentration*	Age, sex, race, study centre, education
					IFNG (C–1615T) TT	243	1.2 (0.1–2.4)	
					IL4 (5′-UTR, Ex1-168C>T) CC	403	1.0 (0.1–1.9)	
					IL16 (3′-UTR, Ex22-871A>G) AA	330	1.1 (0.1–2.1)	
					IL8 (T–251A) TT	172	1.4 (0.05–2.8	
					IL10 (A–1082G) AG/GG	431	0.9 (0.05–1.8)	
	100 100	Population		PCB-180 in plasma	*IFNG* (C–1615T) TT	39	16.9 (3.7–31.6)	
					IL4 (5′-UTR, Ex1-168C>T) CC	62	9.3 (0.9–18.3)	
					IL16 (3′-UTR, Ex22-871A>G) AA	46	15 (3.2–28.0)	
					IL8 (T–251A) TT	27	28.9 (6.4–56.1)	
					IL10 (A–1082G) AG/GG	59	9.9 (1.2–19.4)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Colt et al. (2009), USA (cont.)				TEQ in plasma	*IFNG* (C–1615T) TT	39	19.2 (4.8–35.7)	
					IL4 (5′-UTR, Ex1-168C>T) CC	60	12.5 (3.0–22.9)	
					IL16 (3′-UTR, Ex22-871A>G) AA	44	11.2 (–0.3–24.0)	
					IL8 (T–251A) TT	61	9.1 (0.4–18.6)	
					IL10 (A–1082G) AG/GG	57	5.0 (–3.0–13.8)	
Wang *et al.* (2011), USA	685 646	Population	NHL (ICDO-3)	PCB-180 in carpet dust	> 20.7 ng/g HLA-DRB1*0101 absent	81	1.36 (0.93–1.99)	Age, sex, race, study centre
					> 20.7 ng/g HLA-DRB1*0101 present	17	1.25 (0.66–2.38)	No risk estimates presented for AH 8.1 present genotype. In analysis by major lymphoma subtypes, no increase in risk for DLBCL or follicular lymphoma
	100 100	Population		PCB-180 lipid-adjusted plasma concentration	> 28.7 ng/g lipid HLA-DRB1*0101 absent	65	3.93 (1.49–10.35)	
					> 28.7 ng/g lipid HLA-DRB1*0101 present	10	0.66 (0.18–2.37)	

BMI, body mass index; DLBCL, diffuse large B-cell lymphoma; DL-PCB, dioxin-like PCB; EA, early antigen; EBV, Epstein–Barr virus; Ex, exon; IFNG, inferon gamma; IL, interleukin; LOD, limit of detection; NA, not applicable; NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; ref, reference; NDL-PCB, non-dioxin-like PCB; TEF, toxic equivalency factor; TEQ, toxic equivalent; vs, versus

Risk was highest for those who had resided 10–19 years in the most polluted area (OR, 3.8; 95% CI, 1.5–9.8) (Maifredi *et al.*, 2011). [The authors used the ICD-9 classification to define NHL, and therefore did not include chronic lymphocytic leukaemia among their cases, which precluded any feasible analysis of specific NHL subtypes.]

Several small case–control studies in Sweden used adipose tissue or serum levels of total PCBs and individual congeners as the exposure indicator. In a first study with 27 cases and 17 controls (Hardell *et al.*, 1996, 1997), risk of NHL was elevated for total PCB concentrations [17 congeners] above the median among controls (OR, 1.8; 95% CI, 0.4–7.4), after adjusting for age and sex. Thirty-six PCB congeners were measured in a second study with 82 cases of NHL and 83 controls. The odds ratio was significantly increased for concentration of immunotoxic PCBs (Moysich *et al.*, 1999a) above the median among the controls (OR, 3.2; 95% 1.4–7.4) (Hardell *et al.*, 2001). An interaction was observed between elevated concentrations of total and immunotoxic PCBs above the median and EBV-EA antibodies: EBV-EA seropositivity (EBV-EA antibody titre >80) and adipose total PCB concentrations were associated with an increase in risk of NHL of two- to fourfold, which was highest when the immunotoxic PCB subgroup was considered (OR, 6.4; 95% CI, 1.9–24). When the low-grade B-cell NHLs were analysed separately, risk associated with elevated median concentrations of immunotoxic PCBs among subjects with EBV-EA seropositivity was increased 17-fold (95% CI, 3.1–150; 16 cases) (Hardell *et al.*, 2001).

Another case–control study in Sweden included 99 cases of NHL and 99 population controls, matched to cases by age, sex, and health-service region (Hardell *et al.*, 2009). After adjusting by age, sex, and BMI, risk of NHL was elevated for values above the median among controls for the sum of PCBs (OR, 2.0; 95% CI, 0.99–3.9), and to a lesser extent for the subgroups of moderately chlorinated PCBs, highly chlorinated PCBs, or immunotoxic PCBs. Risk was highest for follicular lymphoma for the subgroup of highly chlorinated PCBs (OR, 9.6; 95% CI, 1.9–49; 18 cases); immunotoxic PCBs (OR, 3.0; 95% CI, 0.9–11); and less chlorinated PCBs (OR, 2.8; 95% CI, 0.9–9.0). Risks were only moderately and non-significantly elevated for diffuse large B-cell lymphoma. When stratified by EBV-EA antibody titre, risk of NHL associated with total PCB concentration above the median was 5.2 (95% CI, 1.9–14) among EBV-EA-positive subjects, and ranged from 3.0 to 5.0 for the above-mentioned PCB subgroups; risk for diffuse large B-cell lymphoma ranged from 3.8 to 7.0 by PCB subgroup (all statistically significant), and was 6.2 (95% CI, 1.6–25) for immunotoxic PCBs (Hardell *et al.*, 2009).

A case–control study focused on 54 cases of hairy cell leukaemia [a rare subtype of NHL] identified in the Swedish Cancer registry, and 54 controls drawn from the national population registry, matched to cases by age, sex, and county (Nordström *et al.*, 2000). Concentrations of 36 PCBs were measured in plasma. Overall, risk was not elevated for total PCB concentration greater than the median value (OR, 0.8; 95% CI, 0.3–1.9). When stratifying by EBV-EA antibody titre, the odds ratio for exposure above the median of values was 4.4 (95% CI, 1.2–18.5; 13 cases) for total PCBs and 11.3 (95% CI, 2.3–73.1; 15 cases) for immunotoxic PCBs among subjects with EBV-EA titres ≥ 40 (Nordström *et al.*, 2000). [The Working Group highlighted some methodological concerns about this group of studies, including poor precision, recruitment of cases and controls at different times, some with PCB measurements in adipose tissue and others with measurements in plasma.]

The largest case–control study of PCB body burden in relation to risk of NHL was conducted in Canada (Spinelli *et al.*, 2007). Lipid-adjusted concentrations of 14 PCB congeners were measured in pretreatment samples of plasma from

422 cases of NHL and 460 population controls, frequency-matched to cases by 5-year age-groups, sex, and residence. Odds ratios were adjusted for age, sex, education, BMI, ethnicity, farming, and family history of NHL. Risk of NHL was found to be highest in the highest quartile of the sum of dioxin-like PCBs (OR, 2.40; 95% CI, 1.53–3.77) and of non-dioxin-like congeners (OR, 2.18; 95% CI, 1.41–3.38). Individual congeners showing a significant excess risk in the top quartile of plasma concentration included PCB-118 and PCB-156, among the dioxin-like PCBs, and PCB-138, PCB-153, PCB-170, PCB-180, and PCB-187, among the non-dioxin-like PCBs. The observed associations were consistent across the four NHL subtypes examined, including DLBCL, follicular lymphoma, T-cell lymphoma, and other B-cell lymphomas (Spinelli *et al.*, 2007). [This was one of the largest studies of NHL and PCBs, and accounted for relevant confounders. The Working Group judged it to be a high-quality study, which was notable for providing results for individual congeners and lymphoma subtypes. While the participation rate for controls was less than 50%, the Working Group noted that this was typical of the available case–control studies and that potential confounding factors, including education, were comparable between cases and controls despite differences in participation. The most consistent associations were seen for follicular lymphoma and exposure to dioxin-like PCBs.]

A multicentre European study of NHL included 174 cases and 203 controls from France, Germany, and Spain (Cocco *et al.*, 2008). Patients admitted to the same hospital as the cases for non-cancer diseases not related to known risk factors for NHL were selected as controls in France and Spain; controls in Germany were a random sample of the general population. Concentrations of nine PCB congeners were measured in plasma, and risk estimates were adjusted by age (continuous), sex, education, and centre. Risk of NHL did not increase by quartile of plasma concentration of total PCBs, or specific congeners, or the functional PCB congener groups as defined by Hansen (Hansen, 1998). When exploring risk by lymphoma subtype, a nonsignificant increase was observed for chronic lymphocytic leukaemia in the top quartile of concentration of immunotoxic PCBs and BRCA1-inhibiting PCBs, with no indication of an increasing trend, or of an association with specific PCB congeners. No association was observed with risk of diffuse large B-cell lymphoma. However, risk of chronic lymphocytic leukaemia associated with plasma concentrations of immunotoxic PCBs above the median showed a threefold increase (OR, 3.2; 95% CI, 0.9–11.5), increasing to sixfold (OR, 6.1; 95% CI, 1.0–37.8) in the upper quartile, in subgroup analyses of the German and French subgroups combined, but not in the Spanish subgroup; a significant heterogeneity by country was observed for risk of chronic lymphocytic leukaemia associated with immunotoxic PCBs, but not for the sum of total PCBs. [The Working Group judged this international study to be high in quality; the classification of lymphoma was particularly meticulous. Although the overall results were null, the association of immunotoxic PCBs with chronic lymphocytic leukaemia in two of the three centres is noteworthy. The heterogeneity between countries may have been a result of differences in PCB exposure or distribution of confounding factors.]

Pretreatment plasma samples were available in a subset of 100 cases with a histologically confirmed diagnosis of NHL and 100 controls out of the 1321 cases and 1057 general population controls who participated in a case–control study on NHL conducted by the United States National Cancer Institute in 1998–2000 in four areas with population-based cancer registries (Iowa, Los Angeles, CA, Detroit, MI, and Seattle, WA) (De Roos *et al.*, 2005). Concentrations of 36 non-coplanar and 4 coplanar congeners were measured in plasma. Risk of NHL overall and of its major subtypes was analysed in relation

to 28 PCB congeners detected in at least 30% of samples. Values below the detection limit were estimated by multiple imputation. Odds ratios were adjusted for the matching factors, age, sex, study site, and date of blood draw. Other potential confounders were tested, including education, race, BMI, and family history of NHL, but no confounding was observed. The results showed significant upward trends in risk of NHL with increasing quartiles of plasma concentration of the subgroup of highly chlorinated PCB congeners (test for trend, $P = 0.04$), which included PCB-156, PCB-180, and PCB-194. An increase of 10 TEQ pg/g lipid was associated with a 35% excess risk of NHL (95% CI, 1.02–1.79). Some associations were stronger among the 14 cases of DLBCL than the 25 cases of follicular lymphoma, both in men and women, and trends by exposure quartiles became significant for follicular lymphoma for PCB-180 and PCB-187 (De Roos *et al.*, 2005). [Despite the extensive analysis, this was a relatively small study, with wide confidence intervals.]

Colt *et al.* (2009) used the same data set to explore the interaction between common variants in genes implicated in the immune and inflammatory response and PCB-180, (the non-dioxin like PCB that showed the strongest association between NHL and levels measured in plasma (100 cases and 100 controls) and carpet dust (682 cases and 513 controls) in the analysis by De Roos *et al.* (2005). Sixty-one single nucleotide polymorphisms in 36 proinflammatory and other immunoregulatory genes were analysed in samples of blood or buccal cells. Relative risk estimates were adjusted for sex, age, race, education, and study centre. The concentration of PCB-180 in plasma was associated with increased risk of NHL (OR, 8.3%; 95% CI, 1.9–14.6% per 10% increment), but the concentration in carpet dust was not (OR, 0.7%; 95% CI, 0.0–1.3% per 10% increment). Significant increases in risk of NHL were observed for PCB-180 in both plasma and carpet dust and for *IFNG* (C–1615T) TT, *IL4* (5′-UTR, Ex1-168C>T) CC, *IL16* (3′-UTR, Ex22-871A>G) AA, *IL8* (T–251A) TT, and *IL10* (A–1082G) AG/GG genotypes (Colt *et al.*, 2009).

Another analysis was conducted on the same data set to explore the interaction between status of HLA-DRB1*01:01 class II leukocyte surface antigen and of the extended ancestral haplotype (AH) 8.1 (HLA-A*01-B*08-DR*03-TNF-308A) and blood concentrations of PCB-180 above the median in the control group. Risk of NHL overall was elevated among study subjects lacking the HLA-DRB1*01:01 allele or the AH 8.1 allele (OR, 3.93; 95% CI, 1.49–10.35). No significant increase in risk was observed with PCB-180 in carpet dust or for DLBCL or follicular lymphoma (Wang *et al.*, 2011). [These related studies were well conducted, but the subgroup analyses were based on small numbers.]

2.3.2 Cancer of the breast

See Table 2.10

(a) Smaller studies

Case–control studies of cancer of the breast with 100 or fewer cases, most published before 2000, are reviewed here briefly and are not presented in the table. Most of these studies did not present risk estimates according to PCB concentrations.

One of the earliest studies looked at PCB concentrations in samples of breast adipose tissue from 14 living and 18 deceased patients with cancer of the breast, 21 similar samples from non-cancer patients, and samples of adipose tissue from 35 non-cancer autopsies, and found no significant differences (Unger *et al.*, 1984).

In another study, mean concentrations of PCBs in the breast tissue of 20 women with cancer of the breast were significantly higher ($P = 0.02$) than in 20 women with benign breast disease, and the association persisted after controlling for age, smoking, and BMI (Falck *et al.*, 1992).

Table 2.10 Case-control studies on cancer of the breast and exposure to PCBs

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Recio-Vega *et al.* (2011), Comarca Lagunera, Mexico	70 70	Hospital-based: 70 women with biopsies negative for malignancy, from the same hospital	Questionnaire; serum concentrations of 20 PCB congeners[a] measured by GC	Total PCBs	NR	1.09 (1.02–1.16)	Age, age at menarche, lactation, menopausal status, BMI, family history of breast cancer [The Working Group was not clear on how analysis was performed to obtain risk estimates.] PCb groups according to Wolff & Toniolo (1995)
				Premenopausal	NR	1.08 (0.99–1.17)	
				Postmenopausal	NR	1.13 (1.01–1.25)	
				Group 1a	NR	1.19 (0.81–1.7)	
				Group 1b	NR	1.40 (0.94–2.1)	
				Group 2a	NR	1.22 (0.99–1.49)	
				Group 2b	NR	1.90 (1.25–2.88)	
				Group 3	NR	1.81 (1.08–3.04)	
				Group 4	NR	1.57 (1.20–2.07)	
				Group 5	NR	1.30 (0.84–2.04)	
Moysich *et al.* (1998, 1999b), Erie and Niagara counties of western New York, USA, 1986–1991	154 postmenopausal women with incident primary breast cancer identified from hospitals 192 controls	Community controls frequency matched by age and county of residence	Structured interview; *CYP1A1* polymorphism was determined by PCR-RFLP; Lipid-adjusted serum PCBs (56 congener peaks based on the concentrations of 73 congeners) measured by GC (ng/g lipid)	*Total PCBs:*			Age, education, family history of breast cancer, parity, quetelet index (BMI), duration of lactation, age at first birth, serum lipids, years since last pregnancy, fruit and vegetable intake, serum lipids, and smoking status
				PCB low (0.75–3.72 ng/g):			
				Ile:Ile	62	1.00	
				Ile:Val/Val:Val	8	0.88 (0.29–2.70)	
				PCBs > 3.72 ng/g:			
				Ile:Ile	65	1.08 (0.62–1.89)	
				Ile:Val/Val:Val	19	2.93 (1.18–7.45)	
				Total PCBs:			
				All subjects:			
				2.93–4.43	45	0.70 (0.37–1.29)	
				4.44–19.04	56	1.14 (0.61–2.15)	$P = 0.51$
				Never lactated ($n = 107$):			
				2.93–4.43	15	1.71 (0.55–5.35)	
				4.44–19.04	20	2.87 (1.01–7.29)	$P = 0.07$
				Ever lactated ($n = 191$):			
				2.93–4.43	41	0.38 (0.17–1.03)	
				4.44–19.04	36	0.71 (0.31–1.61)	$P = 0.72$
				Less chlorinated			Data NR for women who never lactated
				0.01–0.31	59	2.04 (1.09–3.83)	
				0.32–1.65	63	1.40 (0.76–2.59)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Moysich et al. (1998, 1999b), (cont.)				*Moderately chlorinated*			
				All subjects:			
				2.20–3.12	41	0.57 (0.03–1.07)	
				3.13–15.07	60	1.37 (0.73–2.59)	$P = 0.69$
				Never lactated:			
				2.20–3.12	12	0.73 (0.22–2.63)	
				3.13–15.07	23	3.57 (1.10–8.60)	P = 0.08
				Highly chlorinated			
				All subjects:			
				0.26–0.44	43	0.79 (0.42–1.52)	
				0.45–1.30	54	1.19 (0.60–2.36)	
				Never lactated:			
				0.26–0.44	11	0.51 (0.15–1.69)	
				0.45–1.30	21	1.53 (0.47–4.95)	
Wolff *et al.* (2000b), New York, New York, USA	175 cases with incident breast cancer 355 controls	Hospital controls matched by age, race/ethnicity	Structured interview in person or by telephone Lipid-adjusted serum PCB concentration (μg/g lipid)	Tertiles of PCB concentration (μg/g lipid)			Age, age^2, menopausal status, race, BMI, family history of breast cancer, lactation, parity Tumor stage and markers (ER, PR, p53, erbB-2) identified histologically and immunohistochemically by pathologist ORs not reported by tumour marker status
				Highly chlorinated			
				0.460–0.798	46	0.88 (0.52–1.5)	
				0.799–3.3	46	0.78 (0.45–1.3)	
				Less chlorinated			
				0.085–0.162	54	1.47 (0.84–2.6)	
				0.163–2.39	38	0.96 (0.53–1.7)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Millikan *et al.* (2000), North Carolina, USA 1993–1996	748 cases, aged 20–74 years 659 controls	Population-based, frequency-matched to cases on race and age	Structured interview. Lipid-adjusted plasma concentrations of PCBs measured by GC (μg/g lipid)	Tertiles of PCB concentration *Total PCBs* All women: 0.283–0.468 ≥ 0.469 African-American: 0.312–0.53 ≥ 0.54 White: 0.265–0.416 ≥ 0.417 *Low to moderately chlorinated* Tertile 2 Tertile 3 *Highly chlorinated* Tertile 2 Tertile 3	 266 243 97 116 172 135 NR NR NR NR	 1.29 (0.97–1.72) 1.09 (0.79–1.52) 1.35 (0.84–2.16) 1.74 (1.00–3.01) 1.32 (0.92–1.90) 1.03 (0.68–1.56) 0.96 (0.73–1.27) 0.99 (0.73–1.35) 1.41 (1.05–1.87) 1.35 (0.97–1.88)	Age, age^2, race (all participants), menopausal status, BMI, parity, lactation, use of HRT, and income Response rates: cases, 76%; controls, 55%. PCB and lipid measurements were available for 748 cases (84%) and 659 controls (78%)
Li *et al.* (2005), North Carolina, USA, 1993–1996 (same population as Millikan *et al.*, 2000)	612 cases 599 controls	Population	Lipid-adjusted plasma PCB concentration by GC (ng/g lipid)	*Total PCBs* African-American: < 0.430 ≥ 0.430 < 0.430 ≥ 0.430 White: < 0.349 ≥ 0.349 < 0.349 ≥ 0.349	*CYP1A1 M1* genotype 66 75 42 59 174 122 45 29	 Non-M1: 1.0 (Ref) Non-M1: 1.5 (0.9–2.5) Any M1: 1.0 (0.6–1.7) Any M1: 1.4 (0.8–2.5) Non-M1: 1.0 (Ref) Non-M1: 0.7 (0.5–1.0) Any M1: 0.8 (0.5–1.2) Any M1: 0.8 (0.4–1.4)	Age, race, parity, use of HRT, oral-contraceptive use, breast feeding, smoking, alcohol consumption, income, education, height, waist/hip ratio, BMI See Millikan *et al.* (2000) for details Interaction contrast ratio: 0.0 (–0.9–0.9) Interaction contrast ratio: 0.4 (–0.2–0.9)

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Li et al. (2005), (cont.)							Likelihood ratio test for both groups not statistically significant
				White:		*CYP1A1 M2* genotype	
				< 0.349	210	Non-M2: 1.0 (Ref)	
				≥ 0.349	138	Non-M2: 0.7 (0.5–1.0)	
				< 0.349	11	Any-M2: 0.4 (0.2–0.8)	
				≥ 0.349	15	Any-M2: 0.9 (0.4–1.9)	Interaction contrast ratio: 0.8 (0.1–1.6)
							Likelihood ratio test: $P = 0.02$
				African-American:		*CYP1A1 M3* genotype	
				< 0.430	95	Non-M3: 1.0 (Ref)	
				≥ 0.430	105	Non-M3: 1.3 (0.8–2.0)	
				< 0.430	13	Any M3: 0.6 (0.3–1.2)	
				≥ 0.430	29	Any M3: 1.6 (0.8–3.2)	Interaction contrast ratio: 0.8 (–0.3–1.9)
							Likelihood ratio test: $P = 0.10$
Demers *et al.* (2000, 2002), Quebec City, Quebec, Canada, 1994–1997	315 women with histologically confirmed infiltrating primary breast cancer 523 controls	Hospital and population, 523 cases frequency-matched by age and rural/urban residence	Telephone interview. Lipid-adjusted serum concentrations for 14 PCB congeners[b] measured by GC/ECD (μg/g lipid)	Quartiles of PCB concentration			Age, region of residence, BMI, history of benign breast disease, breastfeeding duration Participation rate: cases, 91%; hospital controls, 89%; and population controls, 47%. PCBs 28, 52, 101, 105 and 128 were detected in < 70% of women and were excluded from analysis. Results for other PCBs were not statistically significant
				PCB-118			
				9.4– < 14.3	64	0.90 (0.58–1.39)	
				14.3– < 22.1	78	1.12 (0.73–1.74)	
				≥ 22.1	104	1.60 (1.01–2.53)	
				PCB-156:			
				5.8–< 7.6	83	1.44 (0.91–2.26)	
				7.6–< 9.8	80	1.44 (0.90–2.31)	
				≥ 9.8	101	1.80 (1.11–2.94)	
				DL-PCBs (PCB-105, PCB-118, and PCB-156 in TEQ ng/kg)			
				4.2 to < 5.7	85	1.63 (1.04–2.55)	
				5.7 to < 7.4	78	1.45 (0.90–2.32)	
				≥ 7.4	102	2.02 (1.24–3.28)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Gammon *et al.* (2002), Long Island, New York, USA 1996–1997	646 cases 429 controls	Population based, matched by age	In-person interview and non-fasting blood sample Lipid-adjusted serum concentrations for 24 PCB congeners[c]	Quintiles of PCB concentration *(Sum of PCBs 118, 138, 153, and 180)*			Age, race, reproductive history, benign breast disease Interview response rates: cases, 83.2%; controls, 68.0%. No statistically significant results for other PCBs measured Results reported for four most common congeners. Numerous potential confounders investigated
				262.58–325.56	112	0.76 (0.51–1.15)	
				325.57–427.78	132	0.90 (0.60–1.35)	
				427.79–586.74	123	0.82 (0.54–1.24)	
				583.74–3287.34	126	0.83 (0.54–1.29)	
				PCB-118			
				32.66–46.45	133	0.96 (0.64–1.42)	
				46.46–63.39	109	0.77 (0.52–1.16)	
				63.40–94.94	114	0.82 (0.54–1.24)	
				94.95–1015.88	136	0.93 (0.60–1.43)	
				PCB-138			
				49.38–81.09	153	1.26 (0.85–1.88)	
				81.10–111.15	129	1.04 (0.69–1.55)	
				111.16–156.22	106	0.80 (0.52–1.21)	
				156.23–936.75	120	0.96 (0.63–1.48)	
				PCB-153			
				103.75–130.02	115	0.75 (0.50–1.13)	
				130.03–170.81	132	0.85 (0.57–1.27)	
				170.82–227.54	107	0.68 (0.45–1.03)	
				227.55–1130.08	132	0.86 (0.56–1.32)	
				PCB-180			
				51.49–69.70	121	0.87 (0.58–1.31)	
				69.71–87.41	117	0.81 (0.54–1.23)	
				87.42–120.37	128	0.89 (0.58–1.34)	
				120.38–721.29	134	0.95 (0.62–1.46)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Gatto *et al.* (2007), Los Angeles County, USA, 1994–1998	355 African-American women with histologically confirmed invasive breast cancer 327 controls	Population based, African-American women matched by age	Interview with structured questionnaire. Lipid-adjusted serum PCB concentration (congeners NR) measured by GC	Quintiles of total PCBs (μg/g) ≥ 0–0.38 > 0.38–0.47 > 0.47–0.60 > 0.60	 61 46 42 61	 1.06 (0.67–1.67) 0.82 (0.50–1.33) 0.76 (0.47–1.24) 1.01 (0.63–1.63)	Age, BMI, breastfeeding No statistically significant results by ER+/–, *p53*, or HER-2 status *P* for trend = 0.56
Itoh *et al.* (2009), Nagano Prefecture, Japan, 2001–2005	403 women aged 20–74 years with newly diagnosed invasive breast cancer 403 controls	Hospital-based	Self-administered questionnaire; hormone receptor status obtained from medical records; lipid-adjusted serum concentrations of 41 PCB congeners (ng/g lipid)	Total PCB quartiles (median) 110 160 200 290 *Highest vs lowest quartiles of exposure* PCB-153 PCB-138 PCB-180	 126 96 102 79 NR NR NR	 1.00 (ref) 0.79 (0.36–1.72) 0.57 (0.28–1.15) 0.33 (0.14–0.78) 0.40 (0.18–0.91) 0.61 (0.28–1.35) 0.29 (0.13–0.66)	Total lipid concentration in serum, BMI, reproductive risk factors, smoking, diet, medical history *P* for trend = 0.008 *P* for trend = 0.04 *P* for trend = 0.29 *P* for trend = 0.004
Zheng *et al.* (2000a), Connecticut, USA, 1994–1997	304 cases 186 controls	Hospital-based, with benign breast disease or normal tissue	Structured interview; lipid-adjusted breast adipose tissue concentrations of 9 PCB congeners[d] measured by GC (ng/g lipid)	Total PCBs 396.0–562.9 ≥ 563.0	 79 114	 0.6 (0.4–1.0) 0.7 (0.4–1.1)	Age, BMI, fat consumption, income, race, family history of breast cancer, and reproductive risk factors Participation rate: cases, 79%; controls, 74%. Stratification by type of breast disease, menopausal status, parity, lactation and body size showed no association with PCBs

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Zheng *et al.* (2000b), Connecticut, USA, 1995–1997	475 cases 502 controls	Hospital, with benign disease or population matched by age	Structured interview; lipid-adjusted serum concentrations of 9 PCB congeners[d] measured by GC (ng/g lipid)	Total PCBs 604.1–800.0 > 800.0	 160 160	 1.04 (0.76–1.45) 0.95 (0.68–1.32) *P* for trend = 0.41	Age, BMI, reproductive risk factors, HRT, dietary fat intake, family history of breast cancer, income, race, and study site When stratifying by parity, lactation and menopausal and ER status, no association was identified between PCBs and risk of breast cancer
Holford *et al.* (2000), Connecticut, USA, 1994–1997 (same population as Zheng *et al.*, 2000a)	304 cases 186 controls	Hospital-based	Breast adipose tissue analysed for 9 PCB congeners measured by GC (ng/g lipid)	*Linear logistic model* PCB-74 PCB-118 PCB-138 PCB-153 PCB-156 PCB-170 PCB-180 PCB-183 PCB-187 *Logistic ridge regression model* PCB-153 PCB-156 PCB-180 PCB-183	 	10-ppb change in exposure 0.93 (0.84–1.04) 1.04 (0.96–1.12) 1.04 (0.94–1.16) 0.87 (0.78–0.98) 0.79 (0.64–0.99) 0.85 (0.65–1.11) 1.14 (1.0–1.29) 1.82 (1.12–2.98) 1.11 (0.90–1.37) 0.98 (0.96–1.01) 0.87 (0.78–0.99) 1.02 (0.99–1.05) 1.23 (0.98–1.54)	Age, BMI, reproductive risk factors, dietary fat intake, income, fat concentrations of DDE See Zheng *et al.* (2000a) for details

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Zhang *et al.* (2004), Connecticut, USA, 1999–2002	374 Caucasian women 406 controls	Hospital- and population-based, matched by age	Structured in-person interview; lipid-adjusted serum concentrations of 9 PCB congeners[d] measured by GC (ng/g lipid) Genotyping of *CYP1A1 m1*, *m2*, and *m4* by PCR-RFLP	Total PCBs:			See Zheng *et al.* (2000a, b) for details No significant association for *CYP1A1* m1 or m4 genotype or in premenopausal women
				310–610	173	1.00 (ref.)	
				611–2600	201	1.2 (0.9–1.6)	
				CYP 1A1 m2 genotype			
				All women:			
				Wildtype, low	157	1.00 (ref.)	
				Wildtype, high	177	1.2 (0.9–1.6)	
				Variants, low	16	1.6 (0.7–3.5)	
				Variants, high	24	3.6 (1.5–8.2)	
				Postmenopausal women:			
				Wildtype, low	130	1.0	
				Wildtype, high	125	1.1 (0.8–1.6)	
				Variants, low	13	1.8 (0.7–4.5)	
				Variants, high	21	4.3 (1.6–1.2)	
Rusiecki *et al.* (2004), Connecticut USA, 1994–97 (subgroup from same population as Zheng *et al.*, 2000a)	266 cases 347 controls	Hospital-based, benign breast disease	Interview; serum and breast adipose tissue analysed for 9 PCB congeners	*Total PCBs*			Age, reproductive risk factors, BMI, family history of breast cancer in a first-degree relative Tumours were apparent with concentrations of PCB-183 (third tertile vs first: OR, 2.4; 95% CI, 1.0–6.0, *P* for trend = 0.03, but data not otherwise shown) Analyses for individual congeners did not show any association
				ER+PR+			
				394.31–558.69	21	0.6 (0.3–1.2)	
				> 558.69	33	0.6 (0.3–1.3)	
				ER–PR–			
				394.31–558.69	20	0.5 (0.3–1.0)	
				> 558.69	24	0.5 (0.3–1.1)	
				ER+PR-			
				394.31–558.69	17	1.0 (0.4–2.5)	
				> 558.69	16	0.6 (0.2–1.6)	
				ER–PR+			
				394.31–558.69	4	0.2 (0.1–0.7)	
				> 558.69	12	0.5 (0.2–12.0)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Stellman *et al.* (2000), Long Island, New York, USA, 1994–1996	232 cases 323 controls	Hospital	Structured interviews; 14 PCB congeners[e] in breast adipose tissue using GC	Total PCBs (ng/g) 181.82–332.24 > 332.24 PCB-156 5.87–13.59 > 13.60 PCB-183 3.16–5.66 > 5.67	 74 103 NR NR NR NR	 1.06 (0.67–1.69) 1.01 (0.60–1.69) 1.9 (1.1–3.0) 1.5 (0.9–2.5) 1.3 (0.8–2.1) 2.0 (1.2–3.4)	Age, BMI, race > 95% of eligible patients agreed to participate. Adipose tissue was obtained from 86% of all subjects. ORs for other PCB congeners, NR
Aronson *et al.* (2000), Ontario, Canada, 1995–1997	217 cases 213 controls	Hospital-based, cancer-free women, matched by age and study site	Telephone interview or mailed questionnaire; breast tissue analysed for 14 PCB congeners[b] expressed in µg/kg	*PCB-105* 4.2–6.1 6.2–12 ≥ 13 Premenopausal 4.2–6.1 > 6.1 Postmenopausal 4.2–6.1 > 6.1 *PCB-118* 17–27 28–49 ≥ 50 Premenopausal 17–27 > 27 Postmenopausal 17–27 > 27	 NR NR NR 12 30 25 86 NR NR NR 19 28 30 91	 1.16 (0.62–2.14) 2.03 (1.12–3.68) 3.17 (1.51–6.68) *P* for trend ≤ 0.01 1.29 (0.52–3.20) 3.91 (1.73–8.86) 0.98 (0.38–1.49) 1.49 (0.70–3.16) 1.25 (0.68–2.29) 1.88 (1.00–3.55) 2.31 (1.11–4.78) 1.04 (0.46–2.35) 2.85 (1.24–6.52) 1.39 (0.57–3.41) 1.58 (0.70–3.58)	Age, study site, HRT, ethnicity, family history of breast cancer, BMI, fat intake, alcohol intake, smoking, reproductive history Most controls were diagnosed with benign breast disease PCBs 28, 52, 101 and 128 were < LOD for > 30% of subjects and were not investigated

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Aronson et al. (2000), (cont.)				*PCB-170*			
				24–34	NR	1.60 (0.92–2.78)	
				35–53	NR	1.09 (0.61–1.96)	
				≥ 54	NR	1.15 (0.60–2.22)	
				Premenopausal			
				24–34	24	0.83 (0.39–1.78)	
				> 34	25	0.89 (0.49–1.91)	
				Postmenopausal			
				24–34	51	3.27 (1.44–7.44)	
				> 34	76	1.63 (0.77–3.45)	
				PCB-180			
				52–71	NR	1.56 (0.90–2.70)	
				72–105	NR	1.21 (0.68–2.14)	
				≥ 106	NR	1.27 (0.66–2.46)	
				Premenopausal			
				52–714	26	1.07 (0.55–2.27)	
				> 71	23	0.89 (0.42–1.91)	
				Postmenopausal			
				52–714	46	2.43 (1.09–5.43)	
				> 71	80	1.77 (0.85–3.69)	
Aschengrau *et al.* (1998), Cape Cod, Massachusetts, USA, 1983–1986	261 incident cases 753 controls	Population, similar age and race	Structured interview, JEM and expert assessment	Possible or probable	5	3.2 (0.8–12.2).	Age, vital status, family history of breast cancer, age at first birth, personal history of prior breast cancer, benign breast disease, educational level and race PCB congeners to which cases were potentially exposed are not specified. Response rate: cases, 79%; controls, 74–81%

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
McElroy *et al.* (2004), Wisconsin, USA, 1998–2000	1481 cases 1301 controls	Population-based, of similar age	Telephone interview; consumption of sport-caught fish	*Recent consumption of sport-caught fish*			Age, family history of breast cancer, alcohol consumption, weight gain, weight at age 18 years, education, reproductive history
				Any	701	1.00 (0.86–1.17)	
				Premenopausal	286	1.24 (0.96–1.59)	
				Postmenopausal	388	0.91 (0.74–1.11)	
				Recent consumption of Great Lakes fish			
				Any	210	1.06 (0.84–1.33)	
				Premenopausal	95	1.70 (1.16–2.50)	
				Postmenopausal	104	0.78 (0.57–1.07)	

[a] The 20 PCB congeners were PCBs 8, 18, 28, 44, 52, 66, 77, 101, 105, 118, 126, 138, 148, 153, 170, 180, 187, 195, 206 and 209

[b] The 14 PCB congeners were PCBs 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187

[c] The 24 PCB congeners were PCBs 15, 28, 74, 66, 56, 101, 99, 82, 118, 146, 153, 105, 138, 178, 187, 183, 167, 174, 177, 156, 180, 170, 199, and 203

[d] The 9 congeners were PCBs 74, 118, 138, 153, 156, 170, 180, 183, and 187

[e] The 14 PCB congeners were PCBs 74, 99, 118, 138, 146, 153, 156, 167, 170, 172, 178, 180, 183, and 187

BMI, body mass index; CI, confidence interval; ER, estrogen receptor; GC, gas chromatography; HRT, hormone replacement therapy; Ile, isoleucine; JEM, job-exposure matrix; LOD, limit of detection; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PR, progesterone receptor; ref., reference; TEQ, toxic equivalent; Val, valine; vs, versus

In a study in Quebec City, Canada, in 17 women with cancer of the breast and 17 controls (Dewailly *et al.*, 1994), the concentration of PCB-99 was higher in the breast adipose tissue of women with ER-positive (ER+) infiltrating adenocarcinoma than in controls, while there were no significant differences for ER– women with cancer of the breast compared with controls, or for other PCB congeners or total PCBs.

In a study in Sweden, PCB concentrations were measured in non-tumour breast adipose tissue of 43 women with breast cancer and 35 controls (Liljegren *et al.*, 1998). Odds ratios adjusted for age and parity showed no association with concentrations of total PCB congeners in all subjects. However, among the subgroup of women with ER+ tumours, increased risk was observed for PCB-77 (OR, 33; 95% CI, 1.8–588) and PCB-126 [odds ratio not calculated as there were no unexposed cases].

In Hesse, Germany, concentrations of 12 PCB congeners in breast tissue from 45 women with cancer of the breast were compared with those in breast tissue from 20 women with benign breast disease: the average concentration of PCB-118 was significantly higher in the cases, with no statistical difference for other congeners (Güttes *et al.*, 1998).

A case–control study in eastern Slovakia included 24 cases of cancer of the breast diagnosed between 1997 and 1999 and 88 population controls, and measurements were made of 15 PCBs in serum (Pavuk *et al.*, 2003). Median concentrations of total PCBs were slightly higher among controls, and although odds ratios were less than unity, no finding was statistically significant.

In two reports of studies of 100 cases of cancer of the breast and 100 surgical controls in Belgium (Charlier *et al.*, 2003), concentrations of PCB-101 and PCB-153 were significantly higher for cases than controls. A second study of 60 cases and controls by the same authors reported an association only for PCB-153 (OR, 1.8; 95% CI, 1.4–2.5) after adjusting for age and reproductive risk factors (Charlier *et al.*, 2004). [It was not clear whether the same population was studied in both articles.]

In a case–control study in Mexico, 70 cases of cancer of the breast were compared with 70 hospital controls, and blood samples were taken for measurement of 20 PCB congeners (Recio-Vega *et al.*, 2011). An increased risk of cancer of the breast was apparent for total PCBs (OR, 1.09; 95% CI, 1.02–1.16) and for the exposure groups 2b (OR, 1.90; 95% CI, 1.25–2.88), 3 (OR, 1.81; 95% CI, 1.08–3.04), and 4 (OR, 1.57; 95% CI, 1.20–2.07) defined according to Wolff & Toniolo (1995). Elevated odds ratios were reported for several PCB congeners (PCB-118, PCB-128, PCB-138, PCB-170, PCB-180, PCB-187, PCB-195, PCB-206 and PCB-209) and risks were generally higher in postmenopausal women. [Although this was a small study, several increased risks were reported. However, the analytical approach was unclear to the Working Group and the age distribution was notably different in cases and controls, suggesting potential for residual confounding by age.]

Using a registry of banked serum collected between 1981 and 1987 from 63 Alaskan native women who subsequently developed cancer of the breast and 63 age-matched cancer-free women, analyses adjusting for ethnicity, family history of cancer of the breast, and parity showed no association with PCB exposure (Rubin *et al.*, 2006). In a study in Greenland of 31 cases of cancer of the breast and 115 controls, all of Inuit descent, some evidence of higher serum concentrations of PCBs was found for patients with cancer of the breast compared with controls; however, the odds ratios for total PCBs did not demonstrate any association (Bonefeld-Jørgensen *et al.*, 2011). [The populations included in these studies were of special interest due to their documented high exposures to PCBs.]

(b) *Larger studies of PCB concentrations in blood*

In a case–control study in western New York State, USA, 154 postmenopausal women with incident cancer of the breast and 192 postmenopausal community controls were compared in terms of serum concentrations of 73 detected congeners (Moysich *et al.*, 1998). No association with total PCBs, moderately chlorinated PCBs or highly chlorinated PCBs was found, but increased risk was apparent for less chlorinated PCBs above the detection limit (OR, 1.66; 95% CI, 1.07–2.88 for the combined second and third tertiles); among parous women who had never lactated the magnitude of risk was higher in association with total PCBs (OR, 2.87; 95% CI, 1.01–7.29) and moderately chlorinated PCBs (OR, 3.57; 95% CI, 1.10–8.60). In a subsequent study on PCBs and *CYP1A1* polymorphism (found to be induced by PCBs in experimental studies, see Section 4), no association with *CYP1A1* genotype was found among women with a low PCB body burden; among women with a PCB burden above the median for the control group, an increased risk of cancer of the breast was observed when at least one valine allele was present (OR, 2.93; 95% CI, 1.18–7.45) when compared with women who were homozygous for the isoleucine allele (Moysich *et al.*, 1999b). Adjustment for serum lipids and BMI did not affect the magnitude of this association. [Although not large, this study was rigorous in terms of design and implementation.]

Among patients of several ethnic groups in a hospital-based case–control study in New York City, USA, 175 patients with cancer of the breast and 355 control patients were frequency-matched by age and race/ethnicity (Wolff *et al.*, 2000b). Highly chlorinated and less chlorinated biphenyls and other chlorinated compounds were measured in serum, and the tumour markers ER, progesterone receptor (PR), *p53*, and erbB-2 were assessed. Concentration of PCBs was not associated with risk of cancer of the breast. Risk of cancer of the breast was not examined with respect to tumour stage or markers, but PCB concentrations did not differ according to these factors. [This was a high quality study notable for the number of tumour markers investigated, but the analysis focused largely on exposure markers, rather than exposure–disease associations.]

In a population-based case–control study of cancer of the breast in African-American and white women in North Carolina, USA, 748 cases and 659 controls were enrolled (Millikan *et al.*, 2000). Lipid-adjusted concentrations of 35 PCB congeners were measured in plasma, but detailed analyses were presented only for total PCBs. Odds ratios were adjusted for age and age squared, and additionally for race, menopausal status, BMI, parity/lactation, hormone replacement therapy, and income, depending on the stratification factors. Results were presented in strata of race, parity plus lactation, BMI and history of farming. Risk of cancer of the breast was increased with total PCB exposure among African-American women (third tertile OR, 1.74; 95% CI, 1.00–3.01), but not among white women (third tertile OR, 1.03; 95% CI, 0.68–1.56). This risk was particularly high for African-Americans with BMI > 34.2 (third tertile total PCBs, OR, 4.92; 95% CI, 1.63–14.83). [This was a large, high-quality study, and included African-Americans.]

In the same study population as Millikan *et al.* (2000), Li *et al.* (2005) investigated *CYP1A1* polymorphisms and their interaction with PCB exposure in relation to risk of cancer of the breast among the 612 cases and 599 controls who had provided blood. Results showed no evidence of joint effects between *CYP1A1* M1-containing genotypes and total PCBs for either race. Among white women, statistically significant multiplicative interactions were observed between *CYP1A1* M2-containing genotypes and total PCBs (P = 0.02), but the association between PCBs and cancer of the breast was inverse. A multiplicative interaction was suggested among African-American women between *CYP1A1*

M3-containing genotypes and total PCBs, with an odds ratio of 1.6 (95% CI, 0.8–3.2) for women with total plasma PCB concentrations ≥ 0.430 ng/mL and any *CYP1A1* M3 genotype compared with lower PCB concentration and no M3 genotype (*P* for interaction = 0.10). [This large study was able to assess interactions with *CYP1A1*.]

In a case–control study conducted in 1994–7 in Quebec City, Canada, plasma concentrations of 14 PCB congeners were measured in 314 women with cancer of the breast and 523 controls (219 hospital controls, 304 population controls) (Demers *et al.*, 2002). Analyses in relation to cancer of the breast excluded five congeners that were detected in < 70% of the women. The remaining PCB congeners were correlated (Pearson correlation coefficients, 0.29 to 0.96). Risk of cancer of the breast was associated with the highest quartile of concentration of PCB-118 (OR, 1.60; 95% CI, 1.01–2.53) and PCB-156 (OR, 1.80; 95% CI, 1.11–2.94). Among the subgroup of premenopausal women, the odds ratio for the highest quartile of concentration of PCB-118 was 2.87 (95% CI, 1.13–7.31), and for PCB-156 it was 2.90 (95% CI, 1.18–7.15). No significant increase in risk was seen in postmenopausal women. When PCB-105, PCB-118 and PCB-156 were grouped, higher concentration was associated with increased risk of cancer of the breast (OR, 2.02; 95% CI, 1.24–3.28), but the PCBs that were the most abundant (PCB-138, PCB-153 and PCB-180) were not associated with risk of cancer of the breast. An earlier publication from this study investigated associations between organochlorine compounds and cancer of the breast, specifically in relation to axillary-lymph-node involvement and tumour size (Demers *et al.*, 2000). PCB-153 was selected as a surrogate for all PCB congeners because it was the most abundant in plasma samples and was strongly correlated with other prevalent congeners ($r \geq 0.72$; $P < 0.0001$). The relative risk of having a tumour size ≥ 2 cm was increased, but not significantly, with increasing plasma concentration of PCB-153. However, a higher concentration of PCB-153 was significantly associated with increased risk among those with axillary lymph-node involvement (OR, 2.12; 95% CI, 1.05–4.30, adjusted for confounders) and when tumour size > 2 cm and node involvement were considered together, (OR, 3.51; 95% CI, 1.41–8.73), with an exposure–response trend. [This was a well-designed and well-implemented study with two control groups and stratification for menopausal status.]

In a large population-based case–control study of environmental exposures and cancer of the breast conducted in 1996–7 on Long Island, NY, USA, serum concentrations of 24 PCB congeners were measured for 646 cases and 429 controls, with results presented for the four most commonly occurring congeners (PCB-118, PCB-138, PCB-153 and PCB-180) (Gammon *et al.*, 2002). There was no association between cancer of the breast and the sum concentration of the four PCBs, or any specific congener, and there was no effect of lactation, menopausal status, stage of disease, or hormone receptor status. [This was a large, well-designed and well-implemented study.]

In a population-based case–control study of African-American women, serum concentrations of PCBs [congeners not specified] were measured in 355 cases and 327 controls (Gatto *et al.*, 2007). Risk of cancer of the breast was not associated with total PCBs (OR comparing highest with lowest quintile, 1.01; 95% CI, 0.64–1.63), and BMI, parity, breastfeeding, and menopausal status did not modify the measures of effect. PCBs were not associated with an increase in the risk of any subtype of cancer of the breast as defined by PR, ER, *p53*, or HER-2/*neu* status. [Statistical power was limited for subgroup analyses.]

In a hospital-based case–control study of cancer of the breast in Nagano, Japan, including 403 matched pairs collected from 2001 to 2005, serum concentrations of total PCBs were associated with decreased risk of cancer of the

breast for the highest versus lowest quartile of concentration of total PCBs (OR, 0.33; 95% CI, 0.14–0.78) (Itoh *et al.*, 2009). For the specific congeners PCB-153 and PCB-180, the odds ratios were 0.40 (95% CI, 0.18–0.91) and 0.29 (95% CI, 0.13–0.66), respectively. The trend in the inverse relationship persisted when results were stratified by hormone-receptor and menopausal status. [The Working Group was not able to explain the inverse associations reported in this study.]

(c) *Larger studies of PCB concentrations in blood and breast adipose tissue*

Five publications from a research group in Connecticut, USA, were informative, although their potential overlap was not clear. In 1994–1997, 304 cases of cancer of the breast and 186 controls aged 40–79 years were recruited and breast adipose tissue was analysed for nine PCB congeners (PCB-74, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183 and PCB-187) (Zheng *et al.*, 2000a). Age- and lipid-adjusted risk estimates were null in relation to total PCBs, PCB groups, and any of the congeners. Stratification by type of breast disease, menopausal status, parity, lactation, and body size showed null associations with concentrations of PCBs. From the same study population, Holford *et al.* (2000) calculated risk in relation to both linear logistic and logistic ridge regression analyses for nine PCB congeners by incremental (10 ng/g) changes in exposure: PCB-153 and PCB-156 were associated with decreased risk and PCB-180 and PCB-183 were associated with increased risk of cancer of the breast. In analyses using ridge regression and adjusting for covariates, no congeners remained associated with cancer of the breast. In another case–control study from this research group, subjects were recruited in 1995–1997 (overlap in years of study with Zheng *et al.*, 2000a): 475 incident cases of cancer of the breast were included, and 502 controls were randomly selected from the population or from patients with newly diagnosed benign breast disease at the same hospital (Zheng *et al.*, 2000b). Serum concentrations of nine PCB congeners were determined. After adjustment for confounding factors, all odds ratios were null. A related study focused on the potential interaction between CYP1A1 and lipid-adjusted serum concentrations of PCBs on risk of cancer of the breast among Caucasian women recruited in 1999–2002, with 374 cases and 406 controls (Zhang *et al.*, 2004). The odds ratio for high exposure (> 610 ng/g) to PCBs was 1.2 (95% CI, 0.9–1.6). With respect to *CYP1A1* genotype, the risks associated with higher serum concentration of total PCBs was highest for carriers of the *m2* variant genotype both among all women combined (OR, 3.6; 95% CI, 1.5–8.2), and in postmenopausal women (OR, 4.3; 95% CI, 1.6–12.0). No significant association was reported for *CYP1A1 m1* or *m4* genotypes or among premenopausal women. Finally, in another publication on a subset of 266 cases of cancer of the breast and 347 controls with benign breast disease, there was no association for total subjects, adjusted for standard risk factors, between cancer of the breast by joint ER/PR status and serum concentrations of total PCBs and adipose-tissue concentrations of nine PCB congeners (Rusiecki *et al.*, 2004). However, among postmenopausal women, increased risk of cancer of the breast was seen in relation to increased concentrations of PCB-183 among women with ER+PR+ tumours (third versus first tertile, OR, 2.4; 95% CI, 1.0–6.0; *P* for trend = 0.03). [While there appeared to be overlap between this group of studies from Connecticut, the extent of the overlap was difficult to determine, therefore the independence of the findings was not known. Controls were drawn from a mix of hospital and population sources, and the impact of this selection method was difficult to gauge. The large number of subgroup analyses, particularly in the study by Rusiecki *et al.* (2004), which presented 80 odds ratios, increased the probability of chance findings.]

(d) Larger studies of PCB concentrations in adipose tissue

On Long Island, New York, USA, concentrations of 14 PCB congeners in adipose tissue did not differ for 232 women with cancer of the breast and 323 hospital controls with benign breast disease or non-breast-related conditions, after adjustment for age, race, and BMI (Stellman *et al.*, 2000). No increase in risk was observed for total PCBs, but congeners PCB-156 and PCB-183 were associated with significantly increased risk (OR, 1.9; 95% CI, 1.1–3.0 for the second tertile of exposure distribution for PCB-156; and OR, 2.0; 95% 1.2–3.4 for the highest tertile of PCB-183). No other congener was associated with risk of cancer of the breast, and no clear difference in risk was seen for ER+ and ER– tumours. [This was a large, well-designed study, but results were only presented for total PCBs and two congeners.]

In a case–control study in Kingston and Toronto, Ontario, Canada, noncancerous breast adipose tissue collected before treatment from 217 incident cases of cancer of the breast and 213 controls undergoing biopsy was analysed for 14 PCB congeners (Aronson *et al.*, 2000). PCB-105 and PCB-118 were associated consistently with risk of cancer of the breast after adjusting for other factors (OR, 3.17; 95% CI, 1.51–6.68; and OR, 2.31; 95% CI, 1.11–4.78, respectively, for the fourth versus first quartile of the exposure distribution) and these effects increased monotonically. PCB-138 was also associated consistently with increased risk, but the odds ratios were imprecise. Stronger associations were apparent among premenopausal women (PCB-105: OR, 3.91; 95% CI, 1.73–8.86; and PCB-118: OR, 2.85; 95% CI, 1.24–6.52, for the highest exposure category). Among postmenopausal women, risks associated with PCB-170 and PCB-180 were also elevated in the second of three exposure groups (OR, 3.27; 95% CI, 1.44–7.44; and OR, 2.43; 95% CI, 1.09–5.43, respectively), but declined below significance in the highest group (ORs 1.63 and 1.77, respectively). No other PCB congener was significantly associated with risk. Although the odds ratios did not differ significantly by subtype of cancer, the odds ratios for total PCBs were higher for ER– than for ER+ cancer of the breast (Woolcott *et al.*, 2001). Investigation of specific genotype–PCB interactions among 68 cases and 52 controls with blood samples in this study showed increased risk of cancer of the breast for *CYP1A1* M1 wildtype homozygotes with high exposure to PCB-105 (OR, 3.20; 95% CI, 1.14–8.98) (McCready *et al.*, 2004). [This was a large, well-designed study.]

(e) Exposure estimates from occupational or dietary histories

A few case–control studies have estimated PCB exposures from occupational or dietary histories.

A population-based case–control study in Massachusetts, USA, included 261 incident cases of cancer of the breast diagnosed between 1983 and 1986 and 753 controls. The subjects were interviewed to ascertain all full-time jobs held since age 18 years. Probable exposure to PCBs was associated with non-significant increases in the risk of cancer of the breast (adjusted OR, 3.2; 95% CI, 0.8–12.2; five exposed cases and six exposed controls) (Aschengrau *et al.*, 1998). [The Working Group noted imprecise findings.]

Consumption of fish from the Great Lakes as a source of exposure to PCBs was investigated as a potential risk factor for cancer of the breast in a population-based case–control study in Wisconsin, USA (McElroy *et al.*, 2004). There were 1481 cases aged 20–69 years, diagnosed in 1998–2000 in the Wisconsin Cancer Reporting System, and 1301 controls of similar age were randomly selected from licensed drivers and Medicare lists; telephone interviews were used to obtain information on consumption of all sport-caught (Great Lakes and other lakes) fish and risk factors for cancer of the breast. After adjustment for risk factors, including age, education, weight,

alcohol consumption, reproductive history, and family history of cancer of the breast, no association was found between risk of cancer of the breast and recent consumption of sport-caught fish (OR, 1.00; 95% CI, 0.86–1.17), recent consumption of fish from the Great Lakes (OR, 1.06; 95% CI, 0.84–1.33), or the number of fish meals per year. Menopausal status appeared to be an effect modifier, with recent consumption of fish from the Great Lakes not associated with postmenopausal cancer of the breast (OR, 0.78; 95% CI, 0.57–1.07), but with premenopausal breast cancer (OR, 1.70; 95% CI, 1.16–2.50). [This was a large study with exposure assessment that used consumption of sport fish as a proxy for PCB exposure, but did not use biomarkers.]

(f) Combined analysis of five studies in the USA

The results of five case–control studies in the north-east USA conducted before 2000 (of which three are nested in cohort studies) (Moysich *et al.*, 1998; Helzlsouer *et al.*, 1999; Laden *et al.*, 2001a, b and Hunter *et al.*, 1997; Zheng *et al.*, 2000a, b; Wolff *et al.*, 2000b) and in which plasma or serum concentrations of PCBs were measured have been combined into an analysis of 1400 cases and 1642 controls using a standardized approach to confounder and effect-modification assessment, and a random-effects model to estimate associations (Laden *et al.*, 2001b). For women in the fifth quintile of lipid-adjusted values compared with those in the first quintile, the multivariate pooled odds ratio for cancer of the breast associated with the sum of PCBs (PCB-118, PCB-138, PCB-153 and PCB-180) was 0.94 (95% CI, 0.74–1.21). No consistent increase in risk was observed in subgroups defined by parity or lactation. [This combined analysis focused on the most prevalent PCBs that were analysed in all five studies; while this enhanced precision for the overall relationship, it did not show associations for specific PCB congeners and PCB subgroups. The Working Group noted that several informative studies were published after this combined analysis.]

2.3.3 Cancer of the prostate

Several epidemiological studies have investigated possible associations between cancer of the prostate and exposure to PCBs. These studies differed in study design (i.e. case–control studies, nested case–control studies) and in the assessment of PCBs (i.e. job-exposure matrices, measurement of PCB concentrations in blood or adipose tissue).

Seidler *et al.* (1998) described the results of a case-referent study including 192 patients with cancer of the prostate and 210 controls from medical practices or clinic in Germany. Occupational exposure to PCBs was estimated using a British job-exposure matrix (Pannett *et al.*, 1985). Most subjects had no or low exposure to PCBs and no association between exposure and risk of cancer of the prostate was reported. [Due to the relative low participation rate among controls (55%), selection bias could not be excluded. Furthermore, the validity of the job-exposure matrix was unknown and significant exposure misclassification could not be ruled out.]

Ritchie *et al.* (2003, 2005) conducted a hospital-based case–control study in Iowa, USA, in which 30 PCB congeners were measured in serum samples from 58 patients with cancer of the prostate and 99 age-matched controls. Odds ratios were elevated for total PCBs, and for PCB-153, and PCB-180. A monotonic, not statistically significant, exposure–response trend was observed for total PCBs. For PCB-180, the odds ratio was significantly increased (OR, 3.13; 95% CI, 1.33–7.34) only in the middle (but not the highest) category of exposure. [This study was small with multiple comparisons.]

In a population-based case–control study in Sweden, Hardell *et al.* (2006a) compared

concentrations of 37 PCB congeners in samples of fat tissue from 58 cases of cancer of the prostate and 20 controls with benign prostate hyperplasia. The odds ratio for the sum of PCBs and cancer of the prostate was 1.21 (95% CI, 0.42–3.50) in all men. PCB-153 was associated with an increased risk of cancer of the prostate (OR, 3.15; 95% CI, 1.04–9.54). Stronger associations were observed in men with prostate-specific antigen (PSA) > 16.5 ng/mL; the odds ratio was 1.91 (95% CI, 0.55–6.55) for total PCBs, and risks for enzyme and phenobarbital-inducing PCBs (Wolff *et al.*, 1997) and for less chlorinated PCBs (Moysich *et al.*, 1999a) were significantly increased in this subgroup of men. [This study was small and involved multiple comparisons.]

Aronson *et al.* (2010) conducted a case–control study among urology patients in Ontario, Canada. Concentrations of 14 PCB congeners were measured in serum of 79 men with incident cancer of the prostate and 329 age-matched controls. No association was observed between concentrations of individual PCB congeners or the sum of PCBs, and the risk of prostate cancer. [As both cases and controls underwent the same diagnostic procedures and were screened by PSA and digital rectal examination, selection bias was unlikely in this study].

2.3.4 Melanoma

(a) Cutaneous malignant melanoma

See Table 2.11

Gallagher *et al.* (2011) conducted a case–control study of 80 patients with malignant melanoma of the skin and 310 controls. The cases were part of a larger case–control study and were originally recruited to evaluate the effect of exposure to ultraviolet (UV) light and gene variants on risk of melanoma, and the controls were recruited using population-based registries. Lipid-adjusted plasma concentrations of 14 PCB congeners were determined and data were reported for 8, as well as for total PCBs, and dioxin-like and non-dioxin-like PCBs. Statistically significant associations with malignant melanoma were observed for the highest compared with the lowest quartile for: total PCBs (OR, 6.02; 95% CI, 2.0–18.17); summed non-dioxin-like PCBs (OR, 7.02; 95% CI, 2.30 –21.43); summed dioxin-like PCBs (OR, 2.84; 1.01–7.97), and all of the individual PCB congeners examined (PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183 and PCB-187). [The Working Group considered that, in light of its appropriate design and control of relevant potential confounders, this was a high-quality study, despite the relatively small sample size and being described as "preliminary" by the authors. The positive associations for all the individual PCB congeners may have been a result of correlations among congeners. Multiple comparisons were not formally addressed, but it is likely that adjustment for multiple comparisons would not change the interpretation of the results.]

(b) Uveal melanoma

See Table 2.11

In a multicentric case–control study in nine European countries, Behrens *et al.* (2010) investigated the association between risk of uveal melanoma and exposure to PCBs. The 293 men and women with uveal melanoma were frequency-matched to 3198 population and hospital controls by country, age, and sex. Exposure to transformer oils was assessed by questionnaire, with exposures to PCBs classified as "potential" or "confirmed," depending on whether subjects reported exposure to a named brand of oil with known PCB content. Analyses were adjusted for age, country, eye colour, and history of ocular damage from ultraviolet light. Only men reported exposure to transformer/capacitor oils. The odds ratio for any exposure was 2.74 (99.3% CI, 1.07–7.02), and was similar in magnitude for men with more than 10 years of exposure and for "confirmed" exposure. For exposure to Pyralene (the most frequently reported PCB-containing

Table 2.11 Case–control studies on melanoma and exposure to PCBs

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cutaneous malignant melanoma							
Gallagher *et al.* (2011) British Columbia, Canada, 2000–2004	80 310	Population	Lipid-adjusted concentrations of 14 PCBs[a] (units NR)				Age, sex, education, skin reaction to repeated sun exposure, and total recreational sun exposure
				Total PCBs			
				98.01–148.71	11	1.36 (0.45–4.09)	
				148.72–213.44	12	1.27 (0.39–4.12)	
				> 213.44	29	6.02 (2.00–18.17)	*P* for trend < 0.001
				DL-PCBs			
				9.37–15.10	8	0.31 (0.10–0.98)	
				15.11–22.57	16	1.16 (0.41–3.26)	
				> 22.57	25	2.84 (1.01–7.97)	*P* for trend = 0.003
				NDL-PCBs			
				86.68–133.66	12	2.05 (0.66–6.39)	
				133.67–192.39	11	1.19 (0.36–3.90)	
				> 192.39	30	7.02 (2.30–21.43)	*P* for trend < 0.001
				PCB-118			
				> 4.90–8.16	13	0.89 (0.34–2.34)	
				> 8.16–13.32	14	1.13 (0.40–3.23)	
				> 13.32–46.19	23	3.04 (1.05–8.74)	*P* for trend = 0.012
				PCB-138			
				> 12.79–20.76	19	1.89 (0.68–5.28)	
				> 20.76–30.65	8	1.30 (0.37–4.56)	
				> 30.65–104.49	28	4.91 (1.69–14.32)	
				PCB-153			
				> 27.75–42.07	14	2.01 (0.70–5.77)	
				> 42.07–60.43	12	1.35 (0.43–4.25)	
				> 60.43–735.90	27	4.86 (1.68–14.08)	*P* for trend = 0.002
				PCB-156			
				> 4.09–6.07	13	1.04 (0.36–2.97)	
				> 6.07–8.65	13	1.48 (0.49–4.45)	
				> 8.65–113.32	29	4.22 (1.51–11.78)	*P* for trend = 0.001

Table 2.11 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Gallagher et al. (2011) British Columbia, Canada, 2000–2004 (cont.)				*PCB-170*			
				> 7.97–12.16	13	1.50 (0.53–4.29)	
				> 12.16–18.51	13	1.10 (0.32–3.77)	
				> 18.51–901.52	29	4.60 (1.60–13.22)	*P* for trend = 0.001
				PCB-180			
				> 25.20–38.16	12	1.46 (0.49–4.37)	
				> 38.16–59.40	14	1.55 (0.44–5.43)	
				> 59.40–3786.60	30	5.89 (1.87–18.50)	*P* for trend = 0.001
				PCB-183			
				> 1.87–84.86	54	4.27 (1.71–10.68)	
				PCB-187			
				> 6.64–10.45	11	2.54 (0.75–8.58)	
				> 10.45–16.10	15	2.56 (0.76–8.62)	
				> 16.10–833.15	30	11.47 (3.32–39.68)	*P* for trend < 0.001
Uveal melanoma							
Behrens *et al.* (2010), Denmark, France, Germany, Italy, Latvia, Portugal, Sweden, Spain, UK Jan 1994–Dec 1997	293 3198	Hospital and population	Questionnaire on occupational exposure	Exposure to oils potentially containing PCBs			Country, age, ocular damage due to UV, eye colour, exposure to high-voltage installations ORs were Bonferroni-corrected for seven independent tests to control for multiple comparisons, thus all CI are 99.3%. Response rates: cases, 84%; hospital, 84%; population controls, 61% Only men were exposed to oils
				Never exposed	150	1.00	
				Ever exposed	6	2.74 (0.72–10.37)	
				Duration > 10 years	2	2.62 (0.29–24.06)	
				"Confirmed" exposure to PCB oil	4	2.61 (0.54–12.63)	
				Exposure to Pyralene	4	6.43 (1.17–35.30)	

[a] The 14 PCB congeners were PCBs 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187.

CI, confidence intervals; DL-PCB, dioxin-like PCB; NDL-PCB, non-dioxin-like PCB; OR, odds ratio; PCB, polychlorinated biphenyl; UK, United Kingdom; UV, ultraviolet

oil), the odds ratio was 6.43 (99.3% CI, 1.17–35.30; four cases). [This study was notable in being the only large study of a rare cancer. Multiple comparisons were addressed via adjusted 99.3% confidence intervals, but exposure was rare and estimates were imprecise.]

2.3.5 Other cancers

(a) Urothelial cancer

Steineck *et al.* (1990) carried out a population-based case-referent study of urothelial cancer in men in Stockholm, Sweden. Occupational exposures to PCBs and several other agents were assigned by an industrial hygienist. The adjusted odds ratio for estimated exposure to PCBs was 3.3 (95% CI, 0.6–18.4). [The precision of this study was quite limited and the definition of the cancer sites was broad.]

(b) Cancer of the testis

Hardell *et al.* (2003) analysed 38 PCB congeners in blood samples collected from 61 incident cases of cancer of the testis and 58 age-matched controls from the Swedish population registry. No association between cancer of the testis and the sum of PCB concentrations in blood was found. Mothers of 44 cases and 45 controls also provided blood samples; significantly higher PCB concentrations were found for mothers of cases compared with mothers of controls (OR, 3.8; 95% CI, 1.4–10). A difference in the sum of PCBs between mothers of cases and mothers of controls was also reported in two subsequent publications by the same authors (Hardell *et al.*, 2004, 2006b). [Due to the timing of blood collection of the mothers, which was decades after the cases' births, the interpretation of these results was difficult. PCB concentrations in women may be affected by weight changes, child bearing, lactation, and subsequent exposure. Thus it could not be assumed that the concentrations measured in women at the time of the study were representative of their sons' exposures in utero.]

(c) Cancer of the lung

Recio-Vega *et al.* (2012) investigated the association between PCB concentrations, *CYP1A1* polymorphisms and the risk of cancer of the lung in a case–control study in northern Mexico including 43 cases of cancer of the lung and 86 controls without cancer who were recruited from two hospitals. Information including history of exposure to PCBs was collected through in-person interview and 20 PCB congeners were measured in serum. Odds ratios were adjusted for age, agricultural occupation, and tobacco smoking. There was a significant association between PCB-18 and cancer of the lung (OR, 1.13; 95% CI, 1.04–1.38). Odds ratios for PCB-52, PCB-118, and PCB-170 were similar in magnitude, but did not reach statistical significance, while odds ratios for other congeners were close to unity. *CYP1A1* polymorphism was not associated with serum concentrations of total PCBs. [The Working Group noted that this study provided information about less chlorinated PCBs, which are rarely measured; however, the etiological relevance of measurements of PCBs of short half-life was questionable. In addition, the methods used for subject recruitment and for statistical analysis were not clearly described, and the possibility of residual confounding by age was noted.]

(d) Cancer of the colorectum

Howsam *et al.* (2004) assessed associations between cancer of the colorectum and exposure to PCBs and gene–environment interactions in 132 cases and 76 controls sampled from a larger hospital-based case–control study in Barcelona, Spain. Serum concentrations of PCB-28, PCB-52, PCB-101, PCB-118, PCB-138, PCB-153, and PCB-180 were measured. Point mutations in *K-ras* and *p53* genes and expression of p53 protein were assessed in tumour tissue. PCB-28 and PCB-118 were significantly associated with an increased risk of cancer of the colorectum (ORs, 2.75;

95% CI, 1.29–5.83; and 2.02; 95% CI, 1.00–4.08, respectively), for the more exposed category. A statistically significant exposure–response trend was observed for the mono-*ortho* PCB group that combined PCB-28 and PCB-118 (*P* for trend = 0.004). Odds ratios for the other PCBs were not consistently or significantly increased. No significant interaction of mono-*ortho* PCBs with *p53* or *K-ras* mutations was found. [The use of controls representing several diagnostic groups and control for potential confounding factors were strengths of this study. However, the case definition combining cancers of the colon and rectum may mix diseases with potentially different etiologies.]

(e) Cancer of the pancreas

In a population-based case–control study of cancer of the pancreas in the San Francisco area, USA, Hoppin *et al.* (2000) analysed 11 PCB congeners in serum samples from 108 cases of cancer of the pancreas and 82 controls matched by sex and age-group. Total lipid-adjusted PCB concentrations were estimated using the sum of all congeners. A statistically significant dose–response relationship ($P < 0.001$) was observed for total PCBs, with an odds ratio of 4.2 (95% CI, 1.8–9.4) for ≥ 360 versus < 185 ng/g. Significantly elevated odds ratios were also observed for the highest tertiles of PCB-153 (OR, 3.0; 95% CI, 1.4–6.6) and PCB-180 (OR, 8.4; 95% CI, 3.4–21). Odds ratios remained elevated after adjusting for dichlorodiphenyldichloroethylene (DDE) content, and in a sensitivity analysis of the effects of bioconcentration. [A strength of the study was that the issue of confounding by bioconcentration in fat due to adipose-tissue loss was addressed. Nevertheless, the small number of subjects limited a clear interpretation of the results.]

(f) Cancer of the biliary tract

Ahrens *et al.* (2007) investigated the association between cancer of the extrahepatic biliary tract and occupational exposure to endocrine-disrupting compounds in a European multicentre case–control study of 183 men with histologically confirmed carcinoma of the extrahepatic biliary tract and 1938 matched controls. Self-reported job descriptions were converted to semiquantitative indicators of occupational exposure to 14 types of suspected endocrine-disrupting compounds, including PCBs, hormones, phthalates, and pesticides. Odds ratios were adjusted for age, country, and history of gallstones. The adjusted odds ratio for cancer of the extrahepatic biliary tract and ever-exposure to PCBs was 2.8 (95% CI, 1.3–5.9). When exposure intensity was analysed, the highest odds ratio was observed in the low-intensity category. [These results were based on a small number of exposed cases and trends were inconsistent.]

(g) Childhood cancer

Ward *et al.* (2009) conducted a population-based case–control in California, USA of 184 children aged 0–7 years with acute lymphocytic leukaemia and 212 controls from birth certificates matched by birth date, sex, race, and ethnicity. Concentrations of six PCB congeners in residential carpet dust were used as an exposure indicator. The odds ratio for detection of any PCB in dust was 1.97 (95% CI, 1.22–3.17) and the odds ratio for the highest quartile of total PCBs compared with the lowest was 2.78 (95% CI, 1.41–5.48). Significant exposure–response trends were reported for PCB-118, PCB-138 and PCB-153. [The study was well-designed and the method of exposure assessment used was a strength. The authors were able to rule out confounding by several organochlorine pesticides. The Working Group was unable to replicate the *P* values for trend tests.]

(h) Cancer of the endometrium

Sturgeon *et al.* (1998) conducted a multicentric hospital-based case–control study of cancer of the endometrium in five areas of the USA. Serum concentrations of 27 PCB congeners were measured for 90 individually matched case–control pairs. No associations were observed between elevated serum concentrations of several PCB groups, including total PCBs and potentially estrogenic PCBs, and risk of cancer of the endometrium. [The results did not appear to be affected by selection bias, but precision was limited.]

Weiderpass *et al.* (2000) measured serum concentrations of 10 PCB congeners in a population-based case–control study of 154 cases of cancer of the endometrium and 205 controls in Sweden. After adjustment there was no increase in risk associated with high concentrations of any of the congeners evaluated, and there were no significant trends in risk. [The power of this study was limited due to the small number of subjects. However, selection bias was unlikely, as the main reason for non-participation was the failure of the hospital staff to collect blood samples before surgery.]

Hardell *et al.* (2004) conducted a hospital-based case–control study with 76 cases and 39 controls to evaluate the risk of cancer of the endometrium associated with environmental endocrine disruptors. Concentrations of 37 PCB congeners were measured in adipose tissue. No association was found for the sum of PCBs or for any grouping of PCBs by structure or activity. [The power of this study was limited due to the small number of subjects.]

(i) Cancer of the male breast

Occupational risk factors for cancer of the male breast were investigated in a multicentric study of 104 cases and 1901 controls in eight European countries (Villeneuve *et al.*, 2010). Lifetime work history was obtained by in-person interviews, and potential occupational exposures including to PCBs were assessed using expert judgment. Results were reported for PCBs and dioxins combined, for which the fully-adjusted odds ratio was 1.6 (95% CI, 0.7–3.7). [This study had limited power to detect excess risk.]

References

Ahrens W, Mambetova C, Bourdon-Raverdy N, Llopis-González A, Guénel P, Hardell L *et al.* (2007). Occupational exposure to endocrine-disrupting compounds and biliary tract cancer among men. *Scand J Work Environ Health*, 33(5):387–96. doi:10.5271/sjweh.1158 PMID:17973065

Aronson KJ, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA *et al.* (2000). Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 9(1):55–63. PMID:10667464

Aronson KJ, Wilson JW, Hamel M, Diarsvitri W, Fan W, Woolcott C *et al.* (2010). Plasma organochlorine levels and prostate cancer risk. *J Expo Sci Environ Epidemiol*, 20(5):434–45. doi:10.1038/jes.2009.33 PMID:19513097

Aschengrau A, Coogan PF, Quinn M, Cashins LJ (1998). Occupational exposure to estrogenic chemicals and the occurrence of breast cancer: an exploratory analysis. *Am J Ind Med*, 34(1):6–14. doi:10.1002/(SICI)1097-0274(199807)34:1<6::AID-AJIM2>3.0.CO;2-X PMID:9617382

Bahn AK, Rosenwaike I, Hermann N, Grover P, Stellman J, O'Leary K (1976). Letter: Melanoma after exposure to PCB's. *N Engl J Med*, 295(8):450 doi:10.1056/NEJM197608192950820 PMID:819831

Behrens T, Kaerlev L, Cree I, Lutz JM, Afonso N, Eriksson M *et al.* (2010). Hormonal exposures and the risk of uveal melanoma. *Cancer Causes Control*, 21(10):1625–34. doi:10.1007/s10552-010-9591-9 PMID:20524054

Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C (1987). Cancer mortality of capacitor manufacturing workers. *Am J Ind Med*, 11(2):165–76. doi:10.1002/ajim.4700110206 PMID:3103429

Bertazzi PA, Zocchetti C, Guercilena S et al. (1982). Mortality study of male and female workers exposed to PCBs. Prevention of Occupational Cancer — International Symposium. Geneva: International Labour Office, pp. 242–248.

Bertrand KA, Spiegelman D, Aster JC, Altshul LM, Korrick SA, Rodig SJ *et al.* (2010). Plasma organochlorine levels and risk of non-Hodgkin lymphoma in a cohort of men. *Epidemiology*, 21(2):172–80. doi:10.1097/EDE.0b013e3181cb610b PMID:20087190

Bonefeld-Jørgensen EC, Long M, Bossi R, Ayotte P, Asmund G, Krüger T *et al.* (2011). Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: a case control study. *Environ Health*, 10:88 doi:10.1186/1476-069X-10-88 PMID:21978366

Bräuner EV, Sørensen M, Gaudreau E, LeBlanc A, Eriksen KT, Tjønneland A *et al.* (2012). A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma. *Environ Health Perspect*, 120(1):105–11. doi:10.1289/ehp.1103573 PMID:22328999

Brown DP (1987). Mortality of workers exposed to polychlorinated biphenyls–an update. *Arch Environ Health*, 42(6):333–9. doi:10.1080/00039896.1987.9934355 PMID:3125795

Brown DP, Jones M (1981). Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. *Arch Environ Health*, 36(3):120–9. PMID:6787990

Caironi M, Olivari L, Sampietro G, Mandelli G, Mosconi G (2005). Preliminary results of a mortality study in 471 ex-exposed workers to PCBs. *G Ital Med Lav Ergon*, 27(3):279–81. PMID:16240573 [in Italian]

Cammarano G, Crosignani P, Berrino F, Berra G (1984). Cancer mortality among workers in a thermoelectric power plant. *Scand J Work Environ Health*, 10(4):259–61. doi:10.5271/sjweh.2333 PMID:6494846

Cammarano G, Crosignani P, Berrino H, Berra G (1986). Additional follow-up of cancer mortality among workers in a thermoelectric power plant. *Scand J Work Environ Health*, 12(6):631–2. doi:10.5271/sjweh.2090 PMID:3823815

Charles LE, Loomis D, Shy CM, Newman B, Millikan R, Nylander-French LA *et al.* (2003). Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. *Am J Epidemiol*, 157(8):683–91. doi:10.1093/aje/kwg044 PMID:12697572

Charlier C, Pitance F, Plomteux G (2003). PCB residues in a breast cancer patient population. *Bull Environ Contam Toxicol*, 71(5):887–91. doi:10.1007/s00128-003-8948-0 PMID:14705647

Charlier CJ, Albert AI, Zhang L, Dubois NG, Plomteux GJ (2004). Polychlorinated biphenyls contamination in women with breast cancer. *Clin Chim Acta*, 347(1-2):177–81. doi:10.1016/j.cccn.2004.04.025 PMID:15313156

Chia VM, Li Y, Quraishi SM, Graubard BI, Figueroa JD, Weber JP *et al.* (2010). Effect modification of endocrine disruptors and testicular germ cell tumour risk by hormone-metabolizing genes. *Int J Androl*, 33(4):588–96. PMID:19627379

Cocco P, Brennan P, Ibba A, de Sanjosé Llongueras S, Maynadié M, Nieters A *et al.* (2008). Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. *Occup Environ Med*, 65(2):132–40. doi:10.1136/oem.2007.033548 PMID:17699548

Cohn BA, Terry MB, Plumb M, Cirillo PM (2012). Exposure to polychlorinated biphenyl (PCB) congeners measured shortly after giving birth and subsequent risk of maternal breast cancer before age 50. *Breast Cancer Res Treat*, 136(1):267–75. doi:10.1007/s10549-012-2257-4 PMID:23053646

Colt JS, Rothman N, Severson RK, Hartge P, Cerhan JR, Chatterjee N *et al.* (2009). Organochlorine exposure, immune gene variation, and risk of non-Hodgkin lymphoma. *Blood*, 113(9):1899–905. doi:10.1182/blood-2008-04-153858 PMID:19066394

De Guire L, Cyr D, Thériault G, Provencher S, Iturra H, Case BW (1992). Malignant melanoma of the skin among workers in a telecommunications industry: mortality study 1976–83. *Br J Ind Med*, 49(10):728–31. PMID:1419862

De Guire L, Theriault G, Iturra H, Provencher S, Cyr D, Case BW (1988). Increased incidence of malignant melanoma of the skin in workers in a telecommunications industry. *Br J Ind Med*, 45(12):824–8. PMID:3265335

De Roos AJ, Hartge P, Lubin JH, Colt JS, Davis S, Cerhan JR *et al.* (2005). Persistent organochlorine chemicals in plasma and risk of non-Hodgkin's lymphoma. *Cancer Res*, 65(23):11214–26. doi:10.1158/0008-5472.CAN-05-1755 PMID:16322272

Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E (2000). Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. *Cancer Epidemiol Biomarkers Prev*, 9(2):161–6. PMID:10698476

Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E (2002). Plasma concentrations of polychlorinated biphenyls and the risk of breast cancer: a congener-specific analysis. *Am J Epidemiol*, 155(7):629–35. doi:10.1093/aje/155.7.629 PMID:11914190

Dewailly E, Dodin S, Verreault R, Ayotte P, Sauvé L, Morin J *et al.* (1994). High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J Natl Cancer Inst*, 86(3):232–4. doi:10.1093/jnci/86.3.232 PMID:8283497

Dorgan JF, Brock JW, Rothman N, Needham LL, Miller R, Stephenson HE Jr *et al.* (1999). Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). *Cancer Causes Control*, 10(1):1–11. doi:10.1023/A:1008824131727 PMID:10334636

Engel LS, Laden F, Andersen A, Strickland PT, Blair A, Needham LL *et al.* (2007). Polychlorinated biphenyl levels in peripheral blood and non-Hodgkin's lymphoma: a report from three cohorts. *Cancer Res*, 67(11):5545–52. doi:10.1158/0008-5472.CAN-06-3906 PMID:17545638

Falck F Jr, Ricci A Jr, Wolff MS, Godbold J, Deckers P (1992). Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health*, 47(2):143–6. PMID:1567239

Falk C, Hanrahan L, Anderson HA, Kanarek MS, Draheim L, Needham L *et al.*; The Great Lakes Consortium (1999). Body burden levels of dioxin, furans, and PCBs among frequent consumers of Great Lakes sport fish. *Environ Res*, 80(2 Pt 2):S19–25. doi:10.1006/enrs.1998.3906 PMID:10092416

Fritschi L, Benke G, Hughes AM, Kricker A, Vajdic CM, Grulich A *et al.* (2005). Risk of non-Hodgkin lymphoma associated with occupational exposure to solvents, metals, organic dusts and PCBs (Australia). *Cancer Causes Control*, 16(5):599–607. doi:10.1007/s10552-004-7845-0 PMID:15986116

Gallagher RP, Macarthur AC, Lee TK, Weber JP, Leblanc A, Mark Elwood J *et al.* (2011). Plasma levels of polychlorinated biphenyls and risk of cutaneous malignant melanoma: a preliminary study. *Int J Cancer*, 128(8):1872–80. doi:10.1002/ijc.25503 PMID:20533551

Gammon MD, Wolff MS, Neugut AI, Eng SM, Teitelbaum SL, Britton JA *et al.* (2002). Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. *Cancer Epidemiol Biomarkers Prev*, 11(8):686–97. PMID:12163320

Gatto NM, Longnecker MP, Press MF, Sullivan-Halley J, McKean-Cowdin R, Bernstein L (2007). Serum organochlorines and breast cancer: a case-control study among African-American women. *Cancer Causes Control*, 18(1):29–39. doi:10.1007/s10552-006-0070-2 PMID:17186420

Greenland S, Salvan A, Wegman DH, Hallock MF, Smith TJ (1994). A case-control study of cancer mortality at a transformer-assembly facility. *Int Arch Occup Environ Health*, 66(1):49–54. doi:10.1007/BF00386579 PMID:7927843

Gustavsson P, Hogstedt C (1997). A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Am J Ind Med*, 32(3):234–9. doi:10.1002/(SICI)1097-0274(199709)32:3<234::AID-AJIM8>3.0.CO;2-X PMID:9219652

Gustavsson P, Hogstedt C, Rappe C (1986). Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Am J Ind Med*, 10(4):341–4. doi:10.1002/ajim.4700100402 PMID:3098097

Güttes S, Failing K, Neumann K, Kleinstein J, Georgii S, Brunn H (1998). Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. *Arch Environ Contam Toxicol*, 35(1):140–7. doi:10.1007/s002449900361 PMID:9601932

Hansen LG (1998). Stepping backward to improve assessment of PCB congener toxicities. *Environ Health Perspect*, 106:Suppl 1: 171–89. PMID:9539012

Hardell E, Eriksson M, Lindström G, Van Bavel B, Linde A, Carlberg M *et al.* (2001). Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. *Leuk Lymphoma*, 42(4):619–29. doi:10.3109/10428190109099322 PMID:11697490

Hardell K, Carlberg M, Hardell L, Björnfoth H, Ericson Jogsten I, Eriksson M *et al.* (2009). Concentrations of organohalogen compounds and titres of antibodies to Epstein-Barr virus antigens and the risk for non-Hodgkin lymphoma. *Oncol Rep*, 21(6):1567–76. doi:10.3892/or_00000389 PMID:19424638

Hardell L, Andersson SO, Carlberg M, Bohr L, van Bavel B, Lindström G *et al.* (2006a). Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. *J Occup Environ Med*, 48(7):700–7. doi:10.1097/01.jom.0000205989.46603.43 PMID:16832227

Hardell L, Bavel B, Lindström G, Eriksson M, Carlberg M (2006b). In utero exposure to persistent organic pollutants in relation to testicular cancer risk. *Int J Androl*, 29(1):228–34. doi:10.1111/j.1365-2605.2005.00622.x PMID:16371110

Hardell L, Liljegren G, Lindström G, van Bavel B, Fredrikson M, Hagberg H (1997). Polychlorinated biphenyls, chlordanes, and the etiology of non-Hodgkin's lymphoma. *Epidemiology*, 8(6):689 doi:10.1097/00001648-199711000-00023 PMID:9345674

Hardell L, van Bavel B, Lindström G, Carlberg M, Dreifaldt AC, Wijkström H *et al.* (2003). Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. *Environ Health Perspect*, 111(7):930–4. doi:10.1289/ehp.5816 PMID:12782494

Hardell L, Van Bavel B, Lindström G, Carlberg M, Eriksson M, Dreifaldt AC *et al.* (2004). Concentrations of polychlorinated biphenyls in blood and the risk for testicular cancer. *Int J Androl*, 27(5):282–90. doi:10.1111/j.1365-2605.2004.00489.x PMID:15379968

Hardell L, Vanbavel B, Lindstrom G, Fredrikson M, Hagberg H, Liljegren G *et al.* (1996). Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. *Int J Oncol*, 9(4):603–8. PMID:21541557

Hay A, Tarrel J (1997). Mortality of power workers exposed to phenoxy herbicides and polychlorinated biphenyls in waste transformer oil. *Ann N Y Acad Sci*, 837:138–56. doi:10.1111/j.1749-6632.1997.tb56871.x PMID:9472337

Helmfrid I, Berglund M, Löfman O, Wingren G (2012). Health effects and exposure to polychlorinated biphenyls (PCBs) and metals in a contaminated community. *Environ Int*, 44:53–8. doi:10.1016/j.envint.2012.01.009 PMID:22336529

Helzlsouer KJ, Alberg AJ, Huang HY, Hoffman SC, Strickland PT, Brock JW *et al.* (1999). Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 8(6):525–32. PMID:10385143

Holford TR, Zheng T, Mayne ST, Zahm SH, Tessari JD, Boyle P (2000). Joint effects of nine polychlorinated biphenyl (PCB) congeners on breast cancer risk. *Int J Epidemiol*, 29(6):975–82. doi:10.1093/ije/29.6.975 PMID:11101537

Hopf NB, Waters MA, Ruder AM (2009). Cumulative exposure estimates for polychlorinated biphenyls using a job-exposure matrix. *Chemosphere*, 76(2):185–93. doi:10.1016/j.chemosphere.2009.03.058 PMID:19394668

Hopf NB, Waters MA, Ruder AM, Prince MM (2010). Development of a retrospective job exposure matrix for PCB-exposed workers in capacitor manufacturing. *J Occup Health*, 52(4):199–208. doi:10.1539/joh.L9151 PMID:20467200

Hoppin JA, Tolbert PE, Holly EA, Brock JW, Korrick SA, Altshul LM *et al.* (2000). Pancreatic cancer and serum organochlorine levels. *Cancer Epidemiol Biomarkers Prev*, 9(2):199–205. PMID:10698482

Howsam M, Grimalt JO, Guinó E, Navarro M, Martí-Ragué J, Peinado MA *et al.*; Bellvitge Colorectal Cancer Group (2004). Organochlorine exposure and colorectal cancer risk. *Environ Health Perspect*, 112(15):1460–6. doi:10.1289/ehp.7143 PMID:15531428

Høyer AP, Gerdes AM, Jørgensen T, Rank F, Hartvig HB (2002). Organochlorines, p53 mutations in relation to breast cancer risk and survival. A Danish cohort-nested case-controls study. *Breast Cancer Res Treat*, 71(1):59–65. doi:10.1023/A:1013340327099 PMID:11859874

Høyer AP, Grandjean P, Jørgensen T, Brock JW, Hartvig HB (1998). Organochlorine exposure and risk of breast cancer. *Lancet*, 352(9143):1816–20. doi:10.1016/S0140-6736(98)04504-8 PMID:9851382

Høyer AP, Jørgensen T, Grandjean P, Hartvig HB (2000). Repeated measurements of organochlorine exposure and breast cancer risk (Denmark). *Cancer Causes Control*, 11(2):177–84. doi:10.1023/A:1008926219539 PMID:10710203

Høyer AP, Jørgensen T, Rank F, Grandjean P (2001). Organochlorine exposures influence on breast cancer risk and survival according to estrogen receptor status: a Danish cohort-nested case-control study. *BMC Cancer*, 1:8 doi:10.1186/1471-2407-1-8 PMID:11518544

Hsieh SF, Yen YY, Lan SJ, Hsieh CC, Lee CH, Ko YC (1996). A cohort study on mortality and exposure to polychlorinated biphenyls. *Arch Environ Health*, 51(6):417–24. doi:10.1080/00039896.1996.9936040 PMID:9012319

Hunter DJ, Hankinson SE, Laden F, Colditz GA, Manson JE, Willett WC *et al.* (1997). Plasma organochlorine levels and the risk of breast cancer. *N Engl J Med*, 337(18):1253–8. doi:10.1056/NEJM199710303371801 PMID:9345073

Ikeda M, Yoshimura T (1996). Survival of patients. In: Kuratsune M, Yoshimura H, Hori Y, Okumura M, editors. Yusho - A Human Disaster Caused by PCRs and Related Compounds. Fukuoka: Kyushu University Press. pp. 316–323.

Itoh H, Iwasaki M, Hanaoka T, Kasuga Y, Yokoyama S, Onuma H *et al.* (2009). Serum organochlorines and breast cancer risk in Japanese women: a case-control study. *Cancer Causes Control*, 20(5):567–80. doi:10.1007/s10552-008-9265-z PMID:19031103

Kashima S, Yorifuji T, Tsuda T (2011). Acute non-cancer mortality excess after polychlorinated biphenyls and polychlorinated dibenzofurans mixed exposure from contaminated rice oil: Yusho. *Sci Total Environ*, 409(18):3288–94. doi:10.1016/j.scitotenv.2011.05.038 PMID:21684577

Kimbrough RD, Doemland ML, LeVois ME (1999). Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. *J Occup Environ Med*, 41(3):161–71. doi:10.1097/00043764-199903000-00005 PMID:10091139

Kimbrough RD, Doemland ML, Mandel JS (2003). A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. *J Occup Environ Med*, 45(3):271–82. doi:10.1097/01.jom.0000052959.59271.59 PMID:12661184

Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N (1994). Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J Natl Cancer Inst*, 86(8):589–99. doi:10.1093/jnci/86.8.589 PMID:8145274

Kuratsune M (1976). Epidemiologic studies on Yusho. In: Higuchi K, editor. PCB Poisoning and Pollution. Tokyo: Kodansha Ltd. pp. 9–23.

Kuratsune M, Ikeda M, Nakamura M, Hirohata T (1988). A Cohort study on mortality of "Yusho" patients: A preliminary report. In: Miller RW et al., editors. Unusual occurrences as clues to cancer Etiology. Tokyo, Japan: Sci. Soc. Press/Taylor & Francis Ltd. pp. 61–66.

Laden F, Bertrand KA, Altshul L, Aster JC, Korrick SA, Sagiv SK (2010). Plasma organochlorine levels and risk of non-Hodgkin lymphoma in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*, 19(5):1381–4. doi:10.1158/1055-9965.EPI-10-0125 PMID:20406963

Laden F, Collman G, Iwamoto K, Alberg AJ, Berkowitz GS, Freudenheim JL *et al.* (2001b). 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene and polychlorinated biphenyls and breast cancer: combined analysis of five U.S. studies. *J Natl Cancer Inst*, 93(10):768–76. doi:10.1093/jnci/93.10.768 PMID:11353787

Laden F, Hankinson SE, Wolff MS, Colditz GA, Willett WC, Speizer FE *et al.* (2001a). Plasma organochlorine levels and the risk of breast cancer: an extended follow-up in the Nurses' Health Study. *Int J Cancer*, 91(4):568–74. doi:10.1002/1097-0215(200002)9999:9999<::AID-IJC1081>3.0.CO;2-W PMID:11251983

Laden F, Ishibe N, Hankinson SE, Wolff MS, Gertig DM, Hunter DJ *et al.* (2002). Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the

Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*, 11(12):1560–5. PMID:12496044

Li MC, Tsai PC, Chen PC, Hsieh CJ, Leon Guo YL, Rogan WJ (2013). Mortality after exposure to polychlorinated biphenyls and dibenzofurans: 30 years after the "Yucheng accident". *Environ Res*, 120:71–5. doi:10.1016/j.envres.2012.09.003 PMID:23026800

Li Y, Millikan RC, Bell DA, Cui L, Tse CK, Newman B *et al.* (2005). Polychlorinated biphenyls, cytochrome P450 1A1 (CYP1A1) polymorphisms, and breast cancer risk among African American women and white women in North Carolina: a population-based case-control study. *Breast Cancer Res*, 7(1):R12–8. doi:10.1186/bcr941 PMID:15642161

Liljegren G, Hardell L, Lindström G, Dahl P, Magnuson A (1998). Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. *Eur J Cancer Prev*, 7(2):135–40. PMID:9818775

Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA (1997). Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med*, 54(10):720–8. doi:10.1136/oem.54.10.720 PMID:9404319

Maifredi G, Donato F, Magoni M, Orizio G, Gelatti U, Maiolino P *et al.* (2011). Polychlorinated biphenyls and non-Hodgkin's lymphoma: a case-control study in Northern Italy. *Environ Res*, 111(2):254–9. doi:10.1016/j.envres.2010.12.006 PMID:21238956

Mallin K, McCann K, D'Aloisio A, Freels S, Piorkowski J, Dimos J *et al.* (2004). Cohort mortality study of capacitor manufacturing workers, 1944–2000. *J Occup Environ Med*, 46(6):565–76. doi:10.1097/01.jom.0000128156.24767.12 PMID:15213519

McCready D, Aronson KJ, Chu W, Fan W, Vesprini D, Narod SA (2004). Breast tissue organochlorine levels and metabolic genotypes in relation to breast cancer risk Canada. *Cancer Causes Control*, 15(4):399–418. doi:10.1023/B:CACO.0000027505.32564.c2 PMID:15141140

McElroy JA, Kanarek MS, Trentham-Dietz A, Robert SA, Hampton JM, Newcomb PA *et al.* (2004). Potential exposure to PCBs, DDT, and PBDEs from sport-caught fish consumption in relation to breast cancer risk in Wisconsin. *Environ Health Perspect*, 112(2):156–62. doi:10.1289/ehp.6506 PMID:14754569

McGlynn KA, Quraishi SM, Graubard BI, Weber JP, Rubertone MV, Erickson RL (2009). Polychlorinated biphenyls and risk of testicular germ cell tumors. *Cancer Res*, 69(5):1901–9. doi:10.1158/0008-5472.CAN-08-3935 PMID:19223531

Mikoczy Z, Rylander L (2009). Mortality and cancer incidence in cohorts of Swedish fishermen and fishermen's wives: updated findings. *Chemosphere*, 74(7):938–43. doi:10.1016/j.chemosphere.2008.10.006 PMID:19041115

Millikan R, DeVoto E, Duell EJ, Tse CK, Savitz DA, Beach J *et al.* (2000). Dichlorodiphenyldichloroethene, polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. *Cancer Epidemiol Biomarkers Prev*, 9(11):1233–40. PMID:11097232

Moysich KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P *et al.* (1998). Environmental organochlorine exposure and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 7(3):181–8. PMID:9521429

Moysich KB, Mendola P, Schisterman EF, Freudenheim JL, Ambrosone CB, Vena JE *et al.* (1999a). An evaluation of proposed frameworks for grouping polychlorinated biphenyl (PCB) congener data into meaningful analytic units. *Am J Ind Med*, 35(3):223–31. doi:10.1002/(SICI)1097-0274(199903)35:3<223::AID-AJIM2>3.0.CO;2-L PMID:9987555

Moysich KB, Shields PG, Freudenheim JL, Schisterman EF, Vena JE, Kostyniak P *et al.* (1999b). Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 8(1):41–4. PMID:9950238

Nilsen NB, Waters MA, Prince MM *et al.* (2004). Workers exposed to PCBs in a capacitor manufacturing plant (plant 1; 1948–1977) IWS-95–12. NY, Fort Edwards, Hudson Falls: NIOSH, Cincinnati, Ohio. Report nr IWSB 95–12, pp. 1–148.

Nordström M, Hardell L, Lindström G, Wingfors H, Hardell K, Linde A (2000). Concentrations of organochlorines related to titers to Epstein-Barr virus early antigen IgG as risk factors for hairy cell leukemia. *Environ Health Perspect*, 108(5):441–5. doi:10.1289/ehp.00108441 PMID:10811571

Onozuka D, Yoshimura T, Kaneko S, Furue M (2009). Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a 40-year follow-up study of Yusho patients. *Am J Epidemiol*, 169(1):86–95. doi:10.1093/aje/kwn295 PMID:18974082

Pannett B, Coggon D, Acheson ED (1985). A job-exposure matrix for use in population based studies in England and Wales. *Br J Ind Med*, 42(11):777–83. PMID:4063222

Pavuk M, Cerhan JR, Lynch CF, Kocan A, Petrik J, Chovancova J (2003). Case-control study of PCBs, other organochlorines and breast cancer in Eastern Slovakia. *J Expo Anal Environ Epidemiol*, 13(4):267–75. doi:10.1038/sj.jea.7500277 PMID:12923553

Pesatori AC, Grillo P, Consonni D, Caironi M, Sampietro G, Olivari L *et al.* (2013). Update of the mortality study of workers exposed to polychlorinated biphenyls (Pcbs) in two Italian capacitor manufacturing plants. *Med Lav*, 104(2):107–14. PMID:23789517

Prince MM, Hein MJ, Ruder AM, Waters MA, Laber PA, Whelan EA (2006a). Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors,

1940–1998. *Environ Health*, 5:13 doi:10.1186/1476-069X-5-13 PMID:16716225

Prince MM, Ruder AM, Hein MJ, Waters MA, Whelan EA, Nilsen N *et al.* (2006b). Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Environ Health Perspect*, 114(10):1508–14. doi:10.1289/ehp.9175 PMID:17035134

Purdue MP, Engel LS, Langseth H, Needham LL, Andersen A, Barr DB *et al.* (2009). Prediagnostic serum concentrations of organochlorine compounds and risk of testicular germ cell tumors. *Environ Health Perspect*, 117(10):1514–9. doi:10.1289/ehp.0800359 PMID:20019899

Raaschou-Nielsen O, Pavuk M, Leblanc A, Dumas P, Philippe Weber J, Olsen A *et al.* (2005). Adipose organochlorine concentrations and risk of breast cancer among postmenopausal Danish women. *Cancer Epidemiol Biomarkers Prev*, 14(1):67–74. PMID:15668478

Recio-Vega R, Velazco-Rodriguez V, Ocampo-Gómez G, Hernandez-Gonzalez S, Ruiz-Flores P, Lopez-Marquez F (2011). Serum levels of polychlorinated biphenyls in Mexican women and breast cancer risk. *J Appl Toxicol*, 31(3):270–8. doi:10.1002/jat.1672 PMID:21480306

Recio-Vega R, Mendez-Henandez A, Gabriel AP, Jacobo-Avila A, Portales-Castanedo A, Hernandez-Gonzalez S *et al.* (2012). Potentially estrogenic polychlorinated biphenyls congeners serum levels and its relation with lung cancer. *J Appl Toxicol*, PMID:22729568

Ritchie JM, Vial SL, Fuortes LJ, Guo H, Reedy VE, Smith EM (2003). Organochlorines and risk of prostate cancer. *J Occup Environ Med*, 45(7):692–702. doi:10.1097/01.jom.0000071510.96740.0b PMID:12855910

Ritchie JM, Vial SL, Fuortes LJ, Robertson LW, Guo H, Reedy VE *et al.* (2005). Comparison of proposed frameworks for grouping polychlorinated biphenyl congener data applied to a case-control pilot study of prostate cancer. *Environ Res*, 98(1):104–13. doi:10.1016/j.envres.2004.05.013 PMID:15721890

Robinson CF, Petersen M, Palu S (1999). Mortality patterns among electrical workers employed in the U.S. construction industry, 1982–1987. *Am J Ind Med*, 36(6):630–7. doi:10.1002/(SICI)1097-0274(199912)36:6<630::AID-AJIM5>3.0.CO;2-6 PMID:10561683

Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Helzlsouer K *et al.* (1997). A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. *Lancet*, 350(9073):240–4. doi:10.1016/S0140-6736(97)02088-6 PMID:9242800

Rubin CH, Lanier A, Kieszak S, Brock JW, Koller KR, Strosnider H *et al.* (2006). Breast cancer among Alaska Native women potentially exposed to environmental organochlorine chemicals. *Int J Circumpolar Health*, 65(1):18–27. PMID:16544644

Ruder AM, Hein MJ, Hopf NB, Waters MA (2014). Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: a ten-year update. *Int J Hyg Environ Health*, 217:2-3: 176–87. doi:10.1016/j.ijheh.2013.04.006 PMID:23707056

Ruder AM, Hein MJ, Nilsen N, Waters MA, Laber P, Davis-King K *et al.* (2006). Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. *Environ Health Perspect*, 114(1):18–23. doi:10.1289/ehp.8253 PMID:16393652

Rusiecki JA, Holford TR, Zahm SH, Zheng T (2004). Polychlorinated biphenyls and breast cancer risk by combined estrogen and progesterone receptor status. *Eur J Epidemiol*, 19(8):793–801. doi:10.1023/B:EJEP.0000036580.05471.31 PMID:15469037

Rylander L, Hagmar L (1995). Mortality and cancer incidence among women with a high consumption of fatty fish contaminated with persistent organochlorine compounds. *Scand J Work Environ Health*, 21(6):419–26. doi:10.5271/sjweh.57 PMID:8824747

Savitz DA, Loomis DP (1995). Magnetic field exposure in relation to leukemia and brain cancer mortality among electric utility workers. *Am J Epidemiol*, 141(2):123–34. PMID:7817968

Sawada N, Iwasaki M, Inoue M, Itoh H, Sasazuki S, Yamaji T *et al.* (2010). Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: a nested case-control study. *Environ Health Perspect*, 118(5):659–65. doi:10.1289/ehp.0901214 PMID:20435560

Seidler A, Heiskel H, Bickeböller R, Elsner G (1998). Association between diesel exposure at work and prostate cancer. *Scand J Work Environ Health*, 24(6):486–94. doi:10.5271/sjweh.373 PMID:9988091

Silver SR, Whelan EA, Deddens JA, Steenland NK, Hopf NB, Waters MA *et al.* (2009). Occupational exposure to polychlorinated biphenyls and risk of breast cancer. *Environ Health Perspect*, 117(2):276–82. PMID:19270799

Sinks T, Steele G, Smith AB, Watkins K, Shults RA (1992). Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol*, 136(4):389–98. PMID:1415158

Spinelli JJ, Ng CH, Weber JP, Connors JM, Gascoyne RD, Lai AS *et al.* (2007). Organochlorines and risk of non-Hodgkin lymphoma. *Int J Cancer*, 121(12):2767–75. doi:10.1002/ijc.23005 PMID:17722095

Steineck G, Plato N, Gerhardsson M, Norell SE, Hogstedt C (1990). Increased risk of urothelial cancer in Stockholm during 1985–87 after exposure to benzene and exhausts. *Int J Cancer*, 45(6):1012–7. doi:10.1002/ijc.2910450605 PMID:1693598

Stellman SD, Djordjevic MV, Britton JA, Muscat JE, Citron ML, Kemeny M *et al.* (2000). Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long

Island, New York. *Cancer Epidemiol Biomarkers Prev*, 9(11):1241–9. PMID:11097233

Sturgeon SR, Brock JW, Potischman N, Needham LL, Rothman N, Brinton LA *et al.* (1998). Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). *Cancer Causes Control*, 9(4):417–24. doi:10.1023/A:1008823802393 PMID:9794174

Svensson BG, Nilsson A, Jonsson E, Schütz A, Akesson B, Hagmar L (1995). Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium and methylamines among Swedish fishermen. *Scand J Work Environ Health*, 21(2):96–105. doi:10.5271/sjweh.16 PMID:7618064

Tironi A, Pesatori A, Consonni D, Zocchetti C, Bertazzi PA (1996). The mortality of female workers exposed to PCBs *Epidemiol Prev*, 20(2-3):200–2.[Italian] PMID:8766323

Tomasallo C, Anderson H, Haughwout M, Imm P, Knobeloch L (2010). Mortality among frequent consumers of Great Lakes sport fish. *Environ Res*, 110(1):62–9. doi:10.1016/j.envres.2009.09.008 PMID:19811780

Tsai PC, Ko YC, Huang W, Liu HS, Guo YL (2007). Increased liver and lupus mortalities in 24-year follow-up of the Taiwanese people highly exposed to polychlorinated biphenyls and dibenzofurans. *Sci Total Environ*, 374(2-3):216–22. doi:10.1016/j.scitotenv.2006.12.024 PMID:17257654

Turunen AW, Verkasalo PK, Kiviranta H, Pukkala E, Jula A, Männistö S *et al.* (2008). Mortality in a cohort with high fish consumption. *Int J Epidemiol*, 37(5):1008–17. doi:10.1093/ije/dyn117 PMID:18579573

Tynes T, Reitan JB, Andersen A (1994). Incidence of cancer among workers in Norwegian hydroelectric power companies. *Scand J Work Environ Health*, 20(5):339–44. doi:10.5271/sjweh.1388 PMID:7863297

Unger M, Kiaer H, Blichert-Toft M, Olsen J, Clausen J (1984). Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. *Environ Res*, 34(1):24–8. doi:10.1016/0013-9351(84)90072-0 PMID:6426947

Urabe H (1974). The fourth report of the study group on 'Yusho'. *Fukuoka Acta Med.*, 65:1–4.

Villeneuve S, Cyr D, Lynge E, Orsi L, Sabroe S, Merletti F *et al.* (2010). Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. *Occup Environ Med*, 67(12):837–44. doi:10.1136/oem.2009.052175 PMID:20798010

Wang SS, Lu Y, Rothman N, Abdou AM, Cerhan JR, De Roos A *et al.* (2011). Variation in effects of non-Hodgkin lymphoma risk factors according to the human leukocyte antigen (HLA)-DRB1*01:01 allele and ancestral haplotype 8.1. *PLoS One*, 6(11):e26949 doi:10.1371/journal.pone.0026949 PMID:22096508

Ward EM, Schulte P, Grajewski B, Andersen A, Patterson DG Jr, Turner W *et al.* (2000). Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. *Cancer Epidemiol Biomarkers Prev*, 9(12):1357–67. PMID:11142422

Ward MH, Colt JS, Metayer C, Gunier RB, Lubin J, Crouse V *et al.* (2009). Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. *Environ Health Perspect*, 117(6):1007–13. PMID:19590698

Weiderpass E, Adami HO, Baron JA, Wicklund-Glynn A, Aune M, Atuma S *et al.* (2000). Organochlorines and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev*, 9(5):487–93. PMID:10815693

Wolff MS, Berkowitz GS, Brower S, Senie R, Bleiweiss IJ, Tartter P *et al.* (2000b). Organochlorine exposures and breast cancer risk in New York City women. *Environ Res*, 84(2):151–61. doi:10.1006/enrs.2000.4075 PMID:11068929

Wolff MS, Camann D, Gammon M, Stellman SD (1997). Proposed PCB congener groupings for epidemiological studies. *Environ Health Perspect*, 105(1):13–4. doi:10.1289/ehp.9710513 PMID:9074863

Wolff MS, Toniolo PG (1995). Environmental organochlorine exposure as a potential etiologic factor in breast cancer. *Environ Health Perspect*, 103:Suppl 7: 141–5. PMID:8593861

Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N (1993). Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst*, 85(8):648–52. doi:10.1093/jnci/85.8.648 PMID:8468722

Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P (2000a). Risk of breast cancer and organochlorine exposure. *Cancer Epidemiol Biomarkers Prev*, 9(3):271–7. PMID:10750665

Woolcott CG, Aronson KJ, Hanna WM, SenGupta SK, McCready DR, Sterns EE *et al.* (2001). Organochlorines and breast cancer risk by receptor status, tumor size, and grade (Canada). *Cancer Causes Control*, 12(5):395–404. doi:10.1023/A:1011289905751 PMID:11545454

Yassi A, Tate R, Fish D (1994). Cancer mortality in workers employed at a transformer manufacturing plant. *Am J Ind Med*, 25(3):425–37. doi:10.1002/ajim.4700250310 PMID:8160660

Yassi A, Tate RB, Routledge M (2003). Cancer incidence and mortality in workers employed at a transformer manufacturing plant: update to a cohort study. *Am J Ind Med*, 44(1):58–62. doi:10.1002/ajim.10237 PMID:12822136

Yoshimura T (2012). Yusho: 43 years later. *Kaohsiung J Med Sci*, 28(7):Suppl: S49–52. doi:10.1016/j.kjms.2012.05.010 PMID:22871602

Yu ML, Guo YL, Hsu CC, Rogan WJ (1997). Increased mortality from chronic liver disease and cirrhosis 13

years after the Taiwan "yucheng" ("oil disease") incident. *Am J Ind Med*, 31(2):172–5. doi:10.1002/(SICI)1097-0274(199702)31:2<172::AID-AJIM6>3.0.CO;2-1 PMID:9028433

Zhang Y, Wise JP, Holford TR, Xie H, Boyle P, Zahm SH *et al.* (2004). Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut women. *Am J Epidemiol*, 160(12):1177–83. doi:10.1093/aje/kwh346 PMID:15583370

Zheng T, Holford TR, Mayne ST, Tessari J, Ward B, Carter D *et al.* (2000b). Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2′-bis(p-chlorophenyl)ethylene. *Cancer Epidemiol Biomarkers Prev*, 9(2):167–74. PMID:10698477

Zheng T, Holford TR, Tessari J, Mayne ST, Owens PH, Ward B *et al.* (2000a). Breast cancer risk associated with congeners of polychlorinated biphenyls. *Am J Epidemiol*, 152(1):50–8. doi:10.1093/aje/152.1.50 PMID:10901329