2. Studies of Cancer in Humans

2,3,7,8-TCDD is thought to be the most toxic PCDD congener, followed in presumed toxicity by the higher chlorinated PCDDs. Lower chlorinated PCDDs are thought to be much less toxic.

The focus of this review of human studies is on studies in which exposure to 2,3,7,8-TCDD or higher chlorinated PCDDs can be presumed or is documented. Typically this involves exposure to phenoxy herbicides contaminated by 2,3,7,8-TCDD (particularly 2,4,5-T) or to other contaminated chemicals used in manufacturing processes (e.g., TCP).

Studies involving only exposure to herbicides not contaminated by PCDDs (e.g., 4-chloro-2-methylphenoxyacetic acid (MCPA)) are not reviewed (e.g., Coggon *et al.*, 1986; Lynge, 1993). Studies involving only exposure to unspecified combinations of pesticides and herbicides are also not reviewed (e.g., Blair *et al.*, 1983) because the

extent of exposure to PCDD-containing herbicides (if any) is unknown. Studies involving only exposure to 2,4-D, that is not likely to have been contaminated by higher chlorinated PCDDs, are also not discussed. Studies involving exposure to substances contaminated with higher chlorinated PCDDs without 2,3,7,8-TCDD, e.g., PCP, are discussed separately from studies involving exposure to 2,3,7,8-TCDD.

Blood concentrations reported are lipid-based, unless otherwise noted (see Section 1.4).

2.1 Industrial exposures and industrial accidents

The cohort study populations considered by various authors overlap in many instances. However, different publications on overlapping study groups may have different focuses, e.g., incidence/mortality, different follow-up periods, different exposure assessment and other characteristics. Therefore, **Table 32** presents the relationship between different publications which are considered relevant for this monograph in terms of study population size.

2.1.1 *Exposure to 2,3,7,8-TCDD and higher chlorinated PCDDs/PCDFs in chemical plants*

Cohort studies are summarized in **Table 33**.

Workers at chemical plants in the United States which produced chemicals contaminated with PCDDs/PCDFs (primarily TCP and/or 2,4,5-T) have been studied extensively. There has been a series of publications on two separate plants and a larger study of 12 plants which included most United States workers manufacturing these products who were exposed specifically to 2,3,7,8-TCDD. In the latter study, serum PCDD measurements were available for some workers.

(*a*) *Two United States plants*

Nitro plant

Workers at a Monsanto plant in Nitro, WV, have been studied by Zack and Suskind (1980), Zack and Gaffey (1983) and Collins *et al.* (1993). Zack and Suskind (1980) studied 121 male workers (one woman is not included in the mortality analysis) who developed chloracne after an accident during production of TCP in 1949. These workers were followed through 31 December 1978 with person–time at risk beginning at the accident. United States referent rates were used. Thirty-two deaths were observed (standardized mortality ratio (SMR), 0.7; $p < 0.05$), of which nine were cancer deaths (SMR, 1.0). No significant excess was found for any specific cancer, although lung cancer was elevated (5 observed; SMR, 1.8). One soft-tissue sarcoma was observed — a fibrous histiocytoma (classified as a skin cancer (ICD-8, 172–173)), with 0.2 skin cancers expected. Three deaths from lymphatic and haematopoietic cancers were observed (SMR, 3.4).

Table 32. Relationship between industrial cohort study groups with exposure to 2,3,7,8-TCDD

Kogevinas *et al.* (1997)	> Fingerhut *et al.* (1991a,b) (USA, NIOSH, 12 plants)	> Bond *et al.* (1989a), Ott *et al.* (1987), Cook *et al.* (1986) (Dow, Midland, MI)	> Ramlow *et al.* (1996) (Dow, Midland, MI)
		> Zack & Gaffey (1983) (Monsanto, Nitro, WV)	
		> Collins *et al.* (1993) (Monsanto, Nitro, WV)	
	> Saracci *et al.* (1991)	> Bueno de Mesquita *et al.* (1993), Hooiveld *et al.* (1996a) (Netherlands)	
		> Coggon *et al.* (1991) (United Kingdom)	
	> Becher *et al.* (1996) (Boehringer-Ingelheim, Bayer, BASF (not the accident))	> Flesch-Janys *et al.* (1995) (Boehringer-Ingelheim)	Manz *et al.* (1991) (Boehringer-Ingelheim)
Ott & Zober (1996), Zober *et al.* (1994), Zober *et al.* (1990) (accident, BASF)			

A > B denotes that the study population of B is a subset of A.
A, B denotes that the study populations A and B are almost identical.
All publications mentioned contain results considered to be relevant by the Working Group.
The study populations of Collins *et al.* (1993) and Zack & Gaffey (1983) overlap in part.
Specific female cohorts (Kogevinas *et al.*, 1993; Nagel *et al.*, 1994) are not included.

Zack and Gaffey (1983) studied 884 white male employees at the Nitro plant who were active on or after 1 January 1955 with one or more years of employment as hourly workers. This cohort included all workers at the plant, not just those exposed to PCDDs. Follow-up was through 31 December 1977 and United States referent rates were used. There were 163 deaths in this cohort (SMR, 1.0). Nine deaths from urinary bladder cancer were observed (SMR, 9.9). The excess of urinary bladder cancer was attributed to the use of 4-aminobiphenyl (see IARC, 1987f), a known urinary bladder carcinogen. Seven of these cancers had been detected earlier in a screening programme. Work history of decedents was examined to determine if the men had been assigned to 2,4,5-T production. For 58 men so identified, a proportionate mortality study was conducted. Nine cancers were observed (proportionate mortality ratio [PMR], 0.8). Six were lung cancers (PMR, 1.7). No haematopoietic cancer occurred in this group. One soft-tissue sarcoma (a liposarcoma) was observed; no expected number for soft-tissue sarcoma was given. [An unknown, but probably small, number of workers who worked with TCP but not with 2,4,5-T would have been omitted from this analysis].

Collins *et al.* (1993) studied 754 workers who had worked at the Nitro plant for one day or more between 8 March 1949 (the date of the above-mentioned accident) and

Table 33. Industrial cohort studies and populations exposed to industrial exposures and industrial accidents

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Fingerhut *et al.* (1991a), USA	5172 workers 12 plants	Mortality followed from first exposure to 31 December 1987	1987 serum levels of exposed (n = 253) averaged 233 ng/kg fat compared with 7 ng/kg for unexposed workers (n = 79)	Men	All cancers				Combined 2,3,7,8-TCDD-exposed production workers from 12 plants exposed during 1942–84, including Monsanto (Nitro, WV) and Dow (Midland, MI) workers
					≥ 20 years latency	265	1.2	1.0–1.3	
					≥ 1 year exposure	114	1.5	1.2–1.8	
					Digestive system				
					≥ 20 years latency	67	1.1	0.9–1.4	
					≥ 1 year exposure	28	1.4	0.9–2.0	
					Lung				
					≥ 20 years latency	89	1.1	0.9–1.4	
					≥ 1 year exposure	40	1.4	1.0–1.9	
					Haematopoietic (all)				
					≥ 20 years latency	24	1.1	0.7–1.6	
					≥ 1 year exposure	8	1.3	0.5–2.5	
					NHL				
					≥ 20 years latency	10	1.4	0.7–2.5	
					≥ 1 year exposure	2	0.9	0.1–3.4	
					Multiple myeloma				
					≥ 20 years latency	5	1.6	0.5–3.9	
					≥ 1 year exposure	3	2.6	0.5–7.7	
					Leukaemia				
					≥ 20 years latency	6	0.7	0.2–1.5	
					≥ 1 year exposure	2	0.8	0.1–2.8	
					Connective tissue/STS				
					≥ 20 years latency	4	3.4	0.9–8.7	
					≥ 1 year exposure	3	9.2	1.9–27.0	

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Ott & Zober (1996), (BASF) Germany	243 workers accidentally exposed to 2,3,7,8-TCDD in a TCP unit in a chemical plant	Mortality and incidence 1953–92	2,3,7,8-TCDD serum levels in 138 subjects in 1988–92. Model-based estimation for other workers	Men	All cancers				Mortality
					< 0.1 µg/kg bw	8	0.8	0.4–1.6	$[p_{trend} = 0.07]$; local reference
					0.1–0.99 µg/kg bw	8	1.2	0.5–2.3	
					1.0–1.99 µg/kg bw	8	1.4	0.6–2.7	
					≥ 2.0 µg/kg bw	7	2.0	0.8–4.0	
					All cancers	13	2.0	1.0–3.4	> 1 µg/kg bw, ≥ 20 years of latency
					Respiratory	6	3.1	1.1–6.7	
					All cancers	18	1.9	1.1–3.0	113 chloracne cases, latency
					Digestive system	6	1.8	0.7–4.0	> 20 years; mortality
					Respiratory tract	7	2.4	1.0–5.0	
					Respiratory tract	8	2.0	0.9–3.9	Incidence, > 1.0 µg/kg bw
					Digestive tract	11	1.5	1.1–1.9	Cox's regression; deaths
						12	1.4	1.1–1.7	Cox's regression; incident cases; internal comparison controlling for known confounders
Manz *et al.* (1991), (Boehringer-Ingelheim) Germany	1184 men and 399 women employed in a herbicide plant; 496 high exposure; 901 medium exposure; 186 low exposure	Mortality 1952–89	TCP, 2,4,5-T and 2,3,7,8-TCDD; fat levels in 48 subjects in 1985 Median fat 2,3,7,8-TCDD, 137 ng/kg high exposure Median fat 2,3,7,8-TCDD medium + low, 60 ng/kg	Men	All cancers				Gas workers reference
					High exposure	29	1.8	1.2–2.6	$[p_{trend} = 0.24]$
					Medium exposure	39	1.2	0.9–1.6	
					Low exposure	7	1.5	0.6–3.0	
				Women	All cancers	NG	0.9	0.6–1.5	National reference
					Breast	9	2.2	1.0–4.1	

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Flesch-Janys *et al.* (1995); Flesch-Janys *et al.* (1996b) (Boehringer-Ingelheim) Germany	1189 workers employed in a herbicide plant contaminated with PCDDs/PCDFs	Mortality 1952–92	PCDD/PCDF-contaminated herbicides. 2,3,7,8-TCDD biological levels in 190 workers in 1992. Model-based estimation for other workers	Men	All cancers	NG	1.0	0.6–1.8	Blood TEQ 1.0–12.2 ng/kg
						NG	1.3	0.8–2.1	Blood TEQ 12.3–39.5 ng/kg
						NG	1.2	0.7–1.9	Blood TEQ 39.6–98.9 ng/kg
						NG	1.2	0.8–1.9	Blood TEQ 99.0–278.5 ng/kg
						NG	1.3	0.7–2.3	Blood TEQ 278.6–545 ng/kg
						NG	2.7	1.7–4.4	Blood TEQ 545.1–5362 ng/kg $P_{trend} < 0.01$, Cox's regression
						NG	2.0	1.1–3.8	2,3,7,8-TCDD, 344.7–3890 ng/kg, internal comparison
						NG	2.3	1.1–4.6	Internal comparison; subjects exposed to dimethyl sulfate excluded
Becher *et al.* (1996); Kogevinas *et al.* (1997) Germany	2479 workers from four plants involved in production of phenoxy herbicides and chlorophenols	Mortality 1950s–89	Herbicides, PCDDs, PCDFs, 2,4,5-T, TCP, 2,3,7,8-TCDD, chlorophenols	Men	All cancers	138	1.2	1.0–1.4	National reference
					Buccal, pharynx	9	2.9	1.3–5.6	
					Lung	47	1.4	1.0–1.9	
					All haematopoietic	13	1.7	0.9–2.9	
					NHL	6	3.3	1.2–7.1	
			TCP, chlorophenols, 2,3,7,8-TCDD		All cancers	97	1.3	1.1–1.6	Plant I (Boehringer-Ingelheim). Blood 2,3,7,8-TCDD in 190 workers: 3–2252 ng/kg. Numerous cases of chloracne
					Lung	31	1.5	1.0–2.1	
					All haematopoietic	11	2.4	1.2–4.3	
					NHL	4	3.8	1.0–9.6	
					Multiple myeloma	3	5.4	1.1–15.9	
			2,4,5-T, 2,3,7,8-TCDD		NHL	2	12.0	1.5–43.5	Plant II (Bayer-Uerdingen). Blood 2,3,7,8-TCDD in 19 workers: 23–1935 ng/kg. Some cases of chloracne
Coggon *et al.* (1991), (Plant A) United Kingdom	1082 chemical workers producing or formulating phenoxy herbicides and chlorophenols in 1975–85. 2,4,5-T was produced during 1968–78	Mortality 1975–87	Phenoxy compounds including 2,4,5-T and chlorophenols	Men	All cancers	12	1.0	[0.7–1.4]	Workers in one (Factory A) out of four factories included in study
					Lung	6	1.3	[0.5–2.8]	
					NHL	0			

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Bueno de Mesquita *et al.* (1993), The Netherlands	Workers in synthesis and formulation of phenoxy herbicides and chlorophenols in two plants (963 exposed, 1111 unexposed); Factory A, accident in 1963; exposure to 2,3,7,8-TCDD	Mortality 1955–86	2,4,5-T, PCDDs, 2,3,7,8-TCDD	Men	All cancers	26	1.2	0.5–1.7	Factory A only, exposed workers versus national population
					Pancreas	3	2.9	0.6–8.4	
					Large intestine	3	2.4	0.5–7.0	
					Lung	9	1.0	0.5–1.9	
					Prostate	2	2.2	0.3–7.8	
					Lymphosarcoma	1	2.0	0.1–11.4	
					Myeloid leukaemia	1	2.9	0.1–15.9	
					All cancers	31	1.7	0.9–3.4	Both plants; exposed versus unexposed
					Respiratory tract	9	1.7	0.5–6.3	
			Accidental exposure in 1963		All cancers	10	1.4	0.7–2.5	Factory A; national reference
						Case/control	OR		
Kogevinas *et al.* (1995), international	11 STS cases and 55 healthy controls; 32 NHL cases and 158 healthy controls	Nested case–control study within the IARC cohort reported by Saracci *et al.* (1991)	Exposure to 21 chemicals including major phenoxy herbicides, PCDDs, raw materials and other process chemicals	Men and women	STS	10/30	10.3	1.2–90.6	Any phenoxy herbicide
						9/24	5.6	1.1–27.7	Any PCDD or PCDF
						5/13	5.2	0.9–31.9	2,3,7,8-TCDD
					NHL	19/85	1.3	0.5–2.9	Any phenoxy herbicide
						20/78	1.8	0.8–4.3	Any PCDD or PCDF
						11/39	1.9	0.7–5.1	2,3,7,8-TCDD

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Kogevinas *et al.* (1997), international	21 863 in 36 cohorts from 12 countries	Mortality	2,3,7,8-TCDD or higher chlorinated PCDDs versus not exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs or no PCDD exposure	20851 men, 1012 women	All cancers				Combined PCDD-exposed workers (production and spraying) from 36 cohorts with varied follow-up from 1939 to 1992. Includes and updates IARC cohort (Saracci *et al.*, 1991), adds NIOSH cohort (Fingerhut *et al.*, 1991a,b) and adds four plants in Germany (Manz *et al.*, 1991; Becher *et al.*, 1996; Flesch-Janys *et al.*, 1995). Largest combined cohort of PCDD-exposed workers.
					Exposed to 2,3,7,8-TCDD and higher	710	1.1	1.0–1.2	
					Exposed to lower or no PCDD	398	1.0	0.9–1.1	
					Digestive system				
					Exposed to 2,3,7,8-TCDD and higher	190	[1.0]	[0.9–1.2]	
					Exposed to lower or no PCDD	106	[0.9]	[0.7–1.1]	
					Lung				
					Exposed to 2,3,7,8-TCDD and higher	225	1.1	1.0–1.3	
					Exposed to lower or no PCDD	148	1.0	0.9–1.2	
					Haematopoietic (all)				
					Exposed to 2,3,7,8-TCDD and higher	57	1.1	[0.8–1.4]	
					Exposed to 2,3,7,8-lower or no PCDD	35	1.2	[0.8–1.6]	
					NHL				
					Exposed to 2,3,7,8-TCDD and higher	24	1.4	0.9–2.1	
					Exposed to lower or no PCDD	9	1.0	0.5–1.9	
					Multiple myeloma				
					Exposed to 2,3,7,8-TCDD and higher	9	1.2	0.6–2.3	
					Exposed to lower or no PCDD	8	1.6	0.7–3.1	

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Kogevinas *et al.* (1997), international (contd)					Leukaemia				
					Exposed to 2,3,7,8-TCDD and higher	16	0.7	0.4–1.2	
					Exposed to lower or no PCDD	17	1.4	0.8–2.3	
					Connective tissue/STS				
					Exposed to 2,3,7,8-TCDD and higher	6	2.0	0.8–4.4	
					Exposed to lower or no PCDD	2	1.4	0.2–4.9	
Bertazzi *et al.* (1993), Italy	Residents in contaminated zones after the Seveso accident: Zone A, 724; Zone B, 4824; Zone R, 31 647; age, 20–74 years	Incidence 1977–86	2,3,7,8-TCDD: Zone A; soil levels, 15.5–580 μg/m^2; median blood levels in adults, 389 ng/kg (back-calculation)	Men	All cancers	7	0.7	0.3–1.5	Local reference. Median 2,3,7,8-TCDD level in the reference area (52 samples in 1992–93), 5.5 ng/kg blood (Landi *et al.*, 1996)
					Digestive system	2	0.7	0.2–2.8	
					Lung	2	0.8	0.2–3.4	
				Women	All cancers	7	1.0	0.5–2.1	
					Digestive tract	3	1.7	0.6–5.4	
			Zone B; soil levels, < 50 μg/m^2; median blood levels in adults, 78 ng/kg (back-calculation)	Men	All cancers	76	1.1	0.9–1.4	Local reference
					Digestive system	18	0.9	0.6–1.5	
					Hepatobiliary	5	1.8	0.7–4.4	
					Liver	4	2.1	0.8–5.8	
					Lung	18	1.1	0.7–1.8	
					Haematopoietic	8	2.1	1.0–4.3	
					NHL	3	2.3	0.7–7.4	
					Lymphoreticulosarcoma	3	5.7	1.7–19.0	
					Multiple myeloma	2	3.2	0.8–13.3	
					Leukaemia	2	1.6	0.4–6.5	

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Bertazzi *et al.* (1993), Italy (contd)				Women	All cancers	36	0.8	0.6–1.1	Local reference
					Digestive system	12	1.1	0.6–1.9	
					Hepatobiliary	5	3.3	1.3–8.1	
					Gall-bladder	4	4.9	1.8–13.6	
					Breast	10	0.7	0.4–1.4	
					Haematopoietic	6	1.9	0.8–4.4	
					Multiple myeloma	2	5.3	1.2–22.6	
					Myeloid leukaemia	2	3.7	0.9–15.7	
			Zone R; soil levels, < 5 µg/m^2	Men	All cancers	447	0.9	0.9–1.0	Local reference
					Digestive system	131	0.9	0.8–1.1	
					Lung	96	0.8	0.7–1.0	
					STS	6	2.8	1.0–7.3	
					Haematopoietic	25	1.0	0.6–1.5	
					NHL	12	1.3	0.7–2.5	
					Myeloid leukaemia	5	1.4	0.5–3.8	
				Women	All cancers	318	0.9	0.8–1.1	Local reference
					Digestive tract	75	0.9	0.7–1.1	
					Lung	16	1.5	0.8–2.5	
					STS	2	1.6	0.3–7.4	
					Breast	106	1.1	0.9–1.3	
					Haematopoietic	18	0.8	0.5–1.3	
					NHL	10	1.2	0.6–2.3	
					Lymphoreticulosarcoma	6	1.7	0.7–4.2	
Bertazzi *et al.* (1996), Italy	Residents in contaminated zones after the Seveso accident: Zone A, 750; Zone B, 5000; Zone R, 30 000; all ages	Mortality 1976–91	Zone A	Men	All cancers	6	0.4	0.2–1.0	Local reference. Median level in the reference area (52 samples in 1992–93), 5.5 ng/kg (Landi *et al.*, 1996)
					Lung	4	1.0	0.4–2.6	
				Women	All cancers	10	1.2	0.6–2.2	
					Digestive system	5	1.5	0.6–3.6	
					Colon	2	2.6	0.6–10.5	

Table 33 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/cause of death	No. obs.	RR	95% CI	Comments
Bertazzi *et al.* (1996), Italy (contd)			Zone B	Men	All cancers	104	1.1	0.9–1.3	Local reference
					Digestive system	33	0.9	0.7–1.3	
					Rectum	7	2.9	1.4–6.2	
					Lung	34	1.2	0.9–1.7	
					Haematopoietic	12	2.3	1.3–4.2	
					NHL	2	1.5	0.4–6.0	
					Hodgkin's disease	2	3.3	0.8–14.0	
					Leukaemia	7	3.1	1.4–6.7	
				Women	All cancers	48	0.9	0.7–1.2	
					Digestive system	18	0.8	0.5–1.3	
					Stomach	7	1.0	0.5–2.2	
					Hepatobiliary	4	1.1	0.4–3.1	
					Liver	3	1.3	0.4–4.0	
					Breast	9	0.8	0.4–1.5	
					Haematopoietic	7	1.8	0.8–3.8	
					Hodgkin's disease	2	6.5	1.5–30.0	
					Myeloma	4	6.6	2.3–18.5	
				Men and women	Thyroid	2	[3.9]	[0.4–14.1]	
			Zone R	Men	All cancers	607	0.9	0.8–1.0	Local reference
					Digestive system	226	0.9	0.8–1.0	
					Oesophagus	30	1.6	1.1–2.4	
					Lung	176	0.9	0.8–1.1	
					STS	4	2.1	0.7–6.5	
					Haematopoietic	27	0.8	0.5–1.2	
				Women	All cancers	401	0.9	0.8–1.0	Local reference
					Digestive system	158	0.9	0.8–1.0	
					Lung	29	1.0	0.7–1.6	
					Breast	67	0.8	0.6–1.0	
					Haematopoietic	29	0.9	0.6–1.4	

Abbreviations: NHL, non-Hodgkin lymphoma; STS, soft-tissue sarcoma; NG, not given

22 November 1949 (the date of the last reported case of chloracne resulting from the accident clean-up) (this study includes the 122 chloracne cases of Zack & Suskind, 1980). Person–time at risk began on 8 March 1949 or at date of hire, if hired between 8 March and 22 November 1949, and extended through 31 December 1987 (23 198 person–years). Follow-up was complete for 733 workers. United States referent rates were used. The cohort was further subdivided into four groups: (1) 461 workers without chloracne and judged not to have been exposed to 4-aminobiphenyl; (2) 171 workers without chloracne but with exposure to 4-aminobiphenyl; (3) 97 workers with chloracne and no exposure to 4-aminobiphenyl; and (4) 25 workers with chloracne and exposure to 4-aminobiphenyl. Three deaths from soft-tissue sarcoma occurred in the cohort: one in the group without chloracne but with exposure to 4-aminobiphenyl (upon review, this case was not a soft tissue sarcoma) and two in the group with chloracne and with exposure to 4-aminobiphenyl. Excesses of urinary bladder cancer occurred in all groups, but primarily in the group without chloracne but with exposure to 4-aminobiphenyl (10 observed; SMR, 22; 95% CI, 10.4–40.0). The authors considered that the deaths due to soft-tissue sarcoma may have been caused by 4-aminobiphenyl. [The Working Group considered that this argument is weakened by two points. First, the one case of soft-tissue sarcoma occurring in the group without chloracne but with exposure to 4-aminobiphenyl apparently may have been exposed to 2,3,7,8-TCDD, as suggested by additional data presented in the study. Second, there are no human data indicating that 4-aminobiphenyl or other aromatic amines cause soft-tissue sarcoma and hence no strong reason to believe it could act as a confounder for soft-tissue sarcoma occurrence due to PCDDs.] (All but one of the confirmed cases of soft-tissue sarcomas of the Fingerhut *et al.* (1991a) study are included in Collins *et al.* (1993)).

Midland plant

Workers at a Dow plant in Midland, MI, have been studied in a series of publications. Ott *et al.* (1980) studied 204 male workers exposed to 2,4,5-T from 1950 to 1971 (the period during which it was manufactured) (157 with less than one year's exposure). The method of worker selection may have missed some short-term workers, but all workers with at least one year of employment in the 2,4,5-T work area would have been included. Some workers with exposure to TCP (but no exposure to 2,4,5-T) may have been excluded from this analysis. No case of chloracne was identified in this group. Follow-up extended through 1976. United States referent rates were used. Only 11 deaths occurred in this cohort (20 expected) and only one cancer death (a respiratory cancer in a smoker) (3.6 expected).

Cook *et al.* (1980) studied 61 men at the same plant in Midland, MI, who worked in TCP production in 1964 (there was an incident in June 1964 in the plant and these employees have been exposed to 2,3,7,8-TCDD); 49 developed chloracne at that time. Follow-up extended through 1978 and 40 men were still working at the end of 1978. United States referent rates were used. Only four deaths were observed versus 7.8 expected; three were due to cancer versus 1.6 expected (one soft-tissue sarcoma (fibrosarcoma) occurred).

A cohort of 2189 (later 2192) workers at the Midland, MI, plant exposed to higher chlorinated phenols (three or more chlorines) and related products (including 2,4,5-T) was studied by Cook *et al.* (1986), Ott *et al.* (1987) and Bond *et al.* (1989a). (Bond *et al.* (1989a) also included a sub-cohort analysis of the mortality of 323 men diagnosed with chloracne.) The cohort was defined on the basis of work in departments manufacturing TCP, PCP, 2,4,5-T and 2,4,5-T esters. Among these, only PCP did not contain 2,3,7,8-TCDD (Fingerhut *et al.*, 1991b), although it did contain hexa-, hepta- and octa-CDDs. Production of these chemicals began at various dates from 1937 to 1955, and ended between 1971 and 1982. Workers were ranked on a scale of 0 to 4 for intensity of exposure to 2,3,7,8-TCDD and from 0 to 2 for intensity of exposure to hexa-, hepta- and octa-CDDs, with each unit representing an increase on a logarithmic scale. Exposure data were available from wipe samples, process streams and intermediate products. 2,3,7,8-TCDD was present at 1818 mg/kg (mean of 28 samples) in TCP waste streams in the 1960s and 1970s and at much lower levels in other process streams and in the intermediate product (range, 0.1–116 mg/kg) (Ott *et al.*, 1987). Almost all of these workers were included in the United States NIOSH 12-plant cohort studied by Fingerhut *et al.* (1991a,b), which was restricted to workers with some exposure to 2,3,7,8-TCDD; the only workers in the Midland, MI, cohort of 2192 who were excluded from Fingerhut *et al.* (1991a,b) were approximately 100 workers with exposure to PCP only.

Cook *et al.* (1986) followed the cohort of 2189 men from 1940 through 1979 and found an SMR for all causes of death of 0.9 and for all cancers of 1.0. No specific cancer site showed an increase.

Ott *et al.* (1987) followed up the same cohort (2187 men) through 1982 with only 25 (1%) lost to follow-up; United States referent rates were used. Approximately 50% of the cohort had worked in exposed areas for less than one year and only 209 men had worked for 10 years or more; 823 were still employed at the end of follow-up. The overall SMR was 0.9 (95% confidence interval [CI], 0.8–1.0) based on 370 deaths. There were 102 cancer deaths (SMR, 1.0; 95% CI, 0.8–1.3) and the SMR for cancer with 20 or more years' latency was not significantly elevated (SMR, 1.3; 95% CI, 1.0–1.6). There was no significant elevation for cancer deaths, except for the category of other and unspecified neoplasms (12 observed; SMR, 2.6). Respiratory tract cancer mortality (23 deaths; SMR, 0.82) was not elevated. Elevations based on small numbers were observed for stomach cancer (6 observed, SMR, 1.6; 95% CI, 0.6–3.4) and lymphatic and haematopoietic cancers (12 observed; SMR, 1.5; 95% CI, 0.8–2.6), with the excess in the latter category accounted for mainly by non-Hodgkin lymphoma (5 observed; SMR, 1.9; 95% CI, 0.6–4.5) and multiple myeloma (2 observed; SMR, 2.0; 95% CI, 0.2–7.2). One death was initially classified as due to soft-tissue sarcoma (a fibrosarcoma); however, upon pathology review, this cancer was determined to be a renal clear-cell carcinoma. Analyses by cumulative exposure intensity scores showed no significant trend (at the $p = 0.05$ level) with increased exposure to 2,3,7,8-TCDD or to hexa-, hepta- or octa-CDDs for any specific cancer, although there was some increase in digestive tract cancers with increasing 2,3,7,8-TCDD exposure.

Bond *et al.* (1989a) increased by two years (through 1984) the follow-up of the cohort studied by Ott *et al.* (1987) (vital status was established for 2191 subjects). There was an increase in the number of deaths by 36, bringing the total to 406 (SMR, 0.9; [95% CI, 0.8–1.0]). Cancer deaths increased in number by 14 to make a total of 95 (SMR, 1.0; [95% CI, 0.8–1.3]). Two additional deaths from stomach cancer (8 observed [SMR, 2.0; [95% CI, 0.9–3.9]), one (additional) death from soft-tissue sarcoma (2 observed (one misclassified); [SMR, 5.0; 95% CI, 0.6–18.1]) and one additional death from non-Hodgkin lymphoma (6 observed; [SMR, 2.1; 95% CI, 0.8–4.5]) occurred. These elevations felt short of statistical significance. The two cases of soft-tissue sarcoma (one of which was actually misclassified) occurred in workers with chloracne. No other statistically significant trend with cumulative dose (of either 2,3,7,8-TCDD or hexa-, hepta- or octa-CDDs) occurred. Results from a sub-cohort of 323 male workers diagnosed with chloracne were presented, based on a review of 2072 (95% of the cohort) company medical records. Diagnoses of chloracne were included if they were considered 'probable' or 'definite'; person–time at risk began at the time of diagnosis. This sub-cohort had 4871 person–years of observation and 37 deaths (SMR, 0.8; 95% CI, 0.6–1.1) and only seven cancer deaths (SMR, 0.7; 95% CI, 0.3–1.4). The presence of chloracne was more prevalent in those who had the highest cumulative exposure to either 2,3,7,8-TCDD or hexa-, hepta- or octa-CDDs. Mortality in this sub-cohort was unremarkable except for soft-tissue sarcoma, for which two deaths (which included the misclassified case) were observed versus < 0.1 expected.

(*b*) *Comprehensive United States study*

The largest study of United States production workers exposed to PCDDs was conducted by the United States National Institute for Occupational Safety and Health (NIOSH) and published by Fingerhut *et al.* (1991a). A more detailed technical report of this study is also available (Fingerhut *et al.*, 1991b). This 12-plant study included the Nitro, WV, plant of Monsanto and the Midland, MI, plant of Dow discussed above, which represented 9% and 40% of the cohort, respectively. In order to be included into the cohort, all workers had to have had presumed exposure to 2,3,7,8-TCDD. The cohort was constructed by NIOSH after a review of personnel records at 12 United States plants producing chemicals known to be contaminated with 2,3,7,8-TCDD (principally TCP and 2,4,5-T). The cohort included most workers in the United States likely to have been exposed to 2,3,7,8-TCDD in chemical manufacturing, comprising 5000 men with work records showing assignment to a production or maintenance job in a process involving 2,3,7,8-TCDD contamination, as well as an additional 172 men without work history records but known to have been exposed at the Nitro, WV, plant based upon inclusion in a prior cross-sectional medical study by Suskind & Hertzberg (1984). These latter 172 men and an additional 30 men in the NIOSH study lacked sufficient work history information for their inclusion in more detailed analyses by duration of exposure. Follow-up was conducted through 1987 and United States referent rates were used. Serum levels of 2,3,7,8-TCDD in 253 cohort members at two plants measured in 1987 averaged 233 ng/kg lipid, compared with 7 ng/kg lipid in a group of 79 unexposed workers. Levels increased to 418 ng/kg for 119 workers exposed for more than one year

(Fingerhut *et al.*, 1991a). Extrapolation to the date when these workers were employed, assuming a half life of 7.1 years, indicated a mean serum level at that time of 2000 ng/kg lipid (highest level, 32 000 ng/kg). Workers had last been exposed 15–37 years earlier. The correlation between serum 2,3,7,8-TCDD level and duration of exposure was 0.72 (Fingerhut *et al.*, 1991b). There were 1052 deaths in this cohort, with 116 748 person–years. The SMR for all causes was 1.0 (95% CI, 0.9–1.1). Mortality from all cancers (265 deaths) was slightly but significantly elevated (SMR, 1.2; 95% CI, 1.0–1.3). Soft-tissue sarcoma mortality was elevated based on four deaths (SMR, 3.4; 95% CI, 0.9–8.7). Two of the deaths from soft-tissue sarcoma, upon further review of medical records, were found to be misclassified (false positives), but three deaths from other causes, upon review, were found to be soft-tissue sarcomas (false negatives). Other causes of death of interest in this study were not remarkable. There were 10 deaths from non-Hodgkin lymphoma (SMR, 1.4; 95% CI, 0.7–2.5); stomach cancer mortality was not elevated (10 deaths observed; SMR, 1.0; 95% CI, 0.5–1.9); lung cancer showed a slight increase (89 observed; SMR, 1.1; 95% CI, 0.9–1.4). Sub-cohort analyses focused on those workers with more than one year's duration of 2,3,7,8-TCDD exposure and at least 20 years' potential latency (1520 workers, 29% of the cohort; mean duration of employment, 19 years; mean duration of exposure to 2,3,7,8-TCDD, 7 years). In this sub-cohort, mortality from all cancers combined was significantly elevated (114 observed; SMR, 1.5; 95% CI, 1.2–1.8). A wide variety of cancer sites showed some excess, but only soft-tissue sarcoma was significantly elevated (3 observed; SMR, 9.2; 95% CI, 1.9–27). The SMR for lung cancer was 1.4 (95% CI, 1.0–1.9) based on 40 deaths. Conversely, the SMR for non-Hodgkin lymphoma was not elevated in this sub-cohort with presumed higher exposure (2 deaths observed; SMR, 0.9; 95% CI, 0.1–3.4). Internal analyses comparing longer duration of exposure to 2,3,7,8-TCDD to a short duration (< 1 year) referent category found nonsignificant positive trends for all cancers and lung cancer ($p = 0.3$ and $p = 0.2$, respectively). Rate ratios also increased with latency (all cancer SMRs, 0.7, 1.1 and 1.3; lung cancer SMRs, 0.8, 1.0 and 1.2 with latency of < 10 years, 10–20 years and ≥ 20 years, respectively). The authors considered that smoking was not likely to be responsible for the excess of lung cancer for several reasons including that (*a*) there was no increase in non-malignant respiratory disease, which is strongly related to smoking; (*b*) an indirect adjustment for smoking based on known smoking habits for a sample of the cohort did not account for the observed increase; and (*c*) there was no increase in lung cancer among the group with 20 years' potential latency but short duration (< 1 year) of exposure to 2,3,7,8-TCDD (17 observed; SMR, 1.0). [The Working Group noted that these are indirect ways of controlling for confounding.]

(*c*) *German accident cohort*

In the 1953 accident at the BASF TCP production unit at Ludwigshafen, Germany, the total number of employees identified as being involved directly or in the subsequent clean-up, repair or maintenance activities was 247 (243 men, 4 women). Analyses of adipose tissue and blood from groups of these workers are described in Section 1.3.1(*a*)(i). Part of the cohort was first studied by Thiess *et al.* (1982). It was completed by Zober *et al.* (1990) and further studied by Zober *et al.* (1994) and Ott and Zober

(1996). Out of the 247, 69 (1 woman) were identified by a company physician early after the accident as the most directly involved (cohort C1); 84 (2 women) were identified by August 1983 as probably involved (cohort C2); and 94 (1 woman) were recognized by the end of 1987 as possibly exposed during participation in demolition and toxicology investigations, or because they were members of the safety department and plant management at the time of the accident (cohort C3). Their mortality was investigated through 1987, with no loss to follow-up (Zober *et al.*, 1990). Death certificates were obtained for 67 deceased subjects, and 11 additional deaths were ascertained through other means (information from physicians, autopsy reports). Expected deaths were calculated from national rates. All members of cohort C1 were affected by chloracne and their mortality from malignancies was moderately higher than expectation (9 deaths; SMR, 1.3; 95% CI, 0.7–2.3). Other nonsignificant increases were seen for stomach cancer (3 deaths; SMR, 3.0; 95% CI, 0.8–7.7), colon and rectum (2 deaths; SMR, 2.5; 95% CI, 0.4–7.8) and lung cancer (4 deaths; SMR, 2.0; 95% CI, 0.7–4.6). In cohort C2, 17 workers were affected by chloracne and four had other exposure-related skin lesions. Their mortality from all cancers combined after 20 years since first exposure was significantly increased (8 deaths; SMR, 2.4; 95% CI, 1.2–4.3), as was mortality from other and unspecified cancer sites (5 deaths; SMR, 3.2; 95% CI, 1.3–6.8) (whole cohort). A nonsignificant increase was noted for colorectal cancer (2 deaths; SMR, 2.7; 95% CI, 0.5–8.5) (whole cohort). Suicides were elevated in both cohorts C1 and C2. In cohort C3, where 28 persons had experienced mild forms of chloracne, no significant increase for deaths from any cause was seen, although one single leukaemia death represented a greater than five-fold elevated risk. Among all 127 workers affected by chloracne or other skin lesions (erythema), the mortality from all cancers combined was significantly elevated after 20 years since exposure (14 deaths; SMR, 2.0; 95% CI, 1.2–3.2). Nonsignificant increases were seen for cancer of the stomach (3 deaths; SMR, 1.8; 95% CI; 0.5–4.7), colon and rectum (3 deaths; SMR, 2.2; 95% CI, 0.6–5.8) and lung (6 deaths; SMR, 1.8; 95% CI, 0.8–3.6). In 1986, blood concentrations of 2,3,7,8-TCDD were measured in 28 workers. The median values were 24.5 ng/kg in cohort C1 (10 subjects), 9.5 ng/kg in C2 (7 subjects) and 8.4 ng/kg in C3 (11 subjects). The median value for workers with chloracne and other skin lesion was 15 ng/kg versus 5.8 ng/kg in those without skin manifestations. The small size of the study population precludes definitive conclusions.

The cancer incidence and the updated mortality, through 1992, have been reported (Ott & Zober, 1996). The study population comprised the 243 exposed men. One death from a motor vehicle accident had occurred among the four exposed women, and they were not further considered in the analysis. Incident cases were ascertained from available medical and necropsy data and from survey results (the area was not covered by a cancer registry). Death certificates were obtained for all but one of the deceased workers. Expected numbers of incident cases were calculated from the cancer statistics of the state of Saarland and expected deaths were calculated on the basis of national rates. At that time, serum measurements of 2,3,7,8-TCDD were available for 138 cohort members (Ott *et al.*, 1993) (see Section 1.3.1(*a*)(i)). Model-based estimates of the cumulative dose of 2,3,7,8-TCDD (μg/kg bw) were calculated for each study subject.

Chloracne status was also adopted as an indicator of past exposure to 2,3,7,8-TCDD; 113 workers had a diagnosis of chloracne, and 55 were classified as severe. Standardized mortality and incidence ratios and their 95% CIs were estimated using standard techniques. Internal dose–response analyses were performed with the Cox's proportional hazard model, taking into account — among other variables — cigarette smoking and other potentially confounding exposures. Results of the models were reported in terms of conditional risk ratios (CRRs). The conditional risk represents the risk per unit increase (1 μg/kg bw) in 2,3,7,8-TCDD dose. In the mortality analysis, an increased cancer mortality with increasing dose was apparent: 2,3,7,8-TCDD level < 0.1 μg/kg bw, eight deaths (SMR, 0.8; 95% CI, 0.4–1.6); 0.1–0.99 μg/kg bw, eight deaths (SMR, 1.2; 95% CI, 0.5–2.3); 1.0–1.99 μg/kg bw, eight deaths (SMR, 1.4; 95% CI, 0.6–2.7); ≥ 2 μg/kg bw, seven deaths (SMR, 2.0; 95% CI, 0.8–4.0) [*p* for trend = 0.07]. Digestive system and respiratory tract cancers also tended to increase with increasing dose. In the 2,3,7,8-TCDD category > 1 μg/kg bw, after 20 or more years since initial exposure, all-cancer mortality (13 deaths; SMR, 2.0; 95% CI, 1.1–3.4) and respiratory cancer mortality (6 deaths; SMR, 3.1; 95% CI, 1.1–6.7) were significantly increased. In the sub-cohort with chloracne, 20 or more years after first exposure, 18 cancer deaths were observed (SMR, 1.9; 95% CI, 1.1–3.0). An increase was also seen for digestive tract cancer (6 deaths; SMR, 1.8; 95% CI, 0.7–4.0) and respiratory tract cancer (7 deaths; SMR, 2.4; 95% CI, 1.0–5.0). In the incidence analysis, a slight, nonsignificant increase in the risk for all cancers combined with increasing 2,3,7,8-TCDD dose was obtained. Respiratory tract cancer incidence was elevated in the high-dose group (8 cases; SMR, 2.0; 95% CI, 0.9–3.9). With the Cox's regression model, after controlling for other relevant variables, a significant association between 2,3,7,8-TCDD dose and increase in digestive system cancer was obtained, as both cause of death (CRR, 1.5; 95% CI, 1.1-1.9) and incident cases (CRR, 1.4; 95% CI, 1.1–1.7). Joint analysis of 2,3,7,8-TCDD dose and cigarette smoking showed a positive relationship between 2,3,7,8-TCDD dose and all cancers combined among current cigarette smokers (2,3,7,8-TCDD dose, SMR (95% CI) in current smokers: < 0.1, 1.2 (0.3–3.1); 0.1–0.99, 1.4 (0.3–4.2); 1.0–1.99, 3.0 (1.1–6.5); ≥ 2 μg/kg bw, 4.0 (1.5–8.6)) but not among nonsmokers.

(*d*) *Other German plants*

Several reports have considered workers from a chemical plant operated by Boehringer-Ingelheim, in Hamburg, Germany, that produced herbicides heavily contaminated with 2,3,7,8-TCDD and other PCDDs/PCDFs (Manz *et al.*, 1991; Nagel *et al.*, 1994; Flesch-Janys *et al.*, 1995; Becher *et al.*, 1996). In the latter study, workers from three other German plants were also considered.

Manz *et al.* (1991) reported the mortality experience of workers at the Hamburg plant since late 1951. An outbreak of chloracne in 1954 led to a halt in the production of TCP and 2,4,5-T. In 1957, production was resumed using a new process that reduced 2,3,7,8-TCDD formation. The vital status of all permanent employees at the plant for at least three months between 1 January 1952 and 31 December 1984 (1184 men, 399 women) was investigated through 1989. Causes of death were derived from medical records or, when not available, from death certificates. 2,3,7,8-TCDD concentrations were measured

in workers from various production departments, mainly after the plant had closed in 1984. Workers were classified in exposure groups according to their work history: high (496 subjects), medium (901) and low (186). Mean concentrations of 2,3,7,8-TCDD in adipose tissue in 1985 from 48 volunteer surviving members of the cohort were 296 ng/kg (SD, 479; median, 137) in 37 workers in the high-exposure group and 83 ng/kg (SD, 73; median, 60) in 11 workers in the combined medium-/low-exposure groups. For comparison, national death rates and rates from a cohort of some 3500 workers at the Hamburg gas supply company were used. In the latter case, the follow-up period was restricted to 1985. SMRs and 95% CIs were estimated using standard techniques assuming a Poisson distribution. Follow-up was 97% successful. In men, mortality due to all cancers combined was increased in comparison with both the general population (93 deaths; SMR, 1.2; 95% CI, 1.0–1.5) and the gas workers (75 deaths; SMR, 1.4; 95% CI, 1.1–1.8). The increase was highest among those who entered the plant before 1954 (who had the highest exposure to 2,3,7,8-TCDD based on the history of the plant and subsequent serum measurement) and remained employed for 20 or more years. In men, in comparison with gas workers, deaths from all cancers combined were: high exposure, 29 deaths (SMR, 1.8; 95% CI, 1.2–2.6); medium exposure, 39 deaths (SMR, 1.2; 95% CI, 0.9–1.6); and low exposure, seven deaths (SMR, 1.5; 95% CI, 0.6–3.0) [p for trend = 0.24]. Among specific sites, significant increases were seen for lung cancer (26 deaths; SMR, 1.7; 95% CI, 1.1–2.4) and malignancies of the haematopoietic system (9 deaths; SMR, 2.7; 95% CI, 1.2–5.0). Smoking prevalence was similar in chemical (73%) and gas (76%) workers. Suicides were also significantly increased in comparison with both reference populations. Among women, mortality from all cancers combined was close to expectation; an increase was seen for breast cancer (9 deaths; SMR, 2.2; 95% CI, 1.0–4.1).

Mortality of the female workers in the cohort was further investigated by Nagel *et al.* (1994). Compared with the results of Manz *et al.* (1991), one additional breast cancer death was identified (10 cases; SMR, 2.4; 95% CI, 1.1–4.4). Cox's regression analysis yielded increasing breast cancer risk with duration of employment. 2,3,7,8-TCDD levels in blood or adipose tissue were measured for 26 women (22 for blood and 4 for adipose tissue), with an arithmetic mean of 109.7 ng/kg (median, 23 ng/kg; range, 7–1439 ng/kg).

The mortality experience of 1189 male workers employed for at least three months between 1952 and 1984 in the same plant in Hamburg was investigated through 1992 (Flesch-Janys *et al.*, 1995). A quantitative exposure index was constructed. Fourteen relevant production departments were identified and levels of PCDDs/PCDFs were determined in the buildings, products and wastes. A detailed work history for each worker ever employed in these departments was constructed. In a sample of 190 workers, concentrations of each PCDD/PCDF congener in adipose tissue or whole blood were determined, and their levels at the end of workers' exposure were calculated assuming a one-compartment first-order kinetic model; the contribution of working time in each production department to the end-of-exposure levels in these 190 workers was estimated. Based on this model, an estimated total end-of-exposure level was then calculated for each worker employed in these departments. The strongest association with 2,3,7,8-TCDD levels was found for duration of employment in 2,4,5-T (estimated yearly

increase, 75.6 ng/kg blood) and TCP (estimated yearly increase < 1957, 292 ng/kg) production departments. For the entire cohort, the mean estimated 2,3,7,8-TCDD level was 141.4 ng/kg (median, 38.2 ng/kg). Blood measurements of PCDDs are presented in **Table 14**. Exposure to other carcinogens (e.g., dimethyl sulfate (see IARC, 1987g) and benzene (see IARC, 1987h) had occurred in some departments. As a reference, a cohort of 2528 workers from a gas supply company was adopted. Causes of death were ascertained from hospital and medical records whenever possible, or from death certificates, insurance data or next-of-kin interview. The validity of cause of death determination was successfully tested. Relative risks at seven exposure levels (reference, the first four quintiles and the ninth and tenth deciles of the estimated 2,3,7,8-TCDD levels) were estimated using Cox's regression techniques. An internal comparison group was also adopted composed of the chemical workers in the two lowest quintiles of the exposure levels distribution. Follow-up was 99% successful. Total mortality was elevated in all 2,3,7,8-TCDD exposure categories and showed a significant trend (p = 0.01) with increasing exposure level. Updated relative risks (RR) for total TEQ levels (not 2,3,7,8-TCDD levels) were published in an erratum (Flesch-Janys, 1996) and were as follows for all cancers combined (124 cases): 1.0–12.2 ng TEQ/kg, RR, 1.0 (95% CI, 0.6–1.8); 12.3–39.5 ng TEQ/kg, RR, 1.3 (95% CI, 0.8–2.1); 39.6–98.9 ng TEQ/kg, RR, 1.2 (95% CI, 0.7–1.9); 99.0–278.5 ng TEQ/kg, RR, 1.2 (95% CI, 0.8–1.9); 278.6–545.0 ng TEQ/kg, RR, 1.3 (95% CI, 0.7–2.3); 545.1–4362 ng TEQ/kg, RR, 2.7 (95% CI, 1.7–4.4). A significant pattern of increasing risk with increasing TEQ levels was also obtained for cardiovascular and ischaemic heart diseases, but not for other causes of death. The mortality pattern for all causes, all cancers, cardiovascular diseases and ischaemic heart diseases remained virtually unchanged when 2,3,7,8-TCDD exposure levels were used. When the internal comparison group of chemical workers was adopted, the relative risk estimates were lower and the confidence intervals wider. Nevertheless, total mortality (RR, 1.4; 95% CI, 1.0–2.1) and all-cancer mortality (RR, 2.0; 95% CI, 1.1–3.8) remained clearly elevated in the highest exposure category. When the 149 workers with exposure to one of the possible confounders (dimethyl sulfate) were excluded from analysis, the all-cancer mortality remained elevated, especially in the highest exposure category (RR, 2.3; 95% CI, 1.1–4.6) and the dose–response pattern was significant ($p < 0.01$). Smoking habits and socioeconomic status were similar in the chemical and gas worker cohorts. No data on specific cancer sites were reported.

Becher *et al.* (1996) reported the mortality of 2479 male workers employed in four German plants who were involved in the production of phenoxy herbicides and chlorophenols or who were likely to have been in contact with these substances and their contaminants, PCDDs (often including 2,3,7,8-TCDD) and PCDFs. Only workers with German nationality and at least one month of employment were included. The follow-up was performed through 1989 (1992 in one plant). Cause of death was recorded from death certificates or, in some cases, hospital or physician reports. Expected figures were calculated from national rates. Blood concentrations of 2,3,7,8-TCDD were measured in workers from three of the four plants (Kogevinas *et al.*, 1997). Workers in the Hamburg plant (plant I), including a group of females not considered here, had already been under investigation (see above; Manz *et al.*, 1991; Nagel *et al.*, 1994; Flesch-Janys *et al.*, 1995;

Flesch-Janys *et al.*, 1996b). In this plant (1144 male workers), concentrations of 2,3,7,8-TCDD in the order of 5–10 mg/kg were measured in 1957–70 in some products (chlorophenols and 2,4,5-T and its esters) and of 10–50 mg/kg in some process and waste streams. After the early 1970s, the concentrations were below 1 mg/kg. Numerous cases of chloracne occurred in 1954, at the early stage of development of herbicide manufacture. Measurements of blood concentrations from 190 workers in 1985–94 ranged between 3 and 2252 ng/kg (mean, 141 ng/kg). In plant II (135 workers), TCP was manufactured with 2,3,7,8-TCDD levels on average about 10 µg/kg. Eleven cases of chloracne were reported among maintenance workers in the early 1970s and measurements in 1989–92 from 20 workers ranged between 23 and 1935 ng/kg fat (mean, 401.7 ng.kg). In plant III (520 workers), a variety of phenoxy herbicides were produced. 2,3,7,8-TCDD levels in the products were reported to be in the 'sub-ppm range'. In plant IV (680 workers) (BASF, but the cohort is different from that of the accident study), phenoxy herbicides were synthesized in a large building where many other chemicals were also produced. Measurements in 1996 from 19 workers ranged between 1.3 and 6.49 ng/kg fat (mean, 3.2 ng/kg). In this plant, slightly elevated concentrations of higher chlorinated PCDDs were found in synthesis workers. No cases of chloracne were reported in plants III or IV. In the total cohort, mortality increases were seen for all cancers combined (138 deaths; SMR, 1.2; 95% CI, 1.0–1.4), cancer of the buccal cavity and pharynx (9 deaths; SMR, 3.0; 95% CI, 1.4–5.6), lung cancer (47 deaths; SMR, 1.4; 95% CI, 1.1–1.9), lymphatic and haematopoietic neoplasms (13 deaths; SMR, 1.7; 95% CI, 0.9–2.9) and non-Hodgkin lymphoma (6 deaths; SMR, 3.3; 95% CI, 1.2–7.1). Examination of trends with increasing time since first exposure showed: for all cancers combined (0–10 years: 15 deaths; SMR, 0.9; 95% CI, 0.5–1.5; 10–< 20 years: 46 deaths; SMR, 1.3; 95% CI, 0.9–1.7; ≥ 20 years: 77 deaths; SMR, 1.2; 95% CI, 1.0–1.5 [*p* for trend = 0.67]), for lymphatic and haematopoietic neoplasms (0–10 years: 2 deaths; SMR, 1.1; 95% CI, 0.1–4.0; 10–< 20 years: 4 deaths; SMR, 1.7; 95% CI, 0.5–4.4; ≥ 20 years: 7 deaths; SMR, 1.9; 95% CI, 0.8–4.0 [*p* for trend = 0.51]) and for non-Hodgkin lymphoma (0–10 years: 0 deaths; 10–< 20 years: 2 deaths; SMR, 3.6; 95% CI, 0.4–13.1; ≥ 20 years: 4 deaths; SMR, 4.3; 95% CI, 1.2–10.9; [*p* for trend = 0.24]). All-cause (345 deaths; SMR, 1.2; 95% CI, 1.0–1.3) and all-cancer mortality (97 deaths; SMR, 1.3; 95% CI, 1.1–1.6) was elevated only for plant I, where statistically significant increases were also seen for lung cancer (31 deaths; SMR, 1.5; 95% CI, 1.0–2.1), lymphatic and haematopoietic neoplasms (11 deaths; SMR, 2.4; 95% CI, 1.2–4.3), non-Hodgkin lymphoma (4 deaths; SMR, 3.8; 95% CI, 1.0–9.6) and multiple myeloma (3 deaths; SMR, 5.4; 95% CI, 1.1–15.9). Mortality from accidents and suicide was also increased. An increase in the incidence of non-Hodgkin lymphoma for plant II (2 deaths; SMR, 12.0; 95% CI, 1.5–43.5), and in that of cancer of the buccal cavity and pharynx for plant IV (6 deaths; SMR, 8.2; 95% CI, 3.0–17.9) were seen.

(*e*) *British plants*

Four cohorts of workers employed between 1963 and 1985 in British factories producing or formulating — among other chemicals — phenoxy herbicides, including 2,4,5-T (Kauppinen *et al.*, 1993) and chlorophenols (some of which may have been

contaminated by PCDDs) were investigated (Coggon *et al.*, 1991). In one of the plants (factory A), 2,4,5-T was synthesized between 1968 and 1978. In the other plants, 2,4,5-T was formulated only. The study was restricted to men. A total of 2239 subjects (employed during 1963–85) met the inclusion criteria. Job histories were used to classify workers according to potential exposure to phenoxy herbicides and chlorophenols. Approximately 50% of employees had directly worked with phenoxy herbicides. No environmental or personal monitoring had been carried out. Subjects were traced up to December 1987. Information was obtained on cause of death for deceased persons and on any cancers registered among living study subjects. Expected figures were obtained from rates for England and Wales, and in some analyses adjustment for local differences in mortality was applied. In the combined cohort, all-cause mortality was slightly higher than expected (152 deaths; SMR, 1.1; 95% CI, 0.9–1.3), and this was largely due to excesses of circulatory diseases and deaths from violent causes. Mortality from all-cancers combined was as expected (37 deaths; SMR, 1.0; 95% CI, 0.7–1.4). Statistically nonsignificant excesses were present for lung cancer (19 deaths; SMR, 1.3; 95% CI, 0.8–2.1) and non-Hodgkin lymphoma (2 deaths; SMR, 2.3; 95% CI, 0.3–8.3), even after local adjustment. When analysis was restricted to subjects with greater than background exposure to phenoxy compounds or chlorophenols, the SMR for lung cancer was 1.2 (14 observed deaths; [95% CI, 0.7–2.1]). Both non-Hodgkin lymphoma deaths occurred among these workers (SMR, 2.8; [95% CI, 0.3–10.2]). In factory A, 12 cancer deaths were observed (12.3 expected) and six were from lung cancer (SMR, 1.3 [95% CI, 0.5–2.8]).

(*f*) *Dutch plants*

The mortality of two cohorts of workers employed between 1955 and 1986 in the synthesis and formulation of phenoxy herbicides and chlorophenols in the Netherlands was examined (Bueno de Mesquita *et al.*, 1993). In one of the plants (A), where the main production was 2,4,5-T and derivatives, an accident in 1963 caused a release of PCDDs, including 2,3,7,8-TCDD. In factory B, production included MCPA, 4-chloro-2-methyl-phenoxypropionic acid (MCPP) and 2,4-D. The study enrolled 2074 manufacturing male workers from the two plants (963 exposed to phenoxy herbicides and 1111 not exposed). In addition, 145 workers probably exposed to 2,3,7,8-TCDD during the industrial accident and the clean-up operations were examined. Definition of individual exposure to phenoxy herbicides, chlorophenols or contaminants (PCDDs/PCDFs) was based on occupational history derived from job records and personal interviews, including periods of employment in different departments and positions held. Follow-up was 97% complete. The 190 female workers were excluded from the analysis. Of the accident workers, only 139 had sufficient data for analysis. Expected numbers of deaths were calculated from national rates. In addition, mortality rates of exposed and non-exposed workers were internally compared by Poisson regression analysis. Among subjects in factory A only, in comparison with the general population, all-cancer mortality was increased (26 deaths; SMR, 1.2; 95% CI, 0.8–1.7). Statistically nonsignificant increases were also seen for cancers of the pancreas (3 deaths; SMR, 2.9; 95% CI, 0.6–8.4), large intestine (3 deaths; SMR, 2.4; 95% CI, 0.5–7.0) and prostate (2 deaths; SMR, 2.2; 95%

CI, 0.3–7.8), lymphosarcoma (non-Hodgkin lymphoma) (1 death; SMR, 2.0; 95% CI, 0.1–11.4) and myeloid leukaemia (1 death; SMR, 2.9; 95% CI, 0.1–15.9). No death due to soft-tissue sarcoma was reported. In comparison with the non-exposed workers, exposed subjects in both plants exhibited increased mortality from all cancers combined (31 exposed deaths; rate ratio (RR), 1.7; 95% CI, 0.9–3.4) and respiratory tract cancer (9 deaths; RR, 1.7; 95% CI, 0.5–6.3). Six cancers of the urogenital organs were observed among the exposed and none among the non-exposed. A nonsignificant increase in deaths from lymphatic and haematopoietic neoplasms was also noted (4 deaths; RR, 2.6; 95% CI, 0.3–125). Increases in all cancers combined (RR, 2.0; 95% CI, 0.8–4.9) and lung cancer (RR, 3.9; 95% CI, 0.5–31.1) were confined to factory A, where the accident occurred and where the opportunity for exposure to 2,3,7,8-TCDD was highest. In the small group of accident-exposed workers, 10 cancer deaths were observed (SMR, 1.4; 95% CI, 0.7–2.5).

The study was later extended in time (1955–91) and enlarged in size (2298 subjects including 191 females) (Hooiveld *et al.*, 1996a; Kogevinas *et al.*, 1997). More accurate and elaborate proxies of exposure were used in the analysis, based on modelled 2,3,7,8-TCDD levels in serum, measured in 1993 in a subset of 31 surviving exposed (mean concentration, 53 ng/kg; range, 1.9–194) and 16 unexposed (mean concentration, 8 ng/kg) cohort members. Fourteen subjects exposed during the accident in factory A in 1963 had the highest levels (mean concentration, 96 ng/kg; range, 15.8–194). In this factory, both all-cause (139 observed; SMR, 1.3; 95% CI, 1.1–1.5) and all-cancer mortality (51 observed; SMR, 1.5; 95% CI, 1.1–1.9) were significantly increased. Excesses at specific sites were seen for urinary bladder (4 observed; SMR, 3.7; 95% CI, 1.0–9.5), kidney cancer (4 observed; SMR, 4.1; 95% CI, 1.1–10.4) and non-Hodgkin lymphoma (3 observed; SMR, 3.8; 95% CI, 0.8–11.0). Non-Hodgkin lymphoma was also increased in factory B (1 case only). Age- and time-adjusted relative risks comparing exposed and unexposed workers in factory A showed significant increases in mortality from all causes (139 observed; RR, 1.8; 95% CI, 1.2–2.5) and all cancers (51 observed; RR, 3.9; 95% CI, 1.8–8.8). Lung and urinary tract cancers showed numerically higher, but statistically nonsignificant increases. Three non-Hodgkin lymphomas were seen among the exposed and one among the unexposed (a nonsignificant increase). When workers were subdivided into three categories (low, medium and high exposure) according to model-predicted serum levels of 2,3,7,8-TCDD, relative risks for all causes, all cancers and lung cancer were significantly elevated in both middle and high categories, and were highest in the highest exposure group.

(*g*) *IARC multi-country study*

An international cohort of workers exposed to phenoxy herbicides and chlorophenols was set up by the International Agency for Research on Cancer in association with the United States National Institute of Environmental Health Sciences (Saracci *et al.*, 1991). The cohort included 16 863 men and 1527 women employed in production or spraying, distributed among 20 cohorts from 10 countries, including the British and Dutch cohorts described above. Their mortality from 1955 onwards was examined, and follow-up was successful for 95% of the cohort members. National mortality rates were used for

reference. Exposure assessment was based on work histories collected in each factory through questionnaires with the assistance of industrial hygienists, workers and factory personnel. A total of 13 482 workers were classified as 'exposed' to phenoxy herbicides, 416 were classified as 'possibly exposed', 541 had 'unknown' exposure and 3951 were classified as 'non-exposed'. In the entire cohort, all-cause mortality was lower than expected (SMR, 0.95; 95% CI, 0.9–1.0). Among men exposed to phenoxy herbicides or chlorophenols, mortality from all cancers combined was close to expectation (499 observed; SMR, 1.0; 95% CI, 0.9–1.1). Significant increases were seen for thyroid cancer (4 observed; SMR, 3.7; 95% CI, 1.0–9.4) and benign and unspecified neoplasms (12 observed; SMR, 2.0; 95% CI, 1.0–3.5); significant deficits were observed for skin (3 observed; SMR, 0.3; 95% CI, 0.1–0.9) and brain cancer (6 observed; SMR, 0.4; 95% CI, 0.1–0.8). Elevated risks were also seen for cancers of the nose and nasal cavities (3 observed; SMR, 2.9; 95% CI, 0.6–8.5), testis (7 observed; SMR, 2.3; 95% CI, 0.9–4.6) and other endocrine glands (3 observed; SMR, 4.6; 95% CI, 1.0–13.5) and for soft-tissue sarcomas (4 observed; SMR, 2.0; 95% CI, 0.6–5.2). In the probably exposed category, lung cancer mortality was significantly increased (11 observed; SMR, 2.2; 95% CI, 1.1–4.0). Significant increases were also seen among non-exposed workers, for unspecified digestive organs and for benign and unspecified neoplasms. The increase in soft-tissue sarcoma concerned workers after 10–19 years since first exposure (4 observed; SMR, 6.1; 95% CI, 1.7–15.5); no differentiation in risk was noted in relation to duration of exposure or probable 2,3,7,8-TCDD exposure. The SMR estimates for testicular and thyroid cancer were highest among workers probably exposed to 2,3,7,8-TCDD (SMR, 3.0 and 4.3, respectively) compared with those probably not exposed (SMR, 1.6 and 3.1, respectively).

Two nested case–control studies of soft-tissue sarcoma (11 incident cases, 55 controls) and non-Hodgkin lymphoma (32 incident cases, 158 controls) were conducted by Kogevinas *et al.* (1995) within the IARC cohort studied by Saracci *et al.* (1991). Exposures to 21 chemicals or mixtures were estimated by a panel of three industrial hygienists. Levels of exposure were evaluated using a relative scale, since few actual measurements of past exposure were available. A cumulative exposure score was calculated for each subject and chemical, on the basis of estimated level of exposure and duration of exposure (in years). The model that was used as the conceptual framework in deriving levels of exposure included variables related to department/job, emission of chemicals, contact with chemicals, personal protection, and other relevant determinants of exposure. Excess risk for soft-tissue sarcoma was associated with exposure to any phenoxy herbicide (odds ratio, 10.3; 95% CI, 1.2–91.0) and to each of the three major classes of phenoxy herbicides (2,4-D, 2,4,5-T and MCPA). Soft-tissue sarcoma was also associated with exposure to any PCDD/PCDF (odds ratio, 5.6; 95% CI, 1.1–28.0) and with exposure to 2,3,7,8-TCDD (odds ratio, 5.2; 95% CI, 0.9–32.0). Associations between non-Hodgkin lymphoma and phenoxy herbicides were generally weaker. The odds ratio between non-Hodgkin lymphoma and 2,3,7,8-TCDD exposure was 1.9 (95% CI, 0.7–5.1). A monotonic increase in risk was observed for cumulative exposure (categorized in four categories, non-exposed, low, medium, high exposure) to 2,4-D (odds ratio for highest category, 13.7; 95% CI, 0.9–309; p-value for trend = 0.01), 2,4,5-T

(odds ratio for highest category, 7.7; 95% CI, 0.5–477; *p*-value for trend = 0.07), any PCDD/PCDF (odds ratio for highest category, 19.0; 95% CI, 1.3–1236; *p*-value for trend = 0.008) and 2,3,7,8-TCDD (odds ratio for highest category, 10.6; 95% CI, 0.6–671; *p*-value for trend = 0.04). [The Working Group noted that analysis for specific exposures was complicated by the exposure of most workers to a multitude of herbicides.]

While Saracci *et al.* (1991) studied the men in the IARC cohort, 701 women were studied by Kogevinas *et al.* (1993) for both cancer incidence and mortality. Among 169 women probably exposed to 2,3,7,8-TCDD, excess incidence was observed for all cancers combined (9 cases; standardized incidence ratio (SIR), 2.2; 95% CI, 1.0–4.2). There was one case of breast cancer (SIR, 0.9; 95% CI, 0.0–4.8). For 532 women probably not exposed to 2,3,7,8-TCDD, the rate ratio for incidence of all cancers combined was 0.8 (20 cases; 95% CI, 0.5–1.2). Cause-specific analyses were based on small numbers. Mortality results paralleled those for incidence.

The international cohort studied by Saracci *et al.* (1991) was updated and expanded with the data of Fingerhut *et al.* (1991a,b) and Becher *et al.* (1996) (Kogevinas *et al.*, 1997). Follow-up differed by plant, but most European plants were followed through 1991–92, while the United States plants were followed through 1987. Each of the 21 863 male and female workers exposed to phenoxy herbicides or chlorophenols was placed in one of three categories: (1) those exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs (n = 13 831); (2) those not exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs (n = 7553); and (3) those of unknown exposure to 2,3,7,8-TCDD or higher chlorinated PCDDs (n = 479). The latter category included all workers in one British cohort for which production history, particularly for 2,4,5-T, was incomplete. Three criteria were used to classify workers as exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs: (i) employment during the period of production, formulation or spraying of 2,4,5-T, 2,4,5-trichlorophenoxypropionic acid, TCP, hexachlorophene, Erbon, Ronnel, PCP or 2,3,4,6-tetrachlorophenol; and (ii) employment in plants with documented (through serum, adipose tissue or environmental measurements) exposure to 2,3,7,8-TCDD or higher chlorinated PCDDs at levels above background; or (iii) in the absence of PCDD measurements, employment in plants or companies with documented large-scale production, formulation or spraying of the above-mentioned phenoxy herbicides and chlorophenols. An average production of these chemicals of 10 tonnes per year was chosen *a priori*, below which it was considered that the probability of contamination and significant exposure to 2,3,7,8-TCDD and higher chlorinated PCDDs would be minimal for most workers in a cohort. Current mean levels of 2,3,7,8-TCDD, measured in 574 workers from 10 companies in 7 countries, ranged from 3 to 389 ng/kg lipid. Among workers exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs, mortality was elevated for soft-tissue sarcoma (6 deaths; SMR, 2.0; 95% CI, 0.8–4.4). Mortality from all cancers combined (710 deaths; SMR, 1.1; 95% CI, 1.0–1.2), non-Hodgkin lymphoma (24 deaths; SMR, 1.3; 0.9–2.1) and lung cancer (225 deaths; SMR, 1.1; 95% CI, 1.0–1.3) was slightly elevated. Risks for all cancers combined and for soft-tissue sarcomas and lymphomas increased with time since first exposure. Workers not exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs had SMRs of 1.0 for all cancers, for non-Hodgkin lymphoma and for lung cancer; soft-tissue sarcoma was slightly elevated, based on two

deaths (SMR, 1.4; 95% CI, 0.2–4.9). In a direct comparison between those exposed to higher chlorinated PCDDs versus lower ones or none, a rate ratio of 1.3 (95% CI, 1.0–1.8) for all cancers combined was found. This study represents the largest overall cohort of 2,3,7,8-TCDD-exposed workers.

2.1.2 *Population exposure due to industrial accident*

The mortality and cancer incidence among the population of Seveso exposed in the industrial accident described in Section 1.3.1 were investigated. The contaminated area was subdivided into three exposure zones (zone A, zone B and zone R), according to the average levels of 2,3,7,8-TCDD measured in soil samples. The most contaminated, Zone A, extended for 87 hectares and average soil levels between 15.5 $\mu g/m^2$ and 580 $\mu g/m^2$ were found. In Zone B (270 hectares), soil levels did not exceed, on average, 50 $\mu g/m^2$. In Zone R (1430 hectares), soil levels were generally below 5 $\mu g/m^2$. All persons residing in these zones at the time of the accident, as well as all newborn infants and new residents in the subsequent 10-year period, were considered to have been exposed. Measurements of blood levels of 2,3,7,8-TCDD in members of the exposed population are described in Section 1.3.1. Three exposure categories were formed, corresponding to the zone of residence of the subjects at the time of the accident or later entry into the area. As a reference, the population of 11 municipalities surrounding the contaminated area was adopted. Ethnic, social, cultural and occupational characteristics were closely comparable. The exposed and referent populations were followed up as if they were a unique cohort, blindly to the exposure status of the subjects. The follow-up after 15 years was > 99% successful (Bertazzi *et al.*, 1993). Causes of death were derived from death certificates. In the period 1976–91, there were 750 subjects in Zone A and 16 cancer deaths, 5000 subjects in Zone B and 152 cancer deaths, and 30 000 subjects in Zone R and 1008 cancer deaths. The reference population comprised over 200 000 subjects (Bertazzi *et al.*, 1996).

The cause-, age-, gender- and calendar time-specific mortality rates in the exposed and reference populations were compared using Poisson regression methods (Bertazzi *et al.*, 1996). All-cause and all-cancer mortality did not differ significantly from those expected in any of the contaminated zones. Mortality from gastrointestinal cancer was increased. Women had a relative risk for all digestive system cancers combined of 1.5 (5 deaths; 95% CI, 0.6–3.6) in Zone A and liver cancer (3 deaths; RR, 1.3; 95% CI, 0.4–4.0) in Zone B. Among men, increases were seen for rectal cancer (7 deaths; RR, 2.9; 95% CI, 1.4–6.2) in Zone B and for cancer of the oesophagus (30 deaths; RR, 1.6; 95% CI, 1.1–2.4) in Zone R. Neoplasms of the lymphatic and haematopoietic tissues were clearly elevated in Zone B. The highest risks were seen for leukaemia in men (7 deaths; RR, 3.1; 95% CI, 1.4–6.7), multiple myeloma in women (4 deaths; RR, 6.6; 95% CI, 2.3–18.5) and Hodgkin's disease in both men and women (men: 2 deaths; RR, 3.3; 95% CI, 0.8–14.0; women: 2 deaths; RR, 6.5; 95% CI, 1.5–30.0). Two cases of thyroid cancer in Zone B, one each in men and women, represented a notable, although nonsignificant increase [RR, 3.9; 95% CI, 0.4–14.1]. Four cases of soft-tissue sarcoma were seen in

Zone R among men (RR, 2.1; 95% CI, 0.7–6.5). Breast cancer was below expectation in all zones.

Cancer incidence data are available for the period 1977–86 (Bertazzi *et al.*, 1993) for the population aged 20–74 years and residing in the area at the date of the accident. Cancer diagnoses were obtained from the regional registration system of hospital admissions and discharges. Of the 41 801 relevant medical records, 41 778 were successfully reviewed. The proportion of non-detected cases ranged from 2.6% to 6.8% across hospitals, and the overall histological confirmation rate was 72%. Quality and completeness of cancer case ascertainment did not vary appreciably across zones or with the referent population. In Zone A, no significant differences from expectation were seen (14 cancer cases in total). In Zone B, hepatobiliary cancer was increased among both women (5 cases; RR, 3.3; 95% CI, 1.3–8.1) and men (5 cases; RR, 1.8; 95% CI, 0.7–4.4). Haematopoietic system neoplasms were significantly increased. Among women, increases were seen for multiple myeloma (2 cases; RR, 5.3; 95% CI, 1.2–22.6) and myeloid leukaemia (2 cases; RR, 3.7; 95% CI, 0.9–15.7) and, among men, increases were seen for lymphoreticulosarcoma (3 cases; RR, 5.7; 95% CI, 1.7–19.0) and multiple myeloma (2 cases; RR, 3.2; 95% CI, 0.8–13.3). In Zone R, soft-tissue sarcoma incidence was increased in both women (2 cases; RR, 1.6; 95% CI, 0.3–7.4) and men (6 cases; RR, 2.8; 95% CI, 1.0–7.3). Breast and endometrial cancers were below expectation. The cancer incidence among subjects aged 0–19 years was analysed separately (Pesatori *et al.*, 1993). Given the small number of events, the three contaminated zones and both genders were grouped together. Seventeen cancer cases were observed (RR, 1.2; 95% CI, 0.7–2.1). Two ovarian cancer cases were observed versus none expected. Two thyroid gland cancers among girls gave a relative risk of 4.6 (95% CI, 0.6–32.7). Lymphatic and haematopoietic neoplasms were increased (9 cases; RR, 1.6; 95% CI, 0.7–3.4), particularly Hodgkin's lymphoma (3 cases; RR, 2.0; 95% CI, 0.5–7.6) and myeloid leukaemia (3 cases; RR, 2.7; 95% CI, 0.7–11.4). [The Working Group noted that the size of the most exposed population is small and that the latency of 15 years may be short for certain health effects to manifest themselves. Measurements of blood levels of 2,3,7,8-TCDD (see Section 1.3.1) are available for only small samples of the exposed populations.]

2.1.3 *Industrial exposure to higher chlorinated PCDDs*

Two United States studies have focused on cohorts exposed to PCP or chlorophenates (penta and tetra); these chemicals contain predominantly higher chlorinated PCDDs (Cl_6–Cl_8) but not 2,3,7,8-TCDD (United States Environmental Protection Agency, 1994). Many workers in one of these studies also had exposure to 2,3,7,8-TCDD.

In another study of pentachlorophenate-exposed industrial workers, Hertzman *et al.* (1997) studied 23 829 workers from 11 Canadian sawmills in British Columbia which used chlorophenates from the 1940s to the 1970s. Another 2658 unexposed workers from three sawmills not using chlorophenates were also studied. Cohort members had to have worked for at least one year between 1 January 1950 and 31 December 1985. Follow-up was through 1990. Jobs were rated according to level of chlorophenate exposure and a

quantitative exposure score was developed. Most exposure was dermal, although some inhalation exposure could occur. In the 1960s and 1970s, sawmills switched from using predominantly pentachlorophenates, which would be expected to have contained higher chlorinated PCDDs and PCP, to tetrachlorophenates (less contaminated with higher chlorinated PCDDs). Exposure to chlorophenates was widespread in the industry. Wood was dipped in chlorophenates and then planed; exposures occurred during both processes. Urine samples taken in the 1980s showed significant levels of chlorophenates (median, 180 μg/L) (Hertzman *et al.*, 1988). Mortality and cancer incidence rates were compared with the population of British Columbia; cases were identified from either cancer registry data or death certificates. There were 583 190 person–years in chlorophenate mills and 41 280 in non-chlorophenate mills, with 70 119 potential person–years lost to follow-up (11.2%); analyses were conducted either assuming that lost-to-follow-up workers were alive until the end of 1990 (method 1) or assuming that person–time ended when a worker was lost to follow-up (method 2). There were 4710 deaths in the cohort (1950–89) (4539 in exposed mill workers and 171 in non-exposed mill workers) and 1547 incident cancer cases (1969–89) (1498 in exposed mill workers and 49 in non-exposed mill workers). The SMR for all causes of death among workers at chlorophenate mills was 0.81 (95% CI, 0.79–0.83) by method 1 of treating loss to follow-up and 0.96 (95% CI, 0.94–0.99) by method 2; the SMR for non-chlorophenate mills was 0.89 (95% CI, 0.78–1.01) with method 2. In the chlorophenate mill workers, there were six deaths from soft-tissue sarcoma (SMR using method 1 for loss to follow-up, 1.2; 95% CI, 0.5–2.3; SMR using method 2, 1.4; 95% CI, 0.6–2.8). There were 11 incident cases of soft-tissue sarcoma (SIR using method 1, 1.0; 95% CI, 0.6–1.7; and using method 2, 1.2; 95% CI, 0.7–1.9). There were 36 deaths from non-Hodgkin lymphoma (SMR using method 1, 0.9; 95% CI, 0.7–1.2 or SMR using method 2, 1.1; 95% CI, 0.8–1.4) and 23 deaths from lymphosarcoma (SMR using method 1, 1.3; 95% CI, 0.9–1.8 or SMR using method 2, 1.5; 95% CI, 1.0–2.1). There were 63 incident cases of non-Hodgkin lymphoma during the study period (SMR using method 1, 1.0; 95% CI, 0.8–1.2 or SMR using method 2, 1.2; 95% CI, 1.0–1.5). While no trend was observed for mortality from non-Hodgkin lymphoma with cumulative exposure, a significant positive trend of SIR for non-Hodgkin lymphoma was seen with increasing cumulative exposure to chlorophenate ($p = 0.02$). The SIR for the group with the highest cumulative exposure and 20 or more years' exposure was 1.5 ($p = 0.04$).

Ramlow *et al.* (1996) studied 770 workers from the occupational cohort in Midland, MI, studied by Ott *et al.* (1987) and Bond *et al.* (1989a) (see Section 2.1.1), but restricted to those cohort members with some exposure to PCP. Although the authors provide no details, most of these workers (approximately 85%) were also exposed to 2,3,7,8-TCDD based on detailed data from the United States NIOSH cohort (Fingerhut *et al.*, 1991b). Follow-up was from 1940 through 1989; both the United States population and another group of unexposed male workers from the same company were used as referent groups. Exposure scores for PCP were developed, in addition to the exposure scores for 2,3,7,8-TCDD and hexa-, hepta- or octa-CDDs used previously by Ott *et al.* (1987). The average length of follow-up was 26.1 years and there were 20 107 person–years in the study. There were 229 deaths from all causes in the whole cohort (SMR, 0.9; 95% CI, 0.8–1.1)

and 50 cancer deaths (SMR, 1.0; 95% CI, 0.7–1.3). The SMR for a category of non-Hodgkin lymphoma and myeloma combined was 2.0 (5 deaths; 95% CI, 0.7–4.7); the authors noted that two of these cancers were myeloma (versus approximately 0.8 expected), while three were non-Hodgkin lymphomas [approximately 1.7 expected]. Stomach cancer mortality was slightly elevated (4 deaths; SMR, 1.7; 95% CI, 0.5–4.3), as was kidney cancer mortality (3 deaths; SMR, 2.3; 95% CI, 0.5–6.7). No deaths from liver cancer were observed (1.1 expected) nor from thyroid cancer (0.1 expected), cancers *a priori* of interest from animal studies. Results of analyses for ≥ 15 years' potential latency were also presented, which differed little from those of the overall analysis. Analyses by cumulative exposure to PCP were conducted for 'low PCP' and 'high PCP' groups compared with unexposed workers using a variety of lag periods. A significant positive trend was noted for kidney cancer with increasing exposure when a 15-year lag was used ($p = 0.03$) and a nearly significant positive trend was noted for the combined category of non-Hodgkin lymphoma and myeloma ($p = 0.08$). Similar trends were seen for these two cancer categories when the data were stratified by level of exposure to 2,3,7,8-TCDD or hexa-, hepta or octa-CDDs.

In three cohorts included in the IARC international cohort, 842 workers were evaluated to have been exposed to higher chlorinated PCDDs but not to 2,3,7,8-TCDD. The workers had been producing PCP in a plant in England, 2,3,4,6-tetrachlorophenol in a plant in Finland and a variety of phenoxy herbicides in a plant in Germany. In the latter group of workers, serum levels of 2,3,7,8-TCDD were around background, while an elevation was seen for higher chlorinated PCDDs, especially among synthesis workers (Messerer *et al.*, 1996). Mortality from all neoplasms was around that expected from national mortality rates (41 deaths; SMR, 1.0; 95% CI, 0.7–1.4). No deaths from soft-tissue sarcoma (0.2 expected) or non-Hodgkin lymphoma (0.7 expected) were registered in these three cohorts, while mortality from lung cancer was higher (19 deaths; SMR, 1.5; 95% CI, 0.9–2.3) than in 2,3,7,8-TCDD-exposed workers (Kogevinas *et al.*, 1997).

2.2 Herbicide exposures

Introduction

Studies of herbicide exposure among farmers, pesticide applicators and other non-industrial populations were included in this review either if there was explicit evidence that exposure included 2,4,5-T (known to be contaminated with 2,3,7,8-TCDD), or if data on individual exposure to phenoxy herbicides as a class was available and it was known that 2,4,5-T was used in the area. Several studies of applicators without adequate documentation of exposure to 2,4,5-T or other phenoxy herbicides were not considered informative, such as those of Barthel (1981), Corrao *et al.* (1989) and Eriksson *et al.* (1992). In addition, studies with exposure to phenoxy herbicides limited to 2,4-D, MCPA or other compounds typically not found to be contaminated with higher chlorinated PCDDs were excluded, such as those of Wigle *et al.* (1990) and Morrison *et al.* (1993, 1994). Similarly, studies of paper and pulp mill workers were not considered, because measurements of PCDDs in biological tissues of workers have not shown that their levels were elevated (Rosenberg *et al.*, 1994, 1995; Mouradian *et al.*, 1995; see Section 1.3.1).

In these studies, direct evidence of exposure to 2,3,7,8-TCDD is often lacking. The limited data available indicate that exposure to 2,3,7,8-TCDD is likely to be substantially lower than exposure in industrial cohorts (see Section 1.3.1). For example, in the most heavily exposed applicators of 2,4,5-T in New Zealand, who applied 2,4,5-T for at least 180 months, the estimated mean serum level of 2,3,7,8-TCDD at the time of blood drawing was 53 ng/kg (Smith *et al.*, 1992a). Back extrapolation of this level to the period when 2,4,5-T was likely to be most contaminated with 2,3,7,8-TCDD gave a value of around 300 ng/kg. Among United States Air Force personnel (Ranch Hand) who applied Agent Orange from 1962 to 1971, generally for relatively short periods, the median serum 2,3,7,8-TCDD level in 1987 was 13 ng/kg, which when back-extrapolated would be about 50 ng/kg (Roegner *et al.*, 1991). These levels are about one order of magnitude lower than the back-extrapolated 2,3,7,8-TCDD levels estimated for many industrial cohorts. In data from Australia (Johnson *et al.*, 1992a), the range of serum 2,3,7,8-TCDD levels at time of blood drawing in 1990 in 33 applicators randomly selected from a group of 654 men who had applied 2,4,5-T and 2,4-D for at least 12 months was 2–34 ng/kg. Back-extrapolation to the time exposure ceased, using a half life of 7.1 years, revealed that those who sprayed after 1974 (the period when 2,3,7,8-TCDD contamination of 2,4,5-T was markedly reduced) had a significantly lower mean exposure rate (0.06 ng/kg per month) compared with workers who sprayed before 1965 (2.7 ng/kg per month) or during 1965–74 (2.3 ng/kg per month). For those workers who sprayed during 1965–74, the estimated serum TCDD concentrations at termination of employment ranged from 13 to 329 ng/kg.

In Sweden, no difference in 2,3,7,8-TCDD levels in adipose tissue was found between 13 exposed (mean 2,3,7,8-TCDD, 2 ng/kg) and 18 non-exposed subjects (mean 2,3,7,8-TCDD, 3 ng/kg) (Nygren *et al.*, 1986; see Section 1.3.1(*a*)(ii)). Exposure was defined as in the Swedish case–control studies on soft-tissue sarcoma and non-Hodgkin lymphoma (e.g., Hardell *et al.*, 1981) (see Section 2.2.2). The 13 exposed subjects sampled were not a representative sample of phenoxy herbicide applicators in Sweden, and these results may not be generalizable.

Applicators of phenoxy herbicides in most of the epidemiological studies applied these herbicides for only a short time. Analyses restricted to 'long duration' often included only a few subjects exposed for more than a year. In light of the above data, it is to be expected that 2,3,7,8-TCDD levels in herbicide applicators would be very low.

2.2.1 *Applicator cohorts* (**Table 34**)

(*a*) *Commercial*

A cohort study of 348 male railroad workers in Sweden exposed to herbicides during the period 1957–72 was initially followed through 1972 (Axelson & Sundell, 1974) and subsequently through 1978 (Axelson *et al.*, 1980). The workers had been exposed to amitrole (see IARC, 1987i) and to phenoxy herbicides, particularly 2,4-D and 2,4,5-T. Only workers with a minimum of 45 days of exposure, not necessarily continuous, were included in the cohort. Workers were classified into three sub-cohorts depending on the type of herbicide used: those with exposure to amitrole, those with exposure to

Table 34. Cohort studies of cancer in relation to herbicide application

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/ cause of death	No obs.	RR	95% CI	Comments
Axelson *et al.* (1980), Sweden	348 railroad herbicide sprayers	Mortality 1957–78. Latency ≥ 10 years	2,4-D, 2,4,5-T, amitrole and combinations, others	Men	All cancers	13	2.4	[1.3–4.1]	Exposed in 1957–61
					Stomach	3	5.3	[1.1–15.5]	Exposed in 1957–61
					All cancers	3	1.5	[0.3–4.4]	Exposed to amitrole
						6	1.9	[0.7–4.1]	Exposed to phenoxy herbicides
						6	3.4	[1.2–7.4]	Exposed to both
					All cancers	6	2.3	[0.8–5.0]	Follow-up 1972–78
					Stomach	2	7.7	[0.9–27.8]	Exposed to phenoxy herbicides
Riihimäki *et al.* (1982), Finland	1926 herbicide applicators during 1955–71	Mortality, 1972–80	2,4-D, 2,4,5-T, ≥ 2 weeks per year	Men	All cancers				
					No latency	26	[0.7]	[0.5–1.0]	
					≥ 10 years latency	20	[0.8]	[0.5–1.3]	
					≥ 15 years latency	5	[0.4]	[0.1–1.0]	
					Lung				
					≥ 10 years latency	12	[1.1]	[0.6–1.9]	
					≥ 15 years latency	4	[0.9]	[0.2–2.2]	
					Prostate				
					≥ 10 years latency	2	[1.8]	[0.2–6.6]	
					Multiple myeloma				
					≥ 10 years latency	1	[5.0]	[0.1–28]	
			Most heavily exposed ≥ 8 weeks per year or during 5 years		All cancers				
					≥ 10 years latency	5	[0.5]	[0.2–1.2]	
					≥ 15 years latency	1	[0.2]	[0.0–1.1]	

Table 34 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/ cause of death	No obs.	RR	95% CI	Comments
Hansen *et al.* (1992), Denmark	4015 gardeners, 1975–84	Incidence, 1975–84	Greenhouse workers (10–20%): fungicides, insecticides; outdoor gardeners (80–90%): 2,4-D, 2,4,5-T, MCPA, amitrole, other herbicides	Men	All cancers	184	1.1	0.9–1.2	
					Respiratory tract	41	1.0	0.7–1.3	
					STS	3	5.3	1.1–15	
					Haematopoietic (all)	15	1.4	0.8–2.4	
					NHL	6	1.7	0.6–3.8	
					CLL	6	2.8	1.0–6.0	
					Other leukaemia	3	1.4	0.3–4.2	
				Women	All cancers	33	0.9	0.6–1.3	
					Respiratory tract	2	0.7	0.1–2.6	
					Breast	10	1.1	0.5–2.1	
					STS	0	0	0–41	
					Haematopoietic (all)	2	1.4	0.2–5.0	
					NHL	2	3.6	0.4–13	
					CLL	0	0	0–17	
					Other leukaemias	0	0	0–11	
Hogstedt & Westerlund (1980), Sweden	145 forestry workers, 251 unexposed foresters	Mortality 1954–78, incidence 1958–78	2,4-D, 2,4,5-T ≥ 5 days	Men	All cancers (mortality)	2	[0.4]	[0.0–1.3]	Exposed
						3	[3.0]	[0.6–8.8]	Foremen
						5	[0.8]	[0.3–1.8]	Unexposed
					All cancers (incidence)	3	[0.4]	[0.1–1.0]	Exposed
						5	[3.6]	[1.2–8.3]	Foremen

Table 34 (contd)

Reference, country	Study subjects	Study type/ Period of follow-up	Exposure	Gender	Cancer site/ cause of death	No obs.	RR	95% CI	Comments
Wiklund *et al.* (1987, 1988, 1989), Sweden	20 245 pesticide applicators, licensed 1965–76	Incidence, 1965–82	Herbicides (20–70%): MCPA, dinoseb, 2,4-D, 2,4,5-T; insecticides (15–50%): DDT, fenitrothion; fungicides (10–30%): maneb, triadimefon	Men (99%); Women (1%)	All cancers				
					No latency	558	0.9	0.8–0.9	
					≥ 10 years latency	281	0.9	[0.8–1.0]	
					Lung				
					No latency	38	0.5	0.4–0.7	
					≥ 10 years latency	23	0.6	[0.4–0.8]	
					NHL				
					No latency	21	1.0	0.6–1.5	
					≥ 10 years latency	12	1.2	0.6–2.0	
					Hodgkin's disease				
					No latency	11	1.2	0.6–2.2	
					≥ 10 years latency	4	1.5	0.4–3.7	
					STS				
					No latency	7	0.9	0.4–1.9	
					≥ 10 years latency	4	1.0	0.3–2.7	
Ketchum & Akhtar (1996), USA	1261 Ranch Hand veterans (Viet Nam)	Mortality through 1993	Agent Orange median serum 2,3,7,8-TCDD 12 ng/kg in 1987 (comparison 4 ng/kg)	Men	All cancers	30	0.9	0.6–1.3	US Air Force Viet Nam veterans who applied Agent Orange, compared to 19 101 Air Force Viet Nam veterans who did not apply Agent Orange
					Lung	3	[0.9	0.5–1.6]	
					All haematopoietic	12	[0.9	0.2–2.5]	
					NHL	1	[1.4	0.0–7.7]	
					STS	1	[2.4	0.1–13.6]	
					Digestive system	5	[0.7	0.2–1.5]	

Abbreviations: NHL, non-Hodgkin lymphoma; STS, soft-tissue sarcoma; CLL, chronic lymphocytic leukaemia

phenoxyherbicides and those with exposure to both. Workers had also been exposed to some less commonly used herbicides such as monuron, diuron, or atrazine (see IARC, 1991). None of the 348 individuals was lost to follow-up. Underlying cause of death was recorded on the basis of information from death certificates as classified by the National Central Bureau of Statistics. Expected numbers of deaths were calculated using cause-, calendar period- and age-specific national mortality rates. Mortality rates for 1975 were used for the period 1975–78 since national rates were not available at the time of the study for the last three years. In the total cohort, all-cause mortality was approximately that expected (45 deaths; SMR, 0.9, [95% CI, 0.7–1.2]) and mortality from all cancers combined was slightly elevated (17 deaths; SMR, 1.4 [95% CI, 0.8–2.3]). The SMRs for all cancers in the sub-cohort exposed to phenoxy herbicides was 1.1 (6 deaths [95% CI, 0.4–2.3]), with an excess observed for stomach cancer (2 deaths; SMR, 3.1 [95% CI, 0.4–11.1]). The SMR for all cancers combined in the sub-cohort exposed to both phenoxy herbicides and amitrole was 2.1 (6 deaths [95% CI, 0.8–4.5]) with an excess for stomach cancer based on only one death (0.3 expected) and lung cancer (one death; 0.5 expected). When a 10-year latency period was applied, the SMR for all cancers combined for the phenoxy herbicides sub-cohort was 1.9 (6 deaths [95% CI, 0.7–4.2]) and that for the sub-cohort exposed to both phenoxy herbicides and amitrole was 3.4 (6 deaths [95% CI, 1.2–7.3]).

A follow-up study was conducted among forestry workers in Sweden (Hogstedt & Westerlund, 1980). One hundred and forty-five male forestry workers registered as having worked with phenoxy herbicides (2,4-D and 2,4,5-T) for at least five days, 16 foremen (claimed to be highly exposed) and 251 unexposed foresters were identified from pay lists of a timber company in Hälsingland between 1954 and 1967. Persons who worked for more than five days with other herbicides were not included. Vital status and cause of death were assessed for the period 1954–78 from national health registers, except for three exposed and seven unexposed foresters. Incident cancer cases between 1958 and 1978 were identified through cancer registries. National statistics were used as a reference. The average duration of exposure was 30 days (range, 6–114) among forest workers and 176 days (range, 16–317) among foremen. In the exposed cohort, 29 deaths occurred versus 28.0 expected; 47 deaths were observed in the unexposed versus 64.4 expected. Tumour deaths were three (versus 1.0 expected) among foremen, two (versus 5.4 expected) among exposed workers and five (versus 6.4 expected) among unexposed workers. Incident cancer cases were in excess among foremen (5 versus 1.4 expected; $p < 0.02$) and less than expected in the other exposed workers (3 versus 8.4 expected). No specific cancer site was remarkable (stomach (1), pancreas (2), lung (1), skin (1), prostate (2), urinary bladder (1)).

A cohort of male phenoxy herbicide applicators in Finland was followed prospectively from 1972 to 1980 (Riihimäki *et al.*, 1982). The herbicides 2,4-D and 2,4,5-T had been used in Finland since the mid-1950s, with the peak consumption (about 50–70 tonnes of active ingredient per year) occurring in the late 1960s. Analysis of some old herbicide preparations used in Finland in 1962–67 suggested that the 2,3,7,8-TCDD content ranged between 0.1 and 0.9 mg/kg. After 1972, the use of these chemicals declined. The cohort of herbicide applicators was identified in 1972 from the personnel

records of the four main Finnish employers involved in chemical control of brushwood. The cohort included 1971 men exposed to 2,4-D and 2,4,5-T for at least two weeks during 1955–71. The data were collected by office personnel in the companies from various sources such as payrolls. In some cases, supplementary information was sought through interviews with foremen and clerks. About a quarter of the population had been exposed for more than eight weeks, as of 1971. During 1955–71, 45 individuals died, leaving 1926 subjects alive followed during 1972–80; fifteen subjects were not located in the population data register and were excluded from the cohort. The underlying cause of death for all deceased subjects was retrieved from death certificates registered at the Central Statistical Office. National age- and sex-specific mortality rates for 1975 were used to calculate expected numbers of deaths. Mortality from all cancers during the period 1972–80 was lower than expected from national rates (26 deaths [SMR, 0.7; 95% CI, 0.5–1.0]), with a slightly higher rate observed during the last years of follow-up, (1977–80; 17 deaths [SMR, 0.9; 95% CI, 0.5–1.5]). Similar results were obtained when allowing for a 10-year or a 15-year latency period, or when the analysis was restricted to subjects with the longest duration of exposure. The SMR for lung cancer, allowing for a 10-year latency period, was 1.1 (12 deaths [95% CI, 0.6–1.9]). There were no deaths registered from malignant lymphomas or soft-tissue sarcoma.

Cancer incidence was studied in a cohort of 20 245 licensed pesticide applicators in Sweden (Wiklund *et al.*, 1987, 1988, 1989). Since 1965, a licence has been mandatory for using the most acutely toxic pesticides. The workers in the study had been issued a licence between 1965 and 1976 and were followed up for cancer incidence to 31 December 1982. A survey of a random sample of 273 workers showed that 72% had been exposed to phenoxy herbicides for one day or more during the 1950s, 1960s and 1970s. Phenoxy herbicides had been used in Sweden since the late 1940s. The main compound used in agriculture was MCPA and, since the mid-1960s, MCPP and dichlorprop (2-(2,4-dichlorophenoxy)propionic acid). 2,4-D and 2,4,5-T were used to a lesser extent. Cancer incidence rates for the Swedish population were used for comparison. A total of 558 cancer cases were observed in the cohort (SIR, 0.86; 95% CI, 0.79–0.93). Excess risks were observed for lip cancer (14 observed; SIR, 1.8; 95% CI, 1.0–2.9), testicular cancer (18 observed; SIR, 1.6; 95% CI, 0.9–2.5) and Hodgkin's disease (11 observed; SIR, 1.2; 95% CI, 0.6–2.2) but not for lung cancer (38 observed; SIR, 0.5; 95% CI, 0.4–0.7), non-Hodgkin lymphoma (21 observed; SIR, 1.0; 95% CI, 0.6–1.5) or cancer at any other site. The SIR for testicular cancer increased with time since licence (0–4 years, 0.9; 5–9 years, 1.4; ≥ 10 years, 2.5; based on four, six and eight cases, respectively). The SIR for lung cancer increased with years since first employment from 0.3 (0–4 years) to 0.5 (5–9 years) to 0.6 (≥ 10 years). The authors provided data showing that smoking was less prevalent among pesticide applicators than among other occupational categories in Sweden, strongly suggesting that the observed deficit of lung cancer was due to lower cigarette consumption. A follow-up from the date of licence until 31 December 1984 indicated no excess risk for soft-tissue sarcoma (7 cases observed; SIR, 0.9; 95% CI, 0.4–1.9) (Wiklund *et al.*, 1988).

A historical cohort study was conducted among Danish gardeners heavily exposed to pesticides (Hansen *et al.*, 1992). The cohort comprised 859 women and 3156 men and

included all employed persons who, in May 1975, were members of one of the 10 local trade unions of gardeners associated with the Danish Union of General Workers. Subjects were followed from 1 May 1975 to 1 January 1985 through the records of the Danish Central Population Register, with 100% of the subjects being traced. Cancer incidence was recorded through the Danish Cancer Registry. The analysis was limited to subjects 30–79 years of age. The gardeners constituted three fairly separate groups, namely workers in greenhouses (nearly all female), a small group of nursery gardeners and gardeners in public parks, gardens and cemeteries (the majority of workers). Gardeners working outdoors had been exposed to phenoxy herbicides (2,4-D, MCPA, 2,4,5-T) and amitrole. This exposure took place regularly throughout the growing season. Data on individual job histories were not obtained, except for a limited subset of cancer cases. A total of 219 cancer cases were identified in the study, 217 among subjects aged 30–79 years. There was no elevation in incidence of all cancers combined (SIR, 1.0; 95% CI, 0.9–1.2) or of most common neoplasms. An increased risk was seen for soft-tissue sarcoma (code 197 in ICD 7th revision), with an SIR of 4.6 (3 cases; 95% CI, 0.9–13.3) which was statistically significant among men (3 cases; SIR, 5.3; 95% CI, 1.1–15.4). Elevated risks were seen for non-Hodgkin lymphoma (8 cases; SIR, 2.0; 95% CI, 0.9–3.9) and for chronic lymphatic leukaemia (6 cases; SIR, 2.5; 95% CI, 0.9–5.5). Two individuals with soft-tissue sarcoma, six with non-Hodgkin lymphoma and three with chronic lymphatic leukaemia had worked as gardeners for more than 10 years. No additional soft-tissue sarcoma cases were identified in this cohort when the records of the cancer registry were searched for sarcomas which might have occurred in parenchymal organs and consequently not been included in the ICD code (code 197, 7th rev.) used for the main analysis.

(*b*) *Military*

United States Viet Nam veterans as a group, with the exception of those known to have directly handled Agent Orange, show no evidence of exposure to PCDDs or PCDFs above that of other veterans who did not serve in Viet Nam (i.e., beyond background levels), on the basis of serum measurements. However, veterans actually involved in spraying, as members of the Air Force Operation Ranch Hand or of the Army Chemical Corps, have shown elevated serum levels of 2,3,7,8-TCDD (see Section 1.3.1(*a*)(ii)).

The mortality of 1261 Ranch Hand veterans has been compared with that of 19 101 other Air Force Viet Nam veterans who were not exposed to Agent Orange (Michalek *et al.*, 1990). Person–time at risk began when the tour of duty in Viet Nam began. The most recent mortality report extends follow-up through 1993 (Ketchum & Akhtar, 1996), with 31 394 person–years among Ranch Hand personnel and 490 792 person–years among the comparison group. The SMR for all causes of death was 1.0 (95% CI, 0.8–1.2), based on 118 deaths. There were 30 cancer deaths (SMR, 0.9; 95% CI, 0.6–1.3) and 12 lung cancer deaths (13.0 expected). There was one death from soft-tissue sarcoma (a fibroma; ICD 171.3) versus 0.4 expected for the category cancer of the connective tissue (ICD 171.0–171.9), and one from non-Hodgkin lymphoma (0.7 expected). No case of chloracne has been reported among Ranch Hand veterans.

The mortality of 894 members of the Army Chemical Corps was studied by Thomas and Kang (1990). Follow-up extended through 1987, and the United States population was used as the referent. Person–time at risk was taken to begin when service ended in Viet Nam. There were 53 deaths (SMR, 1.1) in this cohort, with about 16 000 person–years and an average follow-up of 18 years. There were six cancer deaths (SMR, 0.9): two lung cancer deaths versus 1.8 expected, two leukaemias versus 0.5 expected and two brain cancers versus 0.4 expected. Review of medical records found two incident cases of Hodgkin's disease, with approximately 0.7 expected.

2.2.2 *Community-based case–control studies*

Although many case–control studies may include one or more questions concerning exposure to herbicides, the Working Group considered only those in which exposure to PCDD-containing herbicides was a major hypothesis being tested, and where such exposure was evaluated in detail.

Studies of soft-tissue sarcoma and haematopoietic tumours have been systematically reviewed. For other sites (Section 2.2.2(*d*)), studies in which phenoxy herbicides were not a main focus of interest have not been examined.

(*a*) *Soft-tissue sarcoma* (see **Table 35**)

A series of studies on soft-tissue sarcoma were conducted in Sweden applying similar methodology (Hardell & Sändstrom, 1979; Eriksson *et al.*, 1981; Hardell & Eriksson, 1988; Eriksson *et al.*, 1990). Relevant exposure measurements are presented in **Tables 16 and 17**.

The first case–control study associating phenoxy herbicides and chlorophenols with soft-tissue sarcoma was conducted in 1978 in the population of the region of Umeå, in northern Sweden (Hardell & Sändstrom, 1979). The study was initiated following a case report of three soft-tissue sarcoma patients who had been exposed to phenoxy herbicides (Hardell, 1977). The study included 21 living and 31 deceased pathologically verified soft-tissue sarcoma male cases, diagnosed in one hospital during 1970–77. Four population controls matched for age, sex, place of residence and vital status were selected per case. Living controls were selected from the national population registry and deceased controls from the national registry of causes of death. The response rate was 100% for cases and 99% for the controls. A self-administered questionnaire was sent to living subjects and to the next-of-kin of deceased subjects (approximately 60% of all questionnaires). Information was requested about a variety of exposures and the questionnaire was supplemented by telephone interviews of selected subjects. Any subject exposed for more than one day was characterized as exposed. Exposure to phenoxy herbicides and/or chlorophenols was associated with a six-fold increased risk. In the matched analysis, the odds ratio was 6.2 [confidence intervals not provided]. In an unmatched analysis, the odds ratio was 5.7 (95% CI, 2.9–11.3). The odds ratio among living subjects was 9.9 and that among deceased subjects was 3.8. The odds ratio for exposure only to phenoxy herbicides was 5.3 (95% CI, 2.4–11.5). After excluding the three index cases [but not

Table 35. Case–control studies on soft-tissue sarcoma containing information on exposure to phenoxy herbicides, chlorophenols or PCDDs

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Hardell & Sandström (1979), Sweden	52/208	Men	Exposure to phenoxy herbicides or chlorophenols for more than one day	5.7 (2.9–11.3)	Odds ratios for living subjects were higher than those for deceased subjects
			Exposure to phenoxy herbicides only	5.3 (2.4–11.5)	
Ericksson *et al.* (1981), Sweden	110/220	Men	Exposure to phenoxy herbicides or chlorophenols for more than one day	5.1 (2.5–10.4)	Odds ratio from matched analysis
			Exposure for more than one day to phenoxy herbicides contaminated with 2,3,7,8-TCDD	17.0 (NR)	
			Exposure for more than one day to phenoxy herbicides not contaminated with 2,3,7,8-TCDD	4.2 (NR)	
			Exposure to chlorophenols for one week continuously or one month discontinuously	3.3 (1.3–8.1)	
Hardell & Eriksson (1988), Sweden	54/490 (311 population controls, 179 cancer controls)	Men	Exposure to phenoxy herbicides for more than one day (comparison with population controls)	3.3 (1.4–8.1)	Odds ratio from matched analysis. Odds ratio was slightly lower (2.2; 95% CI, 0.9–5.3) when comparing with cancer controls.
Eriksson *et al.* (1990), Sweden	218/212	Men	Exposure to phenoxy herbicides for more than one day	1.3 (0.7–2.6)	Odds ratio from matched analysis. Risk for exposure to 2,4,5-T before 1950 was higher (odds ratio, 2.9; 95% CI, 1.1–8.0)
			Exposure to 2,4,5-T	1.8 (0.9–3.9)	
			Exposure to PCP for one week continuously or one month discontinuously	3.9 (1.2–12.9)	

Table 35 (contd)

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Hardell *et al.* (1991), Sweden	352/865	Men	*2,3,7,8-TCDD exposure*		Odds ratios (90% CI)
			Non-exposed	1.0	Referent group non-exposed to phenoxy herbicides or chlorophenols. Pooled analysis of the four above-mentioned studies by Hardell, Eriksson and colleagues
			Less than one year to phenoxy herbicides contaminated with 2,3,7,8-TCDD	3.0 (2.0–4.5)	
			More than one year to phenoxy herbicides contaminated with 2,3,7,8-TCDD	7.2 (2.6–20)	
			Exposure to other PCDDs		
			Non-exposed	1.0	
			Less than one year to phenoxy herbicides contaminated with other PCDDs	1.7 (1.0–2.9)	
			More than one year to phenoxy herbicides contaminated with other PCDDs	6.2 (2.9–13)	
Smith *et al.* (1984b), New Zealand	82/92	Men	*Phenoxy herbicides*		Odds ratios (90% CI)
			Potentially exposed > 1 day not in 5 years before cancer registration	1.3 (0.6–2.5)	
			Probably or definitely exposed for > 5 days not in 10 years before cancer registration	1.3 (0.6–2.9)	
			Chlorophenols		
			Potentially exposed > 1 day not in 5 years before cancer registration	1.5 (0.5–4.5)	
			Probably or definitely exposed for > 5 days not in 10 years before cancer registration	1.6 (0.5–5.2)	
Smith & Pearce (1986), New Zealand	51/315 (new study)	Men	Phenoxy herbicides	0.7 (0.3–1.5)	Odds ratios (90% CI)
			Potentially exposed for > 1 day not in 5 years before cancer registration		
	133/407 (combined)			1.1 (0.7–1.8)	

Table 35 (contd)

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Woods *et al.* (1987), USA	128/694	Men	All occupations with potential exposure to phenoxy herbicides or chlorophenols	0.8 (0.5–1.2)	Risk for soft-tissue sarcoma was not associated with exposure to phenoxy herbicides or chlorophenols and no incresed risk with increasing length of exposure
			Estimated intensity of exposure to phenoxy herbicides:		
			Low	0.6 (0.3–1.1)	
			Medium	1.0 (0.6–1.7)	
			High	0.9 (0.4–1.9)	
			Estimated intensity of exposure to chlorophenols:		
			Low	0.9 (0.5–1.6)	
			Medium	0.9 (0.6–1.5)	
			High	0.9 (0.5–1.8)	
Vineis *et al.* (1986), Italy	37/85	Men	Living men whose exposure could not be ruled out	0.9 (0.2–3.9)	Age-adjusted estimates. 90% CI. Risk higher in women exposed during 1950–55 when highest exposures occurred. No excess risk in men. No excess risk for deceased cases and controls
	31/73	Women	Living women 'definitely' exposed to phenoxy herbicides	2.7 (0.6–12.4)	
Smith & Christophers (1992), Australia	30/30/30 cancer and population controls	Men	At least one day of exposure to phenoxy herbicides or chlorophenols	1.0 (0.3–3.1)	Exposure to phenoxy herbicides and chlorophenols coded as 'none', 'possible' and 'definite/probable' by expert assessment. Matched analysis on age, gender and residence
			At least one day only to phenoxy herbicides	1.3 (0.4–4.1)	
			More than 30 days of exposure to phenoxy herbicides or chlorophenols	2.0 (0.5–8.0)	

NR, not reported

four additional cases included in a pilot study], this odds ratio became 4.7 (95% CI, 2.0–10.7). Tobacco smoking, exposure to DDT, exhaust fumes and emulsion agents did not appear to be associated with risk for soft-tissue sarcoma.

Responding to criticisms that selection and information bias could have affected the results of the previous study (Hardell & Sändstrom, 1979) and of a study on malignant lymphomas (Hardell *et al.*, 1981), Hardell (1981) conducted a further analysis using colon cancer patients as controls. The study is fully described in Section 2.2.4(*d*). Results obtained when using colon cancer patients as controls were very similar to the original results obtained when using population controls.

A case–control study of the association between soft-tissue sarcoma and phenoxy herbicides and chlorophenols was conducted among the population of the five southernmost counties of Sweden (Eriksson *et al.*, 1981). The study included 110 pathologically verified soft-tissue sarcoma cases (including 38 deceased cases) reported to the cancer registry during 1974–78. Two population controls matched for age, place of residence and vital status were selected per case. Living controls were selected from the national population registry and deceased controls from the national registry of causes of death. A self-administered questionnaire was sent to living subjects and to the next-of-kin (approximately 35% of all questionnaires) of deceased subjects. Information was requested about a variety of exposures. The questionnaire was supplemented by telephone interviews for subjects with incomplete or obscure replies to questions on exposure to solvents or pesticides, and also for all subjects reporting work in agriculture, forestry or horticulture. Any subject exposed to phenoxy herbicides for more than one day was characterized as exposed. The predominant exposure in this area was to MCPA, considered to be free of 2,3,7,8-TCDD contamination, to 2,4-D and the analogous phenoxypropionic acids, MCPP and dichlorprop, possibly contaminated by PCDDs other than 2,3,7,8-TCDD. A high level of exposure to chlorophenols used as wood preservatives was defined as one week of continuous or one month of discontinuous exposure. The odds ratio for exposure to phenoxy herbicides and/or chlorophenols was 5.1 in the matched analysis (95% CI, 2.5–10.4). The odds ratio for exposure to any phenoxy herbicide was 6.8 (95% CI, 2.6–17.3). A higher relative risk was observed for exposure to phenoxy herbicides considered to be contaminated with 2,3,7,8-TCDD (odds ratio, 17.0) compared with herbicides uncontaminated with 2,3,7,8-TCDD (odds ratio, 4.2). Longer duration of exposure to phenoxy herbicides (more or less than 30 days) was not associated with an increased risk. High-level exposure to chlorophenols was associated with an increased risk (odds ratio, 3.3; 95% CI, 1.3–8.1), while low-level exposure was not associated with an increased risk. Tobacco smoking or exposure to organic solvents, various pesticides or other chemical agents did not appear to be associated with risk for soft-tissue sarcoma.

A case–control study on soft-tissue sarcoma was conducted in the population of three northern counties of Sweden (Hardell & Eriksson, 1988). The study included 55 male histopathologically confirmed soft-tissue sarcoma cases (18 alive, 37 deceased) aged 25–80 years. Cases were diagnosed during 1978–83 and were identified through the regional cancer registry in Umeå. In eight cases, the tumour was classified as probable soft-tissue

sarcoma but another malignancy could not be excluded. Three groups of controls were selected. A first group of 220 living population controls was matched with cases by age and residence at the time of diagnosis. The second group consisted of 110 dead controls. The third group consisted of 190 cancer cases (112 alive) (except for malignant lymphomas and nasopharyngeal cancer) drawn at random from the population cancer registry. A self-administered postal questionnaire was used and information was requested on lifetime occupational history, exposure to specific agents at work or leisure and lifestyle factors. The questionnaire was supplemented by telephone interviews for subjects with incomplete or obscure replies, and also for all subjects reporting work in agriculture, forestry, horticulture, carpentry and sawmills. The participation rate among both cases and controls was about 95%. The odds ratios for at least one day of exposure to phenoxy herbicides were 3.3 (95% CI, 1.4–8.1) when the two combined population control groups were used and 2.2 when cancer controls were used (95% CI, 0.9–5.3). Exclusion of the eight soft-tissue sarcoma cases with uncertain diagnosis gave a higher estimate of the risk (odds ratio, 3.7 (95% CI, 1.5–9.1) for population controls and 2.4 (95% CI, 1.0–5.9) for cancer controls). No association with exposure to chlorophenols was found. Exposure to 2,3,7,8-TCDD gave a crude rate ratio of 3.5 when population-based referents were used and 3.1 with cancer referents. A higher risk associated with exposure to DDT was present only among subjects with concomitant exposure to phenoxy herbicides. No statistically significant results were observed for other occupational exposures or for smoking.

A case–control study on soft-tissue sarcoma was conducted among the population of seven counties of central Sweden covered by the population cancer registry of Uppsala (Eriksson *et al.*, 1990). The study included 218 male histopathologically confirmed soft-tissue sarcoma cases (78 alive, 140 deceased) aged 25–80 years. Cases were diagnosed during 1978–86 and were identified through the regional cancer registry. One group of population controls was selected, matched for age, gender, county of residence and vital status. A self-administered postal questionnaire was used and information was requested on lifetime occupational history (including details of 16 specific occupations), exposure to specific agents at work or leisure and lifestyle factors. The questionnaire was supplemented by telephone interviews for subjects with incomplete or obscure replies, and also for all subjects reporting work in agriculture, forestry, horticulture, carpentry and sawmills. The participation rate for the cases was 92% (218/237 originally identified cases) and that for controls was 89% (212/237 originally identified controls). The odds ratio for exposure (at least one day) to phenoxy herbicides was 1.3 (95% CI, 0.7–2.6). The risk associated with use of 2,4,5-T was higher (odds ratio, 1.8; 95% CI, 0.9–3.9), especially for use before the 1950s (odds ratio, 2.9; 95% CI, 1.1–8.0) when contamination with PCDDs could be expected to be highest. A high risk was associated with exposure to chlorophenols (odds ratio, 5.3; 95% CI, 1.7–16.3), particularly PCP (odds ratio, 3.9; 95% CI, 1.2–12.9) among subjects characterized as having a high level of exposure (continuous exposure for more than one week or discontinuous exposure for more than one month). No clear dose–response relationship was observed for exposure to phenoxy herbicides. Exposure to phenoxy herbicides not contaminated with 2,3,7,8-TCDD was

not associated with an increased risk. No statistically significant associations were observed for other occupational exposures or for smoking.

The data from the four Swedish case–control studies on soft-tissue sarcoma were aggregated (for a total of 434 cases and 948 controls) and re-analysed according to duration of exposure, latency and type of PCDD exposure, reported in a letter to the editor (Hardell *et al.*, 1991). For exposure to PCDDs of any type, less than one year of exposure gave an odds ratio of 2.4 (58 exposed cases; 90% CI, 1.7–3.4), and more than one year gave an odds ratio of 6.4 (24 exposed cases; 90% CI, 3.5–12). Forty-six cases were exposed to 2,4,5-T, presumed to be contaminated with 2,3,7,8-TCDD, yielding odds ratios of 3.0 (40 exposed cases; 90% CI, 2.0–4.5) for less than one year of exposure and 7.2 (6 exposed cases; 90% CI, 2.6–20) for more than one year of exposure. However, even exposure to other PCDDs was associated with an increased risk for soft-tissue sarcoma (< 1 year: 18 exposed cases; odds ratio, 1.7; 90% CI, 1.0–2.9; > 1 year: 18 exposed cases; odds ratio, 6.2; 90% CI, 2.9–13). It was concluded that PCDDs other than 2,3,7,8-TCDD might have contributed to the noted effect.

A case–control study evaluating the association between exposure to phenoxy herbicides and chlorophenols with the occurrence of soft-tissue sarcoma was carried out in New Zealand (Smith *et al.*, 1984b). Preliminary results had been reported earlier (Smith *et al.*, 1982a, 1983). The study included 82 living or deceased male cases with histopathologically verified soft-tissue sarcoma reported to the national cancer registry between 1976 and 1980. One control per case was selected randomly from other cancer patients in the national cancer registry matched for age, gender and year of registration. The participation rate was 84% among cases (82/98 eligible) and 83% among controls (92/111 eligible). Interviews were conducted with the subjects or the next-of-kin (43% of cases, 34% of controls). Subjects were interviewed by telephone concerning work in particular occupations with potential exposure to phenoxy herbicides or chlorophenols. Exposure to phenoxy herbicides and chlorophenols was ascertained through a combination of information on occupation, industry, type of cultivation sprayed and self-reported exposure to specific agents. In a separate study, PCDD levels were determined in serum of nine workers first employed before 1960 and having sprayed 2,4,5-T for a minimum of 180 months (Smith *et al.*, 1992a). The mean value of 2,3,7,8-TCDD was 53.3 ng/kg (range, 3–131 ng/kg) (see Table 17). Any potential exposure to a phenoxy herbicide was associated with a small non-statistically significant excess risk (odds ratio, 1.3; 90% CI, 0.7–2.5). A slightly higher risk was observed in subjects with more than one day of probable or definite exposure, after excluding the last five years of exposure before registration (odds ratio, 1.6; 90% CI, 0.7–3.3). Potential exposure to chlorophenols was associated with a small increased risk (odds ratio, 1.3; 90% CI, 0.5–3.6), particularly for those subjects who were potentially exposed for more than five days (odds ratio, 1.6; 90% CI, 0.5–5.2). However, a review of the working histories of those subjects through additional interviews and contacts with their employers indicated that only two cases, out of the seven characterized as potentially exposed, actually had potential for exposure to TCP.

An update was conducted by Smith and Pearce (1986) combining new data, including a general population control group, with the study population of Smith *et al.* (1984b). New cases diagnosed from 1980 to 1982 (n = 51) were compared with population controls (n = 315). The odds ratio estimate was 0.7 (90% CI, 0.3–1.5) for probable or definite exposure to phenoxy herbicides for more than one day not in the five years before cancer registration. The odds ratio estimate for the combined studies was 1.1 (90% CI, 0.7–1.8). There was no evidence in either study of an increase in risk with longer duration of exposure or longer latency since first exposure.

A population-based case–control study was conducted in three provinces of northern Italy where rice growing is the predominant agricultural activity and phenoxy herbicides have been used since 1950 (Vineis *et al.*, 1986). During 1950–55, rice weeding was still done manually, mostly by a seasonal work force of women, who were presumed to have had the highest exposure to phenoxy herbicides, predominantly 2,4,5-T. Incident cases of soft-tissue sarcoma aged 20 years or older, with a proven or suspected histological diagnosis in 1981–83 were identified through all the pathology departments of the three provinces, and six pathology departments of the city of Turin and the National Cancer Institute in Milan. Out of 135 cases initially identified, 37 were excluded because the diagnosis was not confirmed or because the cases were prevalent or were visceral sarcomas. Of the remaining 98 eligible cases, interviews were obtained from 68 patients or next-of-kin (44 living, 24 deceased). The participation rate was 69%. A random sample of living controls was drawn from electoral registers. Deceased controls (any cause of death apart from suicide) matched by age, sex, year of death and municipality were selected through demographic offices of the relevant municipalities. Interviews were obtained from 122/168 eligible controls (participation rate 73%) and 36/40 relatives of deceased subjects (participation rate 90%). Direct interviews were carried out with subjects, who were asked for information on lifetime occupational history, and additional information on jobs with titles indicating potential exposure to phenoxy herbicides or chlorophenols. In addition, supplementary questionnaires were administered to subjects working in agriculture, particularly cultivation of rice and other crops. Two experts assessed exposure to phenoxy herbicides and classified subjects into three categories: (1) those not exposed to phenoxy herbicides; (2) those for whom exposure could not be ruled out; and (3) those 'definitely' exposed, based on occupational histories primarily as rice weeders. Among living subjects, no men were 'definitely' exposed. Among living women, four cases and five controls were 'definitely' exposed (odds ratio, 2.7; 90% CI, 0.6–12.4). The odds ratio for the combined categories 2 and 3 was 2.4 (5 exposed cases; 90% CI, 0.6–10.3). Among living women continuously exposed during 1950–55, the crude odds ratio was [9.9] (3 exposed cases, 1 exposed control). No excess risk was observed when analyses were limited to deceased subjects. [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

A population-based case–control study was conducted in western Washington State, United States, to evaluate the relationship between occupational exposure to phenoxy herbicides and chlorophenols and risk for soft-tissue sarcoma and non-Hodgkin lymphoma (Woods *et al.*, 1987). Living and deceased cases, aged 20–79 years and

diagnosed during 1981–84, were identified from the population-based tumour registry that covers 13 counties of the state. Enrolled in the study were 128 pathologically reviewed soft-tissue sarcoma cases (97 alive, 31 dead). Population controls were selected using random digit dialling or from social security records (for older cases) or non-cancer death certificates (for deceased cases). Controls were matched for age and vital status with a parallel series of non-Hodgkin lymphoma cases. The participation rate was 62% for soft-tissue sarcoma cases (128/206) and 76% for controls. Subjects were interviewed in person and information was requested on occupational exposures to phenoxy herbicides and chlorophenols and to other potential risk factors. Additional information was requested for specific occupations and job activities involving potential exposure to the chemicals of interest. The risk for soft-tissue sarcoma associated with all occupations involving potential exposure to phenoxy herbicides was 0.8 (95% CI, 0.5–1.2). Exposure to phenoxy herbicides or chlorophenols was not associated with increased risk for soft-tissue sarcoma. No association was seen with estimated intensity of exposure to either phenoxy herbicides or chlorophenols. [The Working Group noted that no information was provided on use of specific herbicides.]

A case–control study on patients with soft-tissue sarcoma was undertaken in Victoria, Australia, during 1982–88 (Smith & Christophers, 1992). The study included 30 male cases with soft-tissue sarcoma registered in the Victoria Cancer Registry. Cases were first diagnosed between 1976 and 1987. For each case, one cancer control was selected from the cancer registry, matched for age, sex and residence. A second set of population controls was selected from the electoral register using the same matching criteria. The response rates were 70% for cases, 56% for cancer controls and 70% for population controls. Cases were interviewed mostly before 1986, while both series of controls were mostly interviewed after 1986. A comprehensive occupational history was obtained through a personal interview. Exposures to phenoxy herbicides and to chlorophenols were coded by expert assessment as none, possible or definite/probable. Exposures within the five-year period before the year of diagnosis of a case were ignored, for both cases and their matched controls. The main chlorinated herbicides used in Victoria were 2,4-D, 2,4,5-T and MCPA. There were no significant differences between population and cancer controls with respect to definite exposure and these two groups were combined for the analysis. For soft-tissue sarcoma, the odds ratio was 1.0 (95% CI, 0.3–3.1) for at least one day's exposure to phenoxy herbicides or chlorophenols and 1.3 (95% CI, 0.4–4.1) for exposure only to phenoxy herbicides. The odds ratio for more than 30 days of exposure to phenoxy herbicides or chlorophenols was 2.0 (95% CI, 0.5–8.0). [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

(*b*) *Malignant lymphomas* (see **Table 36**)

A case–control study followed the report in Sweden of 17 cases of histiocytic malignant lymphoma, 11 of whom had been exposed to phenoxy herbicides or chlorophenols (Hardell, 1979). All men aged 25–85 years admitted between 1974 and 1978 to the oncology department of the University Hospital in Umeå, Sweden, with histologically verified malignant lymphoma were included in the study (Hardell *et al.*, 1981). For every living

Table 36. Case–control studies on malignant lymphoma containing information on exposure to phenoxy herbicides, chlorophenols or dioxins

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Hardell *et al.* (1981), Sweden	109 cases with NHL and 60 with Hodgkin's disease/338 controls	Men	Exposure to phenoxy herbicides or chlorophenols for more than one day	6.0 (3.7–9.7)	Odds ratios from matched analysis
			Exposure to phenoxy herbicides for more than one day	4.8 (2.9–8.1)	
			Exposure to chlorophenols for one week continuously or one month discontinuously	8.4 (4.2–16.9)	
Hoar *et al.* (1986), USA	170 with NHL/948	Men	Phenoxy herbicide use	2.2 (1.2–4.1)	Phenoxy herbicide used was almost exclusively 2,4-D. Significant but inconsistent increases in risk were observed in relation to duration, frequency and latency. The increased risk persisted after adjusting for use of other pesticides.
Woods *et al.* (1987), USA	576 with NHL /694	Men	Estimated intensity of exposure to phenoxy herbicides:		Higher risks observed for specific occupational groups
			None	1.0	
			Low	0.9 (0.6–1.3)	
			Medium	1.0 (0.7–1.3)	
			High	1.2 (0.8–1.9)	
			Estimated intensity of exposure to chlorophenols:		
			None	1.0	
			Low	1.0 (0.7–1.3)	
			Medium	0.9 (0.7–1.2)	
			High	0.9 (0.9–1.4)	

Table 36 (contd)

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Olsson & Brandt (1988), Sweden	167 with NHL/130	Men	One day handling phenoxy herbicides One day handling chlorophenols 'Skin lymphoma' exposed to phenoxy herbicides	1.3 (0.8–2.1) 1.2 (0.7–2.0) 10.0 (2.7–31.1)	Age-adjusted odds ratios. No interactions between exposures. Risk not associated with length of exposure
Woods & Polissar (1989), USA	576 with NHL/694	Men	Used more than once or twice per year: All subjects 'Phenoxy *per se*' 2,4,5-T	 0.9 (0.5–1.5) 1.0 (0.4–2.0)	Mantel-Haenszel estimates
	181/196		Farmers 'Phenoxy *per se*' 2,4,5-T	 0.7 (0.3–1.5) 0.7 (0.3–2.1)	
Pearce *et al.* (1987), New Zealand	183 with malignant lymphoma/ 338 cancer controls	Men	Ever potentially exposed to 2,4,5-T Ever potentially exposed to chlorophenols	1.0 (0.7–1.5) 1.4 (0.8–2.3)	No association of the risk with any specific herbicide or with duration or frequency of herbicide use
Cantor *et al.* (1992), USA	622 with NHL/1245	Men	Use of one or more herbicides Ever handling, mixing or applying 2,4-D Ever handling, mixing or applying 2,4,5-T Prior to 1965	1.3 (1.0–1.6) 1.2 (0.9–1.6) 1.2 (0.7–1.9) 1.7 (0.8–3.6)	Odds ratios and CI adjusted for many potential confounding factors. Risk for 2,4,5-T was slightly higher in farmers not using protective equipment
Smith & Christophers (1992), Australia	30 with malignant lymphoma/ 30/30 cancer and population controls	Men	At least one day of exposure to phenoxy herbicides or chlorophenols At least one day only to phenoxy herbicides At least one day only to chlorophenols More than 30 days of exposure to phenoxy herbicides or chlorophenols	1.5 (0.6–3.7) 1.1 (0.4–3.0) 1.4 (0.3–6.1) 2.7 (0.7–9.6)	Exposure to phenoxy herbicides and chlorophenols coded as 'none', 'possible' and 'definite/probable' by expert assessment. Matched analysis on age, gender and residence.

NHL, Non-Hodgkin lymphoma

case (in total 107), eight controls matched for sex, age and place of residence were extracted from the national population registry and the two closest in age were used in the analysis. For the 62 deceased cases, 10 controls per case were selected from the national registry of causes of death among those who had died from causes other than malignant tumour, matched for sex, age, municipality and year of death. The two deceased controls closest in age to the cases were used in the analysis. Exposures were reconstructed by means of a self-administered questionnaire. The data concerning deceased subjects were obtained by contact with next-of-kin. For exposure to phenoxy herbicides or chlorophenols, an odds ratio of 6.0 (95% CI, 3.7–9.7) was obtained. For phenoxy herbicides alone (41 exposed cases), the odds ratios were 4.8 (95% CI, 2.9–8.1) and 7.0 for those exposed for more than 90 days. Five cases and no controls were exposed only to MCPA; 7 cases and 1 control only to 2,4-D. These herbicides were not likely to be contaminated with PCDDs or PCDFs. Fifty cases were exposed to chlorophenols, giving an odds ratio of 2.9 (95% CI, 1.6–5.2) for those with low-level exposure and 8.4 (95% CI, 4.2–16.9) for high-level exposure. High-level exposure to organic solvents was also associated with a significantly increased risk. Combined exposure to solvents and phenoxy herbicides or chlorophenols further increased the odds ratio estimate. Separate analysis for Hodgkin's disease (60 cases) and non-Hodgkin lymphoma (109 cases) yielded similarly increased risks. [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

A population-based case–control study on lymphoma was conducted in Kansas, a major wheat-producing state in the United States (Hoar *et al.*, 1986). All newly diagnosed cases of Hodgkin's disease and non-Hodgkin lymphoma among white male residents in Kansas aged 21 years or older, diagnosed from 1976 through 1982, were identified through the population-based cancer registry covering the state of Kansas. All cases included in the study were histologically confirmed. Interviews were conducted with 121 cases with Hodgkin's disease and 170 with non-Hodgkin lymphoma (96% participation rate). One-half of the patients with non-Hodgkin lymphoma and one-third of those with Hodgkin's disease had died before the study began. Controls were 948 white men resident in Kansas matched to cases for age and vital status. The response rate for controls was 94%. Subjects were interviewed by telephone and detailed information was obtained concerning farming practices, including years lived or worked in farms, crops grown or livestock raised, herbicides and insecticides used, numbers of years and acres of treatment and protective equipment used. Corroborative evidence was sought for a sample of 130 subjects by contacting their suppliers. Farm herbicide use was associated with an increased risk for non-Hodgkin lymphoma (odds ratio, 1.6; 95% CI, 0.9–2.6). The relative risk for non-Hodgkin lymphoma increased significantly with the number of days of herbicide exposure per year and with latency. Men exposed to herbicides for more than 20 days per year had a six-fold increased risk for non-Hodgkin lymphoma (odds ratio, 6.0; 95% CI, 1.9–19.5). Frequent users (> 20 years per year) who mixed or applied the herbicides themselves had an odds ratio of 8.0 (95% CI, 2.3–27.9). Use of phenoxy herbicides (odds ratio, 2.2; 95% CI, 1.2–4.1) essentially indicated use of 2,4-D, since only three cases and 18 controls had used 2,4,5-T, and all but two of these controls

had also used 2,4-D. Farm herbicide use was not associated with risk for Hodgkin's disease (odds ratio, 0.9; 95% CI, 0.5–1.5). For this neoplasm, no consistent pattern of excess risk was observed either with duration or frequency of exposure. The authors noted that the observed excess risk for non-Hodgkin lymphoma was associated with exposure to phenoxy herbicides (2,4-D) which were not contaminated with 2,3,7,8-TCDD, although they might be contaminated with other PCDD congeners.

A population-based case–control study from western Washington State (Woods *et al.*, 1987), described above, included 576 non-Hodgkin lymphoma cases (402 alive, 174 dead). Population controls were selected using random digit dialling or from social security records (for older cases) or non-cancer death certificates (for deceased cases). Controls were frequency matched for age and vital status with the non-Hodgkin lymphoma cases. The participation rate was 77% for non-Hodgkin lymphoma cases and 76% for controls. The risk for non-Hodgkin lymphoma associated with all occupations involving potential exposure to phenoxy herbicides was 1.1 (95% CI, 0.8–1.4). Exposure to phenoxy herbicides or chlorophenols was not associated with increased risk for non-Hodgkin lymphoma. No association was seen with estimated intensity of exposure to either phenoxy herbicides or chlorophenols. A statistically significant excess risk for non-Hodgkin lymphoma was observed for specific occupational groups, including farmers (odds ratio, 1.3; 95% CI, 1.0–1.7) and subjects spraying forests with herbicides (odds ratio, 4.8; 95% CI, 1.2–19.4). All forestry sprayers reported combined use of 2,4-D and 2,4,5-T. [The Working Group noted that no information was provided on use of specific herbicides.]

Following the same methodology, a population-based case–control study was conducted in western Washington State on non-Hodgkin lymphoma and phenoxy herbicide exposure in farmers (Woods & Polissar, 1989). Cases of non-Hodgkin lymphoma occurring between 1983 and 1985 were identified from the cancer surveillance system. A total of 694 control men without cancer selected randomly from the same geographical area were matched with the 576 cases by five-year age group and vital status. Among them, 181 non-Hodgkin lymphoma cases and 196 controls reported having worked as farmers. Information on exposure to phenoxy herbicides was obtained through personal interviews. Regular use was defined as 'more than just once or twice per year'. Mantel–Haenszel odds ratios were calculated for farmers, for all subjects for 2,4,5-T and for 'phenoxy *per se*' exposures, among others. No excess risks were observed in all subjects nor in the group of farmers for the above exposures: for 2,4,5-T, the odds ratios were 0.7 (95% CI, 0.3–2.1) in farmers and 1.0 (95% CI, 0.4–2.0) for all subjects; for 'phenoxy *per se*', the odds ratios were 0.7 (95% CI, 0.3–1.5) and 0.9 (95% CI, 0.5–1.5), respectively.

Pearce *et al.* (1987) expanded a previously reported case–control study on malignant lymphomas and farming in New Zealand (Pearce *et al.*, 1986). The study included male public hospital patients registered under ICD codes 200 or 202 during the period 1977–81, who were under the age of 70 years. All cases were pathologically verified. Out of a total of 215 eligible cases, 183 cases were enrolled in the study (participation rate 85%). For each of the cases, two cancer controls were randomly selected from the cancer

registry files, matched for age and year of cancer registration. In total, 338 controls were enrolled (81% participation rate). Interviews were conducted by telephone with the patients or their next-of-kin [no information was given on the proportion of interviews with next-of-kin]. Information was requested concerning work in particular occupations with potential exposure to phenoxy herbicides or chlorophenols. If the response to a stem question was affirmative, then a series of subsidiary questions were asked to clarify the work done and the actual potential for exposure to specific chemicals. Exposure to phenoxy herbicides and chlorophenols was ascertained through a combination of information on occupation, industry, type of cultivation sprayed and self-reported exposure to specific agents. The proportions of cases and controls who had worked in the occupations examined in this study were very similar. The odds ratio for any potential exposure to phenoxy herbicides was 1.0 (95% CI, 0.7–1.5) and none of the odds ratios relating to specific phenoxy herbicides was elevated. The odds ratio for any potential exposure to chlorophenols was slightly elevated (odds ratio, 1.4; 95% CI, 0.8–2.3), largely due to the results for meat workers, which included workers potentially exposed to 2,4,6-TCP in pelt departments. In a re-analysis of the data (Pearce, 1989), little evidence was found of an association of non-Hodgkin lymphoma either with duration or with frequency of phenoxy herbicide use. Findings were similar in the earlier publication using general population controls (Pearce *et al.*, 1986). [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

Olsson and Brandt (1988) examined the lifetime work history of 167 incident cases of non-Hodgkin lymphoma diagnosed at a hospital in Lund (Sweden) between 1978 and 1981 in adult men and in 130 age-matched population controls, 50 from the same geographical area as the cases and 80 from different parts of Sweden. Exposure to organic solvents, phenoxy herbicides and chlorophenols was given special attention. Interviewers were not blind to subject status (case or control). One day of handling was taken to constitute exposure to phenoxy acids or chlorophenols. Odds ratios were estimated using logistic models, adjusting for age. The roles of different exposures, of their interaction and of length of exposure were examined using logistic regression analysis. In the multivariate analysis, the odds ratio for exposure to phenoxy herbicides was 1.3 (95% CI, 0.8–2.1) and that for chlorophenols was 1.2 (95% CI, 0.7–2.0). Separate analysis for localized 'skin lymphoma' yielded a significantly increased risk (odds ratio, 10.0; 95% CI, 2.7–37.1) for exposure to phenoxy herbicides. No interaction between exposures was detected. Risk for non-Hodgkin lymphoma was significantly associated with length of exposure to solvents but not to phenoxy herbicides and chlorophenols. [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

Concurrent population-based case–control interview studies of leukaemia, non-Hodgkin lymphoma and multiple myeloma in Iowa, United States, and leukaemia and non-Hodgkin lymphoma in Minnesota, United States, were conducted during 1981–84. The studies used the same questionnaire and the same controls. Results from the case–control study on non-Hodgkin lymphoma were reported by Cantor *et al.* (1992). Results for the studies on leukaemia (Morris Brown *et al.*, 1990) and multiple myeloma (Morris

Brown *et al.*, 1993) are described in Section 2.2.2(*c*). All male cases of non-Hodgkin lymphoma aged 30 years or older and newly diagnosed during 1980–82 were ascertained from Iowa State Health Registry records and a special surveillance of Minnesota hospitals and pathology laboratory records. Residents of Iowa and of selected areas of Minnesota were eligible. A review panel of four pathologists confirmed diagnoses. Out of 780 reported non-Hodgkin lymphoma cases, 622 (438 living, 184 deceased) were confirmed as non-Hodgkin lymphoma and interviewed. The participation rate was slightly above 80% [exact proportion not estimable]. A population control group of 1245 white men without haematopoietic or lymphatic cancer was randomly selected and frequency matched with the non-Hodgkin lymphoma and leukaemia cases by five-year age group, vital status at time of interview and state of residence. Random digit dialling was used to select controls for living cases under 65 years of age. A 1% random listing of Medicare files was used for the selection of controls for living cases over 65 years of age. State death certificates were used for deceased cases. The participation rate was around 77% in all three groups of controls. Direct structured interviews were conducted during 1981–84. Detailed information on farming and pesticide use was requested for all subjects who had worked on a farm for at least six months since the age of 18 years. The information recorded included years of farming activity, total acreage, crops grown and detailed history of pesticide use. There was a small increase in risk (odds ratio, 1.2; 95% CI, 1.0–1.5) associated with ever living or working on a farm. The odds ratio for use of one or more herbicides was 1.3 (95% CI, 1.0–1.6), but no single family of herbicides was significantly associated with risk for non-Hodgkin lymphoma. No significant risk elevations were observed for ever handling, mixing or applying specific phenoxy herbicides. The odds ratio for 2,4-D was 1.2 (95%, 0.9–1.6) and that for 2,4,5-T was 1.2 (95% CI, 0.7–1.9). The risk for 2,4,5-T was slightly higher among farmers who did not use protective gear (odds ratio, 1.4; 95% CI, 0.7–2.5). The odds ratios for handling these herbicides before 1965 (assuming a latency of about 15 years) were 1.3 (95% CI, 0.9–1.8) for 2,4-D and 1.7 (95% CI, 0.8–3.6) for 2,4,5-T. The authors stated that there was minimal confounding of results for any single pesticide by exposure to pesticides belonging to other chemical families.

The case–control study conducted in Victoria, Australia, described in Section 2.2.2(*a*) (Smith & Christophers, 1992), also included 52 male cases with malignant lymphoma. The odds ratios for malignant lymphoma were 1.5 (95% CI, 0.6–3.7) for at least one day's exposure to phenoxy herbicides or chlorophenols, 1.1 (95% CI, 0.4–3.0) for exposure only to phenoxy herbicides and 1.4 (95% CI, 0.3–6.1) for exposure only to chlorophenols. The odds ratio for more than 30 days of exposure to phenoxy herbicides or chlorophenols was 2.7 (95% CI, 0.7–9.6). [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

(*c*) *Other haematopoietic malignancies* (see **Table 37**)

A case–control study on leukaemia was conducted in Iowa and Minnesota, United States (Morris Brown *et al.*, 1990) using the same methodology and same control group as that described in Section 2.2.2(*b*) (Cantor *et al.*, 1992). All newly diagnosed cases of

Table 37. Case–control studies on other tumour sites containing information on exposure to phenoxy herbicides, chlorophenols or dioxins

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Leukaemia					
Morris-Brown *et al.* (1990), USA	578/1245	Men	Use of one or more herbicides	1.2 (0.9–1.6)	Cases (340 living/238 deceased). Adjusted for vital status, age, state, tobacco, family history, high-risk occupations and exposures. No consistent dose–response pattern by days per year handled for any herbicide used
			Use of phenoxy herbicides	1.2 (0.9–1.6)	
			Exposure to 2,4,5-T (20 years before interview)	1.8 (0.8–4.0)	
			Mixed, handled or applied 2,4,5-T		
			Acute non-lymphocytic leukaemia	2.1 (0.9–4.9)	
			Chronic lymphocytic leukaemia	1.6 (0.7–3.4)	
			Mixed, handled or applied 2,4,5-T at least 20 years before interview		
			Chronic lymphocytic leukaemia	3.3 (1.2–8.9)	
Multiple myeloma					
Morris-Brown *et al.* (1993), USA	173/650	Men	Mixed, handled or applied 2,4,5-T	0.9 (0.4–2.1)	Adjusted for vital status and age by logistic regression
Liver					
Hardell *et al.* (1984), Sweden	103/206	Men	Exposure to phenoxy herbicides and chlorophenols	1.8 (0.9–4.0)	Analysis restricted to 98 hepatocellular and cholangiocellular carcinomas and 200 controls with exposure data. Mantel-Haenszel estimates adjusted by alcohol consumption
			Exposure to phenoxy herbicides only	1.7 (0.7–4.4)	
			Exposure to chlorophenols only for one week continuously or one month discontinuously	2.2 (0.7–7.3)	
Cordier *et al.* (1993), Viet Nam	152/241	Men	Exposure to Agent Orange during military service in south Viet Nam		Cases were hepatocellular carcinoma. Risks adjusted for matching variables, hepatitis virus status and alcohol
			Any service	1.3 (0.8–2.1)	
			10 years or more	8.8 (1.9–41)	

Table 37 (contd)

Reference, country	No. of cases/ controls	Gender	Exposure	Relative risk (95% CI)	Comments
Colon					
Hardell (1981), Sweden	157/451	Men	More than one day of exposure to:		Mantel-Haenszel estimates adjusted by age, vital status and place of residence
			Phenoxy herbicides	1.3 (0.6–2.8)	
			Chlorophenols	1.8 (0.6–5.3)	
Nasopharynx + nasal					
Hardell *et al.* (1982), Sweden	71/541	Men	Exposure to phenoxy herbicides for more than one day	2.1 (0.9–4.7)	Mantel-Haenszel estimates adjusted by age and vital status
			Exposure to chlorophenols for one week continuously or one month discontinuously	6.7 (2.8–16.2)	

leukaemia among white men aged 30 years or older were ascertained from tumour registry or hospital records retrospectively (one year before the start of the study) or prospectively (two years after the start of the study). Interviews were completed with 86% of the cases (or next-of-kin). The final study population consisted of 578 cases (340 living, 238 deceased) and 1245 population controls. Apart from the main interview (described above), a supplementary interview was conducted including 92 cases and 211 controls (or their next-of-kin) from Iowa who had reported agricultural use of pesticides in their initial interview. There was a small risk for all leukaemias among persons who had lived or worked on a farm as an adult (odds ratio, 1.2; 95% CI, 1.0–1.5). A similar risk was seen for farmers reporting ever having used herbicides (odds ratio, 1.2; 95% CI, 0.9–1.6) or phenoxy herbicides (odds ratio, 1.2; 95% CI, 0.9–1.6). Risks for all leukaemias were not significantly increased among subjects who personally mixed, handled or applied specific herbicides. When analyses were restricted to persons first exposed to specific herbicides more than 20 years before interview, increased risks were observed for exposure to MCPA (odds ratio, 2.4; 95% CI, 0.7–8.2) and 2,4,5-T (odds ratio, 1.8; 95% CI, 0.8–4.0). Among specific cell types, the highest risk for those who handled 2,4-D was seen for chronic myelogenous leukaemia (odds ratio, 1.9; 95% CI, 0.9–3.9). The odds ratios for those who handled 2,4,5-T were 2.1 (95% CI, 0.9–4.9) for acute non-lymphocytic leukaemia and 1.6 (95% CI, 0.7–3.4) for chronic lymphocytic leukaemia. The risk for those who handled 2,4,5-T at least 20 years before interview was significantly elevated for chronic lymphocytic leukaemia (odds ratio, 3.3; 95% CI, 1.2–8.9). No consistent dose–response pattern in terms of days of handling per year was seen for any of the herbicides used.

A case–control study on multiple myeloma was conducted in Iowa, United States (Morris-Brown *et al.*, 1993), using the same methodology and same control group as that described above in Section 2.2.2(*b*) (Cantor *et al.*, 1992). All cases of multiple myeloma among adult white men aged 30 years or older and diagnosed during 1981–84 were identified from the Iowa State Health Registry. Pathological material and laboratory reports were reviewed by an expert pathologist. Included the study were 173 cases (101 alive, 72 deceased) and 650 controls (452 alive, 198 deceased). Interviews were completed for 84% of multiple myeloma cases and 78% of controls. Some farming activity was reported by 64% of the cases and 58% of the controls (odds ratio, 1.2; 95% CI, 0.8–1.7). Risks were not elevated for subjects who handled the phenoxy herbicides 2,4-D (odds ratio, 1.0; 95% CI, 0.6–1.6) or 2,4,5-T (odds ratio, 0.9; 95% CI, 0.4–2.1).

(*d*) *Other solid tumours* (**Table 37**)

Hardell (1981) conducted a case–control study on colon cancer patients following the same methodology as that described earlier (see Section 2.2.2(*a*); Hardell & Sändstrom, 1979; Eriksson *et al.*, 1981; Hardell *et al.*, 1981). Cases were 157 men with colon cancer (response rate, 98.1%) aged 25–85 years who were residents of the region of Umeå, Sweden, and who had been reported to the Swedish Cancer Registry in 1978–79. All had a histopathological diagnosis of adenocarcinoma. Sixty-five cases (41%) were deceased. The 541 controls were derived from two earlier studies (Hardell & Sändstrom, 1979; Hardell *et al.*, 1981). A low excess risk was observed for exposure to phenoxy herbicides

(odds ratio, 1.3; 95% CI, 0.6–2.8) and for exposure to chlorophenols (odds ratio, 1.8; 95% CI, 0.6–5.3). [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

In a case–control study on nasal and nasopharyngeal cancer in the region of Umeå, Sweden, Hardell *et al.* (1982) followed the same methodology as that described above (Hardell & Sändstrom, 1979; Hardell *et al.*, 1981). The cases comprised all male patients aged 25–85 years with histopathologically confirmed nasopharyngeal cancer ($n = 27$) and cancer of the nose and nasal sinuses ($n = 44$). All cases had been reported to the Swedish Cancer Registry in 1970–79 and were residents in the three most northern counties of Sweden. The 541 controls were derived from two earlier studies in the same region (Hardell & Sändstrom, 1979; Hardell *et al.*, 1981). Fifty (70.4%) of the cases were deceased, compared with 245 (45.3%) of the controls. [No information was provided on response rates.] Exposure to phenoxy herbicides was associated with a two-fold risk for the combination of nasopharyngeal and nasal cavity cancer (odds ratio, 2.1; 95% CI, 0.9–4.7). A high risk was found for high-level exposure to chlorophenol, defined as a cumulative exposure of one week of continuous or one month of discontinuous exposure (odds ratio, 6.7; 95% CI, 2.8–16.2). No obvious difference was reported between cases and controls for low-level exposure to chlorophenols. The risk associated with use of chlorophenol exposure was higher among wood workers (odds ratio, 8.4) than in other occupations (odds ratio, 2.7) but, in a stratified analysis, it was shown that occupation as a wood worker was not a confounding factor for exposure to chlorophenols. [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

Men aged 25–80 who had been diagnosed with liver cancer between 1974 and 1981 and reported to the Department of Oncology, Umeå, Sweden, were included in another case–control study (Hardell *et al.*, 1984). Microscope slides were reviewed for the 166 assembled cases, and 103 cases of primary liver cancer were retained for the study; 206 population-based controls were matched with cases for age and residence. Information on exposure was obtained as in previous studies (see Hardell & Sandström, 1979); responses were obtained for 102 cases and 200 controls. The analyses were restricted to the 98 cases of hepatocellular and cholangiocellular carcinoma. Odds ratios, without controlling for other agricultural exposures, were 1.8 (95% CI, 0.9–4.0) for exposure to phenoxy herbicides and chlorophenols, 1.7 (95% CI, 0.7–4.4) for exposure to phenoxy herbicides only and 2.2 (95% CI, 0.7–7.3) for high-level exposure to chlorophenols only. [The Working Group noted that no distinction was made between herbicides likely to be contaminated with PCDDs and others.]

A case–control study conducted in two hospitals in Hanoi (Viet Nam) between 1989 and 1992 included 152 male cases of hepatocellular carcinoma and 241 hospital controls, admitted mainly in abdominal surgery departments, matched for age, sex and area of residence at the time of admission (Cordier *et al.*, 1993). Exposure to Agent Orange may have occurred during stays in the south of Viet Nam after 1960 (date of the beginning of spraying missions) especially for military purposes. Duration of military service in the south, for North Vietnamese soldiers, was considered as a proxy for exposure to Agent

Orange. This is justified by the fact that sprayings were principally aimed at uncovering trails used by the Vietnamese combatants, who stayed one or two years on average in these areas and consumed locally grown (and contaminated) foodstuffs. The overall odds ratio associated with military service in the south was 1.3 (95% CI, 0.8–2.1). The risk rose with increasing duration of stay in the south, reaching 8.8 (95% CI, 1.9–41) after 10 years. Odds ratios were adjusted for matching variables (hospital, age, area of residence), hepatitis B virus surface antigen, anti-hepatitis C virus status and alcohol consumption.

2.3 Combined evidence from high-exposure human populations

Causal inference about the effects of chemicals can best be drawn from studies with well documented exposures. It is important to focus on human studies in which it is clear that exposure to the chemical in question actually occurred. The ideal is to have biological markers of such exposure. In the case of 2,3,7,8-TCDD, the long half-life in humans means that recent biological measurements allow assessment of past human exposure. In addition, chloracne may be an indication of exposure for some studies, although its absence does not rule out exposure.

The most informative studies for causal inference are those with the highest exposures, which if they are causal will produce the highest cancer risks. For these reasons, the Working Group abstracted from published studies data concerning the most highly exposed populations studied in the world. Evidence for their exposure being high is given in Section 1.3.1 (see **Table 22**). The Working Group focused on the most exposed sub-cohorts within cohorts, and also confined its attention to findings with adequate latency when available. The reasons for doing this are that if associations are truly causal, they will become more apparent at the highest exposures with adequate latency. Such studies are identified in **Table 38**. The first line gives the results from the large international cohort study conducted by IARC. The next lines give data from four separate cohorts of industrial production workers, three of which were included within this large cohort. These have been selected because of known high exposure to 2,3,7,8-TCDD, whereas the total combined IARC cohort also included sub-cohorts with much lower exposure. Data from the community exposures resulting from the Seveso accident, although high exposures, are not included because of inadequate duration of follow-up since the accident.

The focus of attention within each of the published studies has been on all cancers combined, and on particular sites of interest, namely cancers of the lung and gastrointestinal tract, non-Hodgkin lymphoma and soft-tissue sarcoma. Observed numbers, SMRs and 95% CIs are given for each of these sites for each study. Below the presentation of the high-exposure industrial cohorts are summary estimates by the Working Group obtained by adding the observed and expected numbers for all cancers combined and each cancer site.

There is an overall increase in mortality from all cancers combined in the high-exposure industrial cohorts in several studies. The overall SMR for all cancers combined calculated by the Working Group was 1.4 (95% CI, 1.2–1.6). Although this overall SMR is low, these findings concerning all cancers are most unlikely to be due to chance, and

Table 38. Summary of the combined international cohort and selected industrial cohort studies with high exposure levels

Reference	All cancers			Lung cancer			Non-Hodgkin lymphoma			Soft-tissue sarcoma			Gastrointestinal cancer		
	Obs.	SMR	95% CI	Obs.	SMR	95% CI	Obs.	SMR	95% CI	Obs.	SMR	95% CI	Obs.	SMR	95% CI
International cohort															
Kogevinas *et al.* (1997)[a]	394	1.2	1.1–1.3	127	1.2	1.0–1.4	14	1.6	0.9–2.7	3	2.3	0.5–6.6	190	1.0	0.9–1.2
Industrial populations (high-exposure subcohorts)															
Fingerhut *et al.* (1991a)[b] (USA)	114	1.5	1.2–1.8	40	1.4	1.0–1.9	2	0.9	0.1–3.4	3	9.2	1.9–27.0	28	1.4	0.9–2.0
Becher *et al.* (1996)[c] (Germany)	105	[1.3]	[1.0–1.5]	33	[1.4]	[1.0–2.0]	6	[4.6]	[1.7–10.0]	0	0.0	–	27	[0.9]	[0.6–1.4]
Hooiveld *et al.* (1996a)[d] (Netherlands)	51	1.5	1.1–1.9	14	1.0	0.5–1.7	3	3.8	0.8–11.0	0	0.00	–	NR		
Ott & Zober (1996)[e] (BASF, accident)	18	1.9	1.1–3.0	7	2.4	1.0–5.0	NR			NR			6	1.8	0.7–4.0
Total	[288]	[1.4]	[1.2–1.6]	[94]	[1.4]	[1.1–1.7]	[11]	[2.6]	[1.3–4.7]	[3]	[4.7]		[61]	[1.2]	[0.9–1.5]
p value			*< 0.001*			*< 0.01*			*< 0.01*						*0.23*

NR, not reported

[a] Kogevinas *et al.* (1997): men and women > 20 years since first exposure, except for digestive cancer for which no latency data were available. These data include the cohorts of Fingerhut *et al.* (1991a,b), Becher *et al.* (1996), Hooiveld *et al.* (1996a), the original IARC cohort (Saracci *et al.*, 1991) and other cohorts.

[b] Fingerhut *et al.* (1991a): Men ≥ 20 years latency and > 1 year exposure

[c] Becher *et al.* (1996): Men, Cohort I and II, summed (Boehringer-Ingelheim, Bayer-Uerdingen cohorts)

[d] Hooiveld *et al.* (1996a): Men and women, Factory A

[e] Ott & Zober (1996): Men, chloracne subgroup, ≥ 20 years latency. Data presented for lung cancer are all respiratory tract cancers combined. No data were available for soft-tissue sarcoma and non-Hodgkin lymphoma.

are consistent across the studies with the highest exposure. Increases in all cancers combined of this magnitude have rarely been found in occupational cohorts.

The combined SMR for lung cancer was calculated to be 1.4 (95% CI, 1.1–1.7). The findings are unlikely to be due to chance. It is the view of the Working Group that these lung cancer results are not the result of confounding by cigarette smoking. As with all cancers combined, the strength of association is again low .

The overall estimate for non-Hodgkin lymphoma was significantly elevated [SMR, 2.6; 95% CI, 1.3–4.7], but there was no increased risk in the large NIOSH cohort. The SMR for gastrointestinal cancer was 1.2 (95% CI, 0.9–1.5). For soft-tissue sarcoma, the overall SMR was approximately 4.7 [calculated by the Working Group, estimating expected values of 0.20 and 0.12 for Becher *et al.* (1996) and Hooiveld *et al.* (1996a) respectively].

The available dose–response data are presented in **Table 39**. Two studies give dose–response relationship data for all cancers combined based on evidence for 2,3,7,8-TCDD exposure. In the Boehringer-Ingelheim cohort (cohort I in Becher *et al.*), the relative risks are given for seven levels of toxic equivalents for 2,3,7,8-TCDD (Flesch-Janys *et al.*, 1995). The rate ratios fluctuate, but there is a clear elevation for the highest exposure group, which involves workers with markedly higher blood and fat 2,3,7,8-TCDD levels than for the other categories (RR, 2.7; 95% CI, 1.7–4.4). The overall test for trend resulted in a p value less than 0.01, but this is largely the result of the high RR for the highest exposure group.

The second study giving dose–response data for all cancers involves the BASF accident cohort, based on the entire cohort (n = 243). Workers were divided into four categories of measured and estimated 2,3,7,8-TCDD levels. There was a trend for increasing SMR with measured exposure up to a relative risk of 2.0 (95% CI, 0.8–4.0). The test for trend using cumulative dose as a continuous variable in Cox's regression analysis yielded confidence intervals indicating a p value of 0.05. Thus this study and the Boehringer-Ingelheim cohort together provide dose–response evidence supporting a causal relationship between 2,3,7,8-TCDD exposure and mortality from all cancers combined. Further subdivision of the data indicates that the positive dose–response was restricted to smokers.

Concerning specific cancer sites, dose–response information from highly exposed populations is available in one publication only involving two cancer sites, non-Hodgkin lymphoma and soft-tissue sarcoma. For each site, there are trends of increasing risks with increasing exposures classified as low, medium and high. While confidence limits are broad, the test for trend gave p values of 0.1 for non-Hodgkin lymphoma and 0.04 for soft-tissue sarcoma.

In summary, the epidemiological evidence from the most highly 2,3,7,8-TCDD-exposed populations studied produces strong evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. This situation appears to be unique, compared with established human carcinogens. The overall findings are unlikely to be due to chance. There is no obvious basis to infer

Table 39. Cohort or nested case–control studies of industrial workers presenting dose–response data

Boehringer-Ingelheim cohort, Germany (Flesch-Janys, 1996), all cancers

PCDD/PCDF TEQ (ng/blood fat)[a]	Rate ratio	(95% CI)
0	1.0	
1.0–12.2	1.0	(0.6–1.8)
12.3–39.5	1.3	(0.8–2.1)
39.6–98.9	1.2	(0.7–1.9)
99.0–278.5	1.2	(0.8–1.9)
278.6–545.0	1.3	(0.7–2.3)
545.1–4 361.9	2.7	(1.7–4.4)
Test for linear trend $p < 0.01$		

BASF accident cohort, Germany (Ott & Zober, 1996), all cancers

2,3,7,8-TCDD (μg/kg bw)	No. of subjects	No. of deaths	SMR	(95% CI)
< 0.1	108	8	0.8	(0.4–1.6)
0.1-0.99	66	8	1.2	(0.5–2.3)
1.0–1.99	47	8	1.4	(0.6–2.7)
≥ 2.0	22	7	2.0	(0.8–4.0)
	[$p = 0.05$]			

IARC nested case–control study (Kogevinas *et al.*, 1995)

2,3,7,8-TCDD exposure	Number of cases/controls	Odds ratio	(95% CI)
Non-Hodgkin lymphoma			
Non-exposed	21/119	1.0	
Low	4/18	1.4	(0.4–4.6)
Medium	3/8	3.6	(0.7–18.7)
High	4/13	3.6	(0.6–19.2)
	Test for linear trend $p = 0.1$		
Soft-tissue sarcoma			
Non-exposed	6/42	1.0	
Low	1/4	2.8	(0.1–54.8)
Medium	1/4	6.6	(0.1–540)
High	3/5	10.6	(0.6–671)
	Test for linear trend $p = 0.04$		

[a]Estimated German PCDD/PCDF TEQ levels at the end of exposure above German median background

that the findings are due to confounding with smoking, nor with occupational exposures to other chemicals, but such confounding cannot be ruled out. There is evidence in some studies of dose–response relationships, although dose–response data are not available for some of the largest studies. The relative risk estimates for all cancers, lung cancer and gastrointestinal cancer involve relatively low strengths of association. Higher relative risk estimates are present in some studies concerning non-Hodgkin lymphoma and soft-tissue sarcoma, but the total numbers of cancers are small, in particular for soft-tissue sarcoma.