2. Studies of Cancer in Humans

2.1 Cohort studies

More than 25 cohort studies have examined the association between formaldehyde and cancer. Since the previous IARC monograph in 1994 (IARC, 1995), three of these have been updated, and six new studies have been published. The following review divides the studies into those that concern professionals (e.g. pathologists, anatomists and embalmers) and those that concern industrial workers (e.g. formaldehyde producers, formaldehyde resin makers, plywood and particle-board manufacturers, garment workers and workers in the abrasives industry). This division was also made in the previous IARC monograph because of differences between these studies with regard to their findings, the nature of the exposure to formaldehyde and the potential for exposures to other carcinogens or other factors that might confound the findings.

The following discussion is focused largely on the results for sites that may come into direct contact with airborne formaldehyde (cancers of the respiratory tract including cancers of the trachea, bronchus and lung, laryngeal cancer, sinonasal cancer, nasopharyngeal cancer, oral cancer and other pharyngeal cancers) and on leukaemia and brain cancer, for which excess mortality has been reported in several studies.

2.1.1 *Cohorts of industrial workers*

Key study features and findings from the cohort and nested case–control studies of industrial workers are summarized chronologically in Table 16, based on the year of publication of the first report of the cohort. Studies have been conducted on workers who were exposed to formaldehyde in the chemical, garment, fibreglass, iron, wood-working, plastics and paper, pulp and plywood industries. Several of these cohort studies have recently been updated, and the results presented below are largely limited to the updated data, grouped by industry.

(*a*) *The National Cancer Institute (NCI) Cohort*

Blair *et al.* (1986, 1990a) at the NCI, USA, conducted the largest of the cohort studies, which included over 25 000 workers (88% men) who had first been employed before 1966 in one of 10 industrial facilities in the USA. These facilities manufactured formaldehyde (three plants), formaldehyde resins (six plants), moulding compounds (six plants), moulded plastic products (two plants), photographic films (two plants) and plywood (one plant). Among all of the workers, 11% were considered to be unexposed.

This study included workers from facilities that were also included in studies by Marsh (1982), Wong (1983) and Liebling *et al*. (1984) and in a case–control study by Fayerweather

Table 16. Cohort studies of industrial workers exposed to formaldehyde

Reference, location, years of study	Cohort description Type of analysis (cohort size)	Exposure assessment	Organ site (ICD code)[a]	No. of cases/ deaths	SMR (95% CI)	Comments
Coggon *et al.* (2003), United Kingdom, 1941–2000 (update of Acheson *et al.*, 1984a; Gardner *et al.*, 1993)	Chemical factories that used or produced formaldehyde Standardized mortality (14 014 men)	Level of exposure (background, low, moderate, high); among highly exposed, time period and duration of exposure	All cancers	1511 deaths	1.10 (1.04–1.16)	
			Nasopharynx	1 death	NR	2.0 expected
			Nose and nasal sinuses	2 deaths	0.87 (0.11–3.14)	Two additional cases identified from registry that could not be used in the analysis
			Lymphohaematopoietic	NR	NR	
			Leukaemia	31 deaths	0.91 (0.47–1.59)	
			Mouth (ICD-9, 143–145)	6 deaths	1.28 (0.47–2.78)	
			Lung	594 deaths	1.22 (1.12–1.32)	Increased risk among highly exposed (1.58; 95% CI, 1.40–1.78); inverse trend with duration of exposure
			Brain and central nervous system	30 deaths	0.85 (0.57–1.21)	
Hauptmann *et al.* (2003, 2004), USA, 1966–94 (update of Blair *et al.*, 1986, 1987)	Manufacturer of formaldehyde, formaldehyde resins, moulding compounds, moulded plastic products, photographic films and plywood Standardized mortality (25 619 workers; 22 493 men, 3126 women)	Duration; quantitative estimates of cumulative, average and highest peak exposure	All cancers	1723 deaths	0.90 (0.86–0.95)	15-year lag for solid cancers; 2-year lag for lymphohaematopoietic cancers
			Nasopharynx	8 deaths	2.10 (1.05–4.21)	The authors noted that the exact CI is 0.91–4.14; statistically significant trend with highest peak exposure; weaker trends observed with duration of, cumulative and average exposures
			Nose and nasal sinuses	3 deaths	1.19 (0.38–3.68)	
			Lymphohaematopoietic	161 deaths	0.80 (0.69–0.94)	
			Leukaemia	65 deaths	0.85 (0.67–1.09)	Statistically significant trend with peak exposure, particularly for myeloid leukaemia; weaker trend with average exposure; no trend with duration of or cumulative exposure
			Buccal cavity	49 deaths	1.01 (0.77–1.34)	
			Lung	641 deaths	0.97 (0.90–1.05)	
			Brain and central nervous system	43 deaths	0.92 (0.68–1.23)	

Table 16 (contd)

Reference, location, years of study	Cohort description Type of analysis (cohort size)	Exposure assessment	Organ site (ICD code)[a]	No. of cases/ deaths	SMR (95% CI)	Comments
Bertazzi *et al.* (1986, 1989), Italy, 1959–86	Formaldehyde resin makers Standardized mortality (1332 men)	Duration of exposure, latency, age at employment, year of employment, time since beginning of employment	All cancers	62 deaths	1.23 [0.94–1.58][b]	Mortality was close to expected when local rates were used as the referent (1.00 [95% CI, 0.64–1.49])
			Nasopharynx	NR	NR	
			Nasal cavity	0 deaths	NA	
			Lymphohaematopoietic	7 deaths	1.77 [0.71–3.65][b]	SMR with local rates as the referent, 1.43 [95% CI, 0.57–2.95]
			Leukaemia	NR	NR	
			Buccal cavity/pharynx	NR	NR	
			Lung	24 deaths	1.56 [1.00–2.32]	
			Brain	NR	NR	
Edling *et al.* (1987a), Sweden, 1955–83	Abrasives industry Standardized mortality, standardized incidence (521 male blue-collar workers)	None (area measurements)	All cancers	24 inc. cases	0.84 [0.54–1.25][c]	All cancer mortality SMR, 0.93 [95% CI, 0.54–1.49]
			Nasopharynx	1 inc. case	NR	
			Nasal cavity	0 inc. cases	NA	
			Lymphohaematopoietic	4 inc. cases	NR	
			Leukaemia	0 inc. cases	NA	
			Buccal cavity	0 inc. cases	NA	
			Lung	2 inc. cases	0.57 [0.07–2.06]	
			Brain and central nervous system	1 inc. case	NR	
Pinkerton *et al.* (2004), USA, 1955–98 (update of Stayner *et al.*, 1988)	Garment industry Standardized mortality (11 039 workers; 2015 men, 9024 women)	Duration, time since first exposure, year of first exposure	All cancers	608 deaths	0.89 (0.82–0.97)	
			Nasopharynx	0 deaths	NA	0.96 expected
			Nasal cavity	0 deaths	NA	0.16 expected
			Lymphohaematopoietic	59 deaths	0.97 (0.74–1.26)	
			Leukaemia	24 deaths	1.09 (0.70–1.62)	
			Myeloid leukaemia	15 deaths	1.44 (0.80–2.37)	Statistically significant excess among workers with both ≥ 10 years of exposure and ≥ 20 years since first exposure (SMR, 2.43; 95% CI, 0.98–5.01)
			Buccal cavity/pharynx	4 deaths	1.33 (0.36–3.41)	
			Lung	147 deaths	0.98 (0.82–1.15)	
			Brain and central nervous system	19 deaths	1.09 (0.66–1.71)	

Table 16 (contd)

Reference, location, years of study	Cohort description Type of analysis (cohort size)	Exposure assessment	Organ site (ICD code)[a]	No. of cases/ deaths	SMR (95% CI)	Comments
Andjelkovich *et al*. (1995), USA, 1960–89	Foundry workers Standardized mortality (3929 men with potential exposure)	Exposed/ unexposed; none, low, medium and high exposure	All cancers	127 deaths	0.99 (0.82–1.17)	
			Nasopharynx	0 deaths	NA	
			Nasal cavity	0 deaths	NA	
			Lymphohaematopoietic	7 deaths	0.59 (0.23–1.21)	
			Leukaemia	2 deaths	0.43 (0.05–1.57)	
			Buccal cavity/pharynx	6 deaths	1.31 (0.48–2.86) 1.16 (0.20–6.51)[d]	
			Lung	51 deaths	1.20 (0.89–1.58) 0.59 (0.28–1.20)[d]	
			Brain and central nervous system	2 deaths	0.62 (0.07–2.23)	
Hansen & Olsen (1995, 1996), Denmark	Workers from companies with a history of use or manufacture of formaldehyde Standardized proportionate incidence (eligible cancer cases: 2041 men, 1263 women diagnosed in 1970–84)	Low (white-collar) and above baseline (blue-collar)	ICD-7	*Men*		
			Nasopharynx	4 cases	1.3 (0.3–3.2)	
			Nasal cavity	13 cases	2.3 (1.3–4.0)	Risk increased among more highly exposed workers with (SPIR, 5.0; 95% CI, 0.5–13.4) or without (SPIR, 3.0; 95% CI, 1.4–5.7) exposure to wood dust
			Lymphohaematopoietic	NR	NR	
			Leukaemia (204)	39 cases	0.8 (0.6–1.6)	Risk not increased among more highly exposed
			Buccal cavity/pharynx	23 cases	1.1 (0.7–1.7)	
			Lung	410 cases	1.0 (0.9–1.1)	Risk not increased among more highly exposed
			Brain and nervous system (193)	54 cases	1.1 (0.9–1.5)	Risk not increased among more highly exposed
				Women		
			Nasal cavity	4 cases	2.4 (0.6–6.0)	
			Lymphohaematopoietic	NR	NR	
			Leukaemia	21 cases	1.2 (0.7–1.8)	
			Lung	108 cases	1.2 (0.96–1.4)	
			Brain and nervous system (193)	39 cases	1.2 (0.8–1.6)	

Table 16 (contd)

Reference, location, years of study	Cohort description Type of analysis (cohort size)	Exposure assessment	Organ site (ICD code)[a]	No. of cases/ deaths	SMR (95% CI)	Comments
Chiazze *et al.* (1997), USA, 1951–91	Fibreglass manufacturing plant workers Standardized mortality and nested case–control (4631 men and women)	Cumulative exposure	All cancers	96 deaths	0.94 (0.77–1.15)[b]	Analysis restricted to 2933 white men
			Nasopharynx	NR	NR	
			Nasal cavity	NR	NR	
			Lymphohaematopoietic	5 deaths	0.46 (0.15–1.08)	
			Leukaemia	1 death	0.24 (0.006–1.36)	
			Buccal cavity/pharynx	2 deaths	0.70 (0.08–2.52)	
			Lung	47 deaths	1.26 (0.93–1.68)	Excess risk for lung cancer reduced when local rates were used (SMR, 1.17; 95% CI, 0.86–1.55); positive trend in case–control study with cumulative exposure to formaldehyde among smokers
			Brain and nervous system	6 deaths	1.48 (0.54–3.23)	
Stellman *et al.* (1998), USA, 1982–88	Workers in the American Cancer Society CPS-II study employed in wood-related occupations or who reported exposure to wood dust Retrospective cohort mortality (45 399 men, of whom 387 reported exposure to formaldehyde)	Dichotomous (yes/no) with and without employment in a wood occupation	All cancers			
			Formaldehyde alone	367 deaths	0.98 (0.86–1.12)	
			Formaldehyde + wood	14 deaths	1.61 (0.95–2.72)	
			Nasopharynx	NR	NR	
			Nasal cavity	NR	NR	
			Lymphohaematopoietic			
			Formaldehyde alone	28 deaths	1.22 (0.84–1.77)	
			Formaldehyde + wood	3 deaths	3.44 (1.11–10.68)	
			Leukaemia			
			Formaldehyde alone	12 deaths	0.96 (0.54–1.71)	
			Formaldehyde + wood	2 deaths	5.79 (1.44–23.25)	
			Buccal cavity/pharynx	NR	NR	
			Lung			
			Formaldehyde alone	104 deaths	0.93 (0.73–1.18)	
			Formaldehyde + wood	7 deaths	2.63 (1.25–5.51)	
			Brain (ICD-9, 191)	NR	NR	

Table 16 (contd)

Reference, location, years of study	Cohort description Type of analysis (cohort size)	Exposure assessment	Organ site (ICD code)[a]	No. of cases/ deaths	SMR (95% CI)	Comments
Marsh *et al*. (2001); Youk *et al*. (2001), USA, 1945–92	Fibreglass workers Standardized mortality and nested case–control (32 000 men and women, 22% of person–years exposed to formaldehyde)	Duration of, cumulative and average exposure	All cancers	2243 deaths	0.98 (0.94–1.02)[b]	
			Nasopharynx	NR	NR	
			Nasal cavity	NR	NR	
			Lymphohaematopoietic	199 deaths	0.92 (0.80–1.06)	
			Leukaemia	NR	NR	
			Buccal cavity/pharynx	63 deaths	1.07 (0.82–1.37)	
			Lung	838 deaths	1.17 (1.09–1.25)	SMR was reduced and no longer significant when local rates were used (SMR, 1.06; 95% CI, 1.00–1.14); a statistically significant excess among formaldehyde-exposed workers observed in the case–control study (smoking-adjusted odds ratio, 1.61; 95% CI, 1.02–2.56); no significant trend with duration of or cumulative exposure; some evidence for a trend with average exposure
			Brain and central nervous system	50 deaths	0.78 (0.58–1.03)	

Nested case–control studies

Reference, location, years of study	Characteristics of cases and controls	Exposure assessment	Organ site/exposure category	No. of cases (exposed)	Odds ratio (95% CI)	Comments
Bond *et al*. (1986), USA, 1944–80	308 male incident cases of lung cancer from a cohort of 19 608 employees at a chemical company; two controls per case matched on race, year of birth (5 years) and year of first employment	Exposure profile developed based on work history at the company	Lung			Formaldehyde was not assessed in great detail.
			No lag period	(9)	0.62 (0.29–1.34)	
			Lag period ≥ 15 years	(4)	0.31 (0.11–0.86)	

Table 16 (contd)

Reference, location, years of study	Characteristics of cases and controls	Exposure assessment	Organ site/exposure category	No. of cases (exposed)	Odds ratio (95% CI)	Comments
Ott *et al*. (1989), USA, 1940–78	Deaths identified within a cohort of 29 139 male workers at two chemical manufacturing facilities and a research and development centre; five controls per case selected from cohort and frequency-matched by decade of first employment	Use of formaldehyde in department where subjects worked	*Ever exposed* Non-Hodgkin lymphoma Multiple myeloma Non-lymphocytic leukaemia Lymphocytic leukaemia	 52 (2) 20 (1) 39 (2) 18 (1)	 2.0 1.0 2.6 2.6	Number of controls overall by exposure status and confidence intervals not given; adjustment for age was evaluated but dropped due to substantial change in risk estimates.
Partanen *et al*. (1990), Finland, 1957–80 (updated from Partanen *et al*., 1985)	136 male incident cases* from a cohort of 7307 workers in 35 particle-board, plywood and formaldehyde glue factories and sawmills who entered the factories in 1944–66; three controls per case selected randomly among the same cohort, matched by year of birth, alive at the time of diagnosis of the corresponding case	Plant- and time-specific job–exposure matrices; work history based on factory registers, interviews of factory personnel and questionnaires to study subjects or relatives	All cancers combined* Ever exposed Peak exposure Dustborne formaldehyde Lung Ever exposed Peak exposure Dustborne formaldehyde	136 (20) (7) (14) 118 (18) (7) (12)	 1.40 (0.72–2.74)[e] 0.95 (0.30–3.05)[e] 1.37 (0.66–2.82)[e] 1.25 (0.60–2.60)[e] 1.10 (0.31–3.85)[e] 1.13 (0.51–2.52)[e]	Adjusted for vital status; adjustment for cigarette smoking did not affect the results. *Tongue, mouth, pharynx, nose and nasal sinuses, larynx and lung/trachea (ICD-7 141, 143–8, 160–1, 162,0–1)

CI, confidence interval; ICD, international classification of diseases; inc., incident; NA, not applicable; NR, not reported; SMR, standardized mortality ratio; SPIR, standardized proportionate incidence ratio

[a] The ICD code is only mentioned when the organ site studied is different from that in the other studies.

[b] The authors presented results using either the national population or the local population as the referent. The results presented here are based on the national population.

[c] Data on cancer incidence and mortality were presented. The results in this column are for cancer incidence.

[d] Relative risk of medium- plus high-exposed groups versus unexposed, adjusted for race, smoking and exposure to silica

[e] 90% confidence interval

et al. (1983). For the purposes of this review, the results from these earlier studies were considered to be subsumed by the NCI study. In the earlier follow-up (Blair *et al*., 1986), the NCI study had found an excess of lung cancer in white men in comparison with the national population of the USA, but the excess did not appear to increase with increasing cumulative exposure to formaldehyde. Several investigators performed re-analyses of the results on lung cancer (Robins *et al*., 1988; Sterling & Weinkam, 1988, 1989a,b; Marsh *et al*., 1992a,b, 1994; Sterling & Weinkam 1994, 1995; Callas *et al*., 1996). The re-analyses by Sterling and Weinkam (1988, 1989a,b, 1994, 1995) did suggest a relationship between cumulative exposure and mortality from lung cancer, although their first two reports were found to have errors (Blair & Stewart, 1989; Sterling & Weinkam, 1989b). A positive exposure–response relationship between cumulative exposure to formaldehyde and lung cancer was not suggested in the re-analyses by Robins *et al*. (1988), Marsh *et al*. (1992a,b, 1994) or Callas *et al*. (1996). The results from these re-analyses are superseded by the most recent findings in the NCI cohort, which are described below.

The cohort that was originally followed for vital status through to 1980 was recently updated by Hauptmann *et al*. (2003, 2004) through to 1994. This study included a comprehensive evaluation of historical levels of exposure to formaldehyde and of other potentially confounding exposures (Stewart *et al*., 1986; Blair & Stewart, 1990). Time-dependent estimates were developed for duration of exposure (years), average exposure (parts per million [ppm]), cumulative exposure (ppm–years) and highest peak exposure (ppm) to formaldehyde. Concomitant exposure to particulates that contained formaldehyde was also assessed. Expected numbers of deaths were estimated using the person–years method and age-, race- and sex-specific rates for the general population in the USA; log-linear Poisson regression models were used to analyse the relationship between the various measures of exposure to formaldehyde and cancer mortality. In the analyses, exposures to formaldehyde were lagged by 2 years for lymphatic and haematopoetic neoplasms and by 15 years for solid cancers. Potential confounding by age, calendar time, sex, race and pay category (Poisson regression only) was controlled for in the analyses. In addition, potential confounding was evaluated for duration of exposure to each of 11 other substances (i.e. antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust and benzene) and for duration of work as a chemist or laboratory technician.

Based on comparisons with the national population, mortality from all cancers was lower than expected in the unexposed (376 deaths; standardized mortality ratio [SMR], 0.76; 95% confidence interval [CI], 0.69–0.84) and, but to a lesser extent, in the population exposed to formaldehyde (1723 deaths; SMR, 0.90; 95% CI, 0.86–0.95) (Hauptmann *et al*., 2004). Decreased mortality was observed in both groups for lymphohaematopoietic neoplasms (exposed: 161 deaths; SMR, 0.80; 95% CI, 0.69–0.94; unexposed: 17 deaths; SMR, 0.62; 95% CI, 0.39–1.00) (Hauptmann *et al*., 2003) and solid tumours (exposed: 1580 deaths; SMR, 0.91; 95% CI, 0.87–0.96; unexposed: 341 deaths; SMR, 0.78; 95% CI, 0.70–0.86) (Hauptmann *et al*., 2004).

A statistically significant exposure–response relationship was observed between peak exposure to formaldehyde and all lymphatic and haematopoietic neoplasms ($p_{trend} = 0.002$) in the Poisson regression analysis. (The trend tests presented here and subsequently were based on analyses that were restricted to the exposed workers.) This relationship was largely due to a strong exposure–response relationship for leukaemia ($p_{trend} = 0.004$) and, to a lesser extent, for Hodgkin disease ($p_{trend} = 0.04$). The relationship was stronger for myeloid leukaemia ($p_{trend} = 0.009$) than for the other histological subtypes of leukaemia. The relative risk for the highest category of peak exposure (≥ 4.0 ppm) was 2.46 (29 deaths; 95% CI, 1.31–4.62) for all leukaemia and 3.46 (14 deaths; 95% CI, 1.27–9.43) for myeloid leukaemia. Weaker and statistically non-significant exposure–response relationships were observed with average intensity of exposure for leukaemia ($p_{trend} = 0.24$) and myeloid leukaemia ($p_{trend} = 0.09$). There was little evidence for a relationship between cumulative exposure or duration of exposure and risk for either leukaemia or myeloid leukaemia (Hauptmann *et al*., 2003). [The Working Group noted the contrast between the findings from the person–years analysis, which did not reveal an excess of leukaemia, and the Poisson regression analysis which demonstrated a significant exposure–response relationship between peak exposure and leukaemia. The Working Group also noted that Poisson regression, which uses internal analysis, is less prone to confounding by socioeconomic status and other factors.]

Based on eight cases, a significant excess mortality from nasopharyngeal cancer was observed among formaldehyde-exposed workers in comparison with the national population (SMR, 2.10; 95% CI, 1.05–4.21). A highly statistically significant ($p_{trend} < 0.001$) exposure–response relationship was observed between peak exposure to formaldehyde and risk for nasopharyngeal cancer in the Poisson regression analysis. All exposed cases were in the highest category of peak exposure, and the relative risk was 1.83. This analysis excluded one case which, according to cancer registry data, had been misclassified as nasopharyngeal cancer. Weaker exposure–response relationships were observed between nasopharyngeal cancer and average, cumulative and duration of exposure ($p_{trend} = 0.07$, 0.03 and 0.15, respectively).

Three cases of cancer of the nose and nasal cavity were observed in the exposed group, which were slightly in excess of the expected (SMR, 1.19; 95% CI, 0.38–3.68). A total of 49 deaths from cancer of the buccal cavity occurred among exposed subjects, which was as expected with respect to mortality in the national population in the USA. Relative risks for the highest exposure categories of average intensity, peak and cumulative exposure were elevated (relative risks, 1.89, 1.83 and 1.74, respectively), but trends were not significant or only of borderline significance ($p_{trend} = 0.50$, 0.07 and 0.37, respectively). No consistent positive association was observed for cancer of the larynx for any of the exposure metrics and the number of deaths (23) was as expected with respect to mortality in the national population. Combination of cancers of the nasopharynx, mouth, salivary gland, nasal cavity and larynx (upper respiratory tract) resulted in increasing relative risks with increasing average intensity (a twofold significantly elevated relative risk in the highest exposure category compared with the low exposure category; $p_{trend} = 0.12$ among the

exposed only) and with peak exposure, but not with cumulative exposure or duration of exposure. Mortality from lung cancer was slightly lower than expected among the formaldehyde-exposed group (641 deaths; SMR, 0.97; 95% CI, 0.90–1.05). No evidence of a positive relationship between mortality from lung cancer and any of the exposure measures was observed. In fact, mortality from lung cancer appeared to decrease with duration of exposure (p_{trend} = 0.03) and with cumulative exposure (p_{trend} = 0.14) to formaldehyde (Hauptmann *et al*., 2004). [The Working Group noted that the strengths of this study included its relatively large number of workers, long period of follow-up and the high quality of the exposure assessment.]

Marsh and Youk (2004) re-analysed the updated data from the NCI cohort (Hauptmann *et al*., 2003). In addition to reproducing the results presented by Hauptmann *et al*. (2003), three further analyses were performed in relation to risk for mortality from leukaemia. Using the cut-off points for exposure categories defined in Hauptmann *et al*. (2003), exposure category-specific SMRs, based on mortality rates for the national population, increased with increasing peak and average intensity of exposure for all leukaemias combined and for myeloid leukaemia; the SMRs for myeloid leukaemia ranged from 0.43 and 0.71 in the lowest exposed category of peak and average intensity, respectively, to 1.42 and 1.45 in the highest category of these metrics. Findings were similar when regional mortality rates were used. The use of alternative cut-off points for average intensity of exposure, in order to achieve similar numbers of deaths from all leukaemias combined in each exposed category, resulted in relative risk estimates similar to those observed by Hauptmann *et al*. (2003). Analyses of duration of time worked in the highest peak category did not generally indicate higher risks among those who had experienced high peaks for a longer time.

Marsh *et al.* (1996) studied one plant (in Wallingford, CT) that was also included in the NCI cohort study (Hauptmann *et al*., 2003). They enumerated the cohort independently and conducted their own exposure assessment, but their general approach was similar. More recently, Marsh *et al*. (2002) analysed mortality through to 1998 and exposure through to 1995 for the 7328 workers (82% white men) who were employed during 1941–84. Overall, vital status was determined for 98% of the cohort and cause of death for 95% of 2872 deaths. The majority of subjects (54%) had worked for less than 1 year at the plant. More than 1300 workers (18%) had been employed for more than 10 years. The updated exposure assessment used the same methods as the earlier study (Marsh *et al*., 1996), and included an examination of data on sporadic measurements from the period 1965–87 and the use of protective equipment. The analysis evaluated malignancies of the upper and lower respiratory tract. Compared with local county mortality rates, SMRs were elevated for cancers of the nasopharynx (seven deaths; SMR, 5.00; 95% CI, 2.01–10.30), all pharynx (22 deaths; SMR, 2.23; 95% CI, 1.40–3.38), all buccal cavity and pharynx (31 deaths; SMR, 1.52; 95% CI, 1.03–2.15), nasal sinus (three deaths; SMR, 3.06; 95% CI, 0.63–8.93), larynx (13 deaths; SMR, 1.59; 95% CI, 0.84–2.71) and lung (262 deaths; SMR, 1.21; 95% CI, 1.06–1.36). SMRs for nasopharyngeal cancer based on local county rates increased monotonically with cumulative exposure to formaldehyde (no death; SMR, 0; 95% CI, 0–15.41 for unexposed; one death; SMR, 3.97; 95% CI, 0.10–22.10 for

> 0–< 0.004 ppm–years; three deaths; SMR, 5.89; 95% CI, 1.22–17.22 for 0.004–0.219 ppm–years; and three deaths; SMR, 7.51; 95% CI, 1.55–21.93 for ≥ 0.22 ppm–years). In a case–control study of pharyngeal cancer nested in the cohort, deaths from cancer of the oropharynx (five), nasopharynx (seven), hypopharynx (three) and unspecified pharynx (seven) were compared with 67 controls matched on race, sex, age and year of birth (within 2 years) with respect to occupational exposure to formaldehyde, and additional information on occupational and non-occupational exposures was obtained by telephone interviews, partly with next of kin [proportion of next-of-kin interviews not reported]. Based on exact conditional logistic regression, relative risks for the combined group of pharyngeal cancers, adjusted for tobacco smoking and years of employment in the factory, increased with increasing duration of exposure to formaldehyde and particularly with increasing duration of exposure to levels of formaldehyde > 0.2 ppm, but not with average intensity of exposure or cumulative exposure. Separate analyses for nasopharyngeal cancer were not presented due to small numbers.

[The earliest year of entry into this cohort was earlier than that in the NCI cohort, the cohort was enumerated independently from the NCI cohort and exposures were assessed separately using measurements and other information provided by the company but not those made by an industrial hygienist for the NCI study. The exposure estimates were generally about 10 times lower than those reported in Hauptmann *et al*. (2003, 2004). Marsh *et al.* (2002) suggested that this difference was because Hauptmann *et al*. (2003, 2004) used data from several plants to estimate exposure in each plant, whereas Marsh *et al*. (2002) based the assessment only on the plant under study. However, this suggestion is incorrect (Blair & Stewart, 1990). All data considered in the exposure estimates in a given plant in the Hauptmann *et al*. (2003, 2004) study were only from that plant.]

(*b*) *Garment workers: The National Institute for Occupational Safety and Health (NIOSH) Cohort*

Stayner *et al*. (1985, 1988) at NIOSH, USA, conducted a proportionate mortality study and a retrospective cohort study of mortality of garment workers exposed to formaldehyde. The cohort study included approximately 11 000 predominantly female (82%) workers from three facilities that manufactured shirts from fabrics that were treated with formaldehyde resins to impart permanent press characteristics. Workers who were included in the cohort study had worked for at least 3 months after the time that formaldehyde-treated fabrics were introduced into the process, which was 1959 in two of the facilities and 1955 in the third. Time-weighted 8-h geometric mean exposure levels in different departments in the three plants were found to range from 0.09 to 0.20 ppm at the time the study was initiated. Continuous air monitoring suggested no substantial peaks. Historical exposure levels were not available; however, exposure levels are believed to have been substantially higher in the earlier years of the study because the methods of treatment with formaldehyde resin have been steadily improved over time to reduce the amount of free formaldehyde in the fabrics. Exposure measurements reported at other facilities before 1970 ranged from 0.3 to 10 ppm (Stayner *et al*., 1988) (see Section 1.3.2(*f*)). The investigators reported

finding no evidence that other potentially carcinogenic exposures were present at the study facilities. Follow-up of the cohort for vital status, which was originally through to 1982, was recently extended to 1998 (Pinkerton *et al*., 2004). Life-table methods that applied national and state rates were used. The results from analyses were similar for the cancer sites of a-priori interest when both national and state rates were used. Life-table analyses that used a multiple cause-of-death approach (Steenland *et al*., 1992) were also conducted. Poisson regression models were used to analyse the relationship between duration of exposure and risk for cancer.

Mortality from all cancers (608 deaths; SMR, 0.89; 95% CI, 0.82–0.97) was shown to be significantly lower than that expected based upon comparisons with the national population. The observed numbers of cases of respiratory cancer (152 deaths; SMR, 0.98; 95% CI, 0.83–1.14) and of cancer of the brain and central nervous system (19 deaths; SMR, 1.09; 95% CI, 0.66–1.71) were found to be close to expectation. Mortality from buccal cancer, which was found to be elevated (four deaths; SMR, 3.53; 95% CI, 0.96–9.02) in the original study (Stayner *et al*., 1988), was only slightly elevated (four deaths; SMR, 1.33; 95% CI, 0.36–3.41) in the updated study (Pinkerton *et al*., 2004). No cases of nasopharyngeal (0.96 expected) or nasal (0.16 expected) cancer were observed. A slight excess of mortality from leukaemia (24 deaths; SMR, 1.09; 95% CI, 0.70–1.62) was observed, which was a certain degree higher for myeloid leukaemia (15 deaths; SMR, 1.44; 95% CI, 0.80–2.37). The excess mortality from myeloid leukaemia was greatest among workers who were first exposed during the earliest years of the study (before 1963) when exposures to formaldehyde were presumably higher (11 deaths; SMR, 1.61 [95% CI, 0.80–2.88]), among workers with 10 or more years of exposure (eight deaths; SMR, 2.19 [95% CI, 0.95–4.32]) and among workers with 20 or more years since first exposure (13 deaths; SMR, 1.91 [95% CI, 1.02–3.27]). A greater than twofold excess in mortality from myeloid leukaemia was observed among workers with both more than 10 years of exposure and 20 or more years since first exposure to formaldehyde (seven deaths; SMR, 2.43; 95% CI, 0.98–5.01). In contrast to leukaemia, the risk for respiratory cancer decreased with duration of employment and time since first exposure. [The Working Group noted that strengths of this study were the apparent absence of other potentially confounding carcinogenic exposures in the workplace and the long follow-up.]

(*c*) *Chemical industry workers*

Acheson *et al*. (1984a) assembled a large cohort of workers from six chemical facilities in the United Kingdom, and Coggon *et al*. (2003) reported the findings from an update of the vital status of the cohort to 2000. The cohort included approximately 14 000 workers who had been employed after 1937 and before 1965, at a time when formaldehyde was used or produced, and personnel records at the plants were believed to be complete. Jobs were classified into one of five categories of exposure to formaldehyde, i.e. background, low, moderate, high or unknown. No exposure measurements were available before 1970. Based on the later measurements and workers' recall of irritant symptoms, it was estimated that the TWA exposure concentrations corresponded to: background, < 0.1 ppm; low

exposure, 0.1–0.5 ppm; moderate exposure, 0.6–2.0 ppm; and high exposure, > 2.0 ppm. Person–years and Poisson regression analyses were conducted. An adjustment for local geographical variations in mortality was made in some analyses, which entailed multiplying the expected deaths by SMRs for the area in which the plant was located.

Mortality was elevated to some extent for all cancers (1511 deaths; SMR, 1.10; 95% CI, 1.04–1.16), and this was more pronounced among workers who had ever worked in a job that was classified as entailing high exposure to formaldehyde (621 deaths; SMR, 1.31; 95% CI, 1.21–1.42). This excess mortality was largely attributable to a statistically significant excess of mortality from cancers of the stomach (150 deaths; SMR, 1.31; 95% CI, 1.11–1.54) and lung (594 deaths; SMR, 1.22; 95% CI, 1.12–1.32). The excess of mortality from lung cancer was greatest among men who had high exposure (272 deaths; SMR, 1.58; 95% CI, 1.40–1.78). The excess incidence of lung cancer among the highly exposed decreased with adjustment for local rates, although it remained statistically significant (SMR, 1.28; 95% CI, 1.13–1.44). Mortality from lung cancer was higher among workers who were highly exposed before 1965 when levels of exposure to formaldehyde would be expected to be higher (243 deaths; SMR, 1.61; 95% CI, 1.41–1.82). Mortality from lung cancer demonstrated a non-significant inverse relationship with the number of years worked in high-exposure jobs ($p_{trend} = 0.13$) and showed no trend with time since first employment in a job that entailed high exposure ($p_{trend} = 0.93$).

A statistically non-significant excess mortality from pharyngeal cancer was observed (15 deaths; SMR, 1.55; 95% CI, 0.87–2.56), which was to some degree greater among highly exposed workers (six deaths; SMR, 1.91; 95% CI, 0.70–4.17). One death from nasopharyngeal cancer was observed where 2.0 were expected; two cases of sinonasal cancer were observed where 2.3 were expected, but neither individual was highly exposed. A review of tumour registry data identified two additional cases of sinonasal cancer, both in individuals who were highly exposed, but it was not possible to determine the expected number of incident cases because of limitations in the tumour registry system. Slight excess mortality, based on a small number of cases, was observed in men who had had high exposure for cancers of the tongue (three deaths; SMR, 1.91; 95% CI, 0.39–5.58) and mouth (two deaths; SMR, 1.32; 95% CI, 0.16–4.75). Mortality from cancer of the brain and central nervous system and from leukaemia was lower than expected among the entire cohort (SMRs, 0.85 and 0.91, respectively) and among the high-exposure group (SMRs, 0.63 and 0.71, respectively). [The Working Group noted that this study probably included a substantial number of workers who had relatively high exposures: 4000 workers had ever worked in jobs that were classified as entailing exposures greater than 2 ppm. The Working Group also noted the long follow-up. However, there was a lack of exposure measurements before 1970, and this may have led to some misclassification of exposures.]

Bond *et al*. (1986) conducted a case–control study in a cohort of 19 608 men who had been employed for 1 year or longer at a large chemical production facility in Texas, USA, between 1940 and 1980, which included all 308 workers who had died from lung cancer and 588 controls chosen at random from among men in the same cohort. Two series of controls, individually matched to cases on race, year of birth (± 5 years) and year of first employment,

were selected: one among men who were still alive when the matched subjects died of lung cancer, and one among men who had died ≤ 5 years after the matched subjects. Exposures (ever or never) to 171 chemical and physical agents, including formaldehyde, were assessed by an industrial hygienist on the basis of a review of documentation on the subject's employment history at the facility and industrial hygiene records; six exposures, not including formaldehyde, were assessed in greater detail. Only nine men who had lung cancer (3%) were judged ever to have been exposed to formaldehyde, and a negative association was seen between this exposure and mortality from lung cancer (not adjusted for other exposure variables), with an odds ratio of 0.62 (95% CI, 0.29–1.34); incorporation into the analysis of a 15-year minimal latency gave an odds ratio of 0.31 (95% CI, 0.11–0.86).

(*d*) *Fibreglass workers*

Marsh *et al*. (2001) updated and expanded an earlier cohort study of mortality of workers who had been employed at any of 10 fibreglass manufacturing plants in the USA that had been previously studied by Enterline *et al*. (1987). The study included over 32 000 workers who had been employed for at least 1 year between 1945 and 1978 in one of the 10 study facilities. The cohort was expanded to include women, workers who had been employed after the original 1963 end date and workers from additional worksites; the vital status of the cohort was established until the end of 1992. In addition to expanding and updating the cohort, the study introduced new information on potential exposures to several known and potential carcinogens other than fibreglass (asbestos, arsenic, asphalt, epoxy, polycyclic aromatic hydrocarbons, phenolics, silica, styrene and urea), including formaldehyde. Exposure to formaldehyde was the most common exposure [22% of the person–years] after respirable fibres [28% of the person–years] in the study. The median exposure to formaldehyde for the cohort was 0.066 ppm and ranged from 0.03 to 0.13 ppm in the different plants. Person–years methods were used to analyse the mortality of the cohort in comparison with both national population and local death rates. Overall cancer mortality was slightly lower than expected in comparison with both national (2243 deaths; SMR_{US}, 0.98; 95% CI, 0.94–1.02) and local rates (SMR_{local}, 0.94; 95% CI, 0.90–0.98). A statistically significant excess of mortality from respiratory cancer was observed for the whole cohort when national rates were used (874 deaths; SMR_{US}, 1.16; 95% CI, 1.08–1.24), which was weaker and of borderline significance ($p = 0.05$) when local rates were used as a referent (SMR_{local}, 1.06; 95% CI, 1.00–1.14). This excess was largely attributable to an excess mortality from cancers of the trachea, bronchus and lung (838 deaths; SMR_{US}, 1.17; 95% CI, 1.09–1.25; SMR_{local}, 1.07; 95% CI, 1.00–1.14).

The association of respiratory cancer with specific exposures was examined in a nested case–control study in which the cases were male members of the cohort who had died from respiratory tumours during 1970–92 (Marsh *et al*., 2001; Stone *et al*., 2001; Youk *et al*., 2001). Each case was randomly matched with a control who had the same date of birth to within 1 year, who was at risk during 1970–92 and who was alive and at risk at the age when the case died. Smoking histories were ascertained through telephone interviews with the subjects themselves or a proxy. Complete data were available for 502 of 713 matched pairs,

and unmatched cases and controls were combined with the matched set nearest in age (at the time of death of the case). Thus, the analysis was based on 631 cases and 570 controls. Of the cases, 96% had been diagnosed with carcinoma of the trachea, bronchus or lung. Individual exposures in the matched set to formaldehyde, respirable fibres and silica before the age at which the case died were estimated from industrial hygiene data using a job–exposure matrix that took into account time period, plant and department. Analysis was performed using conditional logistic regression with adjustment for smoking. In a first analysis (Youk *et al*., 2001), nine different configurations of time lag and window of exposure were examined for average intensity of exposure and cumulative exposure. When exposure was not weighted in relation to the time of case death, the odds ratio for ever exposure to formaldehyde was 1.61 (95% CI, 1.02–2.56) and a similar risk estimate was obtained when a 5-year lag was applied (odds ratio, 1.62; 95% CI, 1.04–2.54). Otherwise, however, the risk estimates for ever exposure were lower, and there were no clear trends with cumulative or average intensity of exposure (which for most subjects were < 2 ppm–years and < 0.14 ppm, respectively).

This analysis was then extended by application of a conditional logistic regression model that adjusted for exposure to respirable fibres as well as tobacco smoking, and used piecewise linear functions (linear splines) with knots at the deciles of the distributions of exposure in the cases. Cumulative exposure to formaldehyde was not significantly associated with increased risk in any of the models examined, but there was a suggestion of increased risk (of borderline statistical significance) with average intensity of exposure at the upper end of the range (Stone *et al*., 2001). [The Working Group noted that exposures to formaldehyde in this cohort of fibreglass workers appeared to be lower than those in the studies of industrial and textile workers reviewed earlier in this section.]

Chiazze *et al*. (1997) conducted a retrospective cohort study of mortality of 4631 workers at a fibreglass manufacturing plant in Anderson, SC, USA. This included a nested case–control study for lung cancer (47 cases) which collected information from interviews on tobacco smoking, socioeconomic factors and a historical reconstruction of several exposures at the plant, including formaldehyde. Controls for this analysis were individuals in the cohort who had not died from lung cancer, or from suicide or homicide (for ethical reasons). The controls were matched to the cases based on year of birth (± 2 years) and survival to the end of follow-up or death (± 2 years). Person–years methods of analysis were used to analyse the cohort study, and conditional logistic regression was used to analyse the case–control study. Cumulative exposure to formaldehyde was the only exposure in the case–control analysis to exhibit a positive relationship with risk for lung cancer. Among smokers only, lung cancer was elevated in the highest (> 1000 ppm–days; odds ratio, 2.07; 95% CI, 0.17–25.5) and next to highest (100–999 ppm–days; odds ratio, 1.72; 95% CI, 0.57–5.23) cumulative exposure groups, but these excesses were based on a small number of cases and were statistically non-significant.

(*e*) *Woodworkers*

Partanen *et al*. (1985) conducted a case–control study in a cohort of 3805 male production workers who had been employed for at least 1 year in one of three particle-board factories, seven plywood factories, eight sawmills and one formaldehyde glue factory between 1944 and 1966. Of these, 57 men were declared to the Finnish Cancer Registry as having cancer of the respiratory tract (including at least 51 cases of lung cancer), oral cavity or pharynx in 1957–80. Three controls were selected at random from the same cohort and were individually matched to the case by year of birth. Plant- and time-specific job–exposure matrices were constructed for 12 chemicals, including formaldehyde (Kauppinen & Partanen, 1988), and were combined with the work histories of the subjects to yield several indicators of exposure; supplementary information on tobacco smoking was collected for 68% of cases and 76% of controls, by means of a postal questionnaire, from study subjects or their relatives. A slight, non-significant increase in risk for all cancers combined was seen among workers who had had any exposure to at least 0.1 ppm (0.12 mg/m^3) formaldehyde in contrast to workers who had had no exposure to formaldehyde, which yielded an odds ratio of 1.44 [95% CI, 0.6–3.5]; an odds ratio of 1.27 [95% CI, 0.5–3.5] was obtained when a minimal latency of 10 years before diagnosis was assumed. No significant association was found with other indicators of exposure to formaldehyde (mean level of and cumulative exposure, repeated peak exposures and 'formaldehyde in wood dust'). Adjustment for cigarette smoking did not change the overall results.

In an expansion of the study to include a total of 35 Finnish factories and 7307 woodworkers who had been employed during 1944–65, Partanen *et al.* (1990) identified 136 newly diagnosed cases of cancer of the respiratory tract (118 lung cancers, 12 laryngeal cancers and one sinonasal cancer), oral cavity (four cases) and pharynx (one case) from the files of the Finnish Cancer Registry for 1957–82. The additional factories were mainly involved in construction carpentry and furniture manufacture. Three controls were provided for each new cancer case, and exposure to formaldehyde and 11 other occupational agents was assessed by the same methods as those described in the initial study (Partanen *et al*., 1985; Kauppinen & Partanen, 1988). Of 20 cases who had had any exposure to formaldehyde (odds ratio, 1.4 [95% CI, 0.6–3.1]), 18 were cancers of the lung (odds ratio, 1.3 [95% CI, 0.5–3.0]) and two were cancers at other sites (odds ratio, 2.4 [95% CI, 0.3–18]). Adjustment for tobacco smoking reduced the odds ratios to 1.1 for all cancers combined and to 0.7 for lung cancer separately and rendered the odds ratio for cancers at other sites unassessable. The unadjusted odds ratios for all cancer cases were 1.5 [95% CI, 0.7–3.6] for an estimated mean level of formaldehyde of 0.1–1 ppm [0.12–1.23 mg/m^3] and 1.0 [95% CI, 0.1–8.2] for > 1 ppm, in comparison with no exposure. Other indicators of exposure to formaldehyde, which included an estimate of cumulative exposure and duration of exposure to peak levels > 2 ppm [2.46 mg/m^3], showed similarly inconsistent dose–response relationships, i.e. the lowest risks in the highest exposure categories. Allowance for a minimal latency of 10 years further reduced the risk estimates for the subgroups who had had the presumed highest exposures to odds ratios generally below 1.0.

[The Working Group noted that there were too few cancers at sites other than the lung to allow a meaningful analysis; consequently, this was essentially a study of lung cancer.]

Stellman *et al*. (1998) studied mortality among workers exposed to wood dust in the American Cancer Society's Cancer Prevention Study. From the original cohort of over half a million men, sufficient data were available for 362 823 who were included in the study. Of these, 45 399 reported either employment in a wood-related occupation or exposure to wood dust. As part of the investigation, data were also collected on self-reported exposure to formaldehyde, and incidence density ratios according to exposure were derived for death from each of several cancers during 6 years of follow-up. This analysis adjusted for age and for smoking habits. In comparison with men who had never been employed in a wood-working occupation and who did not report regular exposure to wood dust, those who had been wood-workers and who reported exposure to formaldehyde had elevated mortality from lung cancer (seven deaths; relative risk, 2.63; 95% CI, 1.25–5.51) and leukaemia (two deaths; relative risk, 5.79; 95% CI, 1.44–23.25). In men exposed to formaldehyde who had not worked in wood-related occupations, the corresponding risk estimates for lung cancer and leukaemia were 0.93 (95% CI, 0.73–1.18) based on 104 deaths and 0.96 (95% CI, 0.54–1.71) based on 12 deaths, respectively. Results for sinonasal and nasopharyngeal cancers were not reported. [The Working Group noted that this study should be given little weight in the evaluation because of the small number of formaldehyde-exposed workers and the limitations in the subjective exposure assessment for formaldehyde.]

(*f*) *Iron foundry workers*

Andjelkovich *et al*. (1990) studied a cohort of 8147 men who had been employed for 6 months or longer at an iron foundry in the USA. In a nested case–control study (Andjelkovich *et al*., 1994), the case group comprised all members of the cohort who died from primary lung cancer during 1950–89 and were ascertained from various sources. They included 200 men in whom lung cancer was certified as the underlying cause of death, 13 in whom it was a contributory cause and seven who died from carcinomatosis with a primary lung tumour that was confirmed from hospital records or through the local cancer registry. Ten controls were selected for each case by incidence density sampling; they were of the same race and had attained at least the same age as their matched case. Just over half of the controls (52.2%) were still alive at the end of the follow-up period. In total, 50.9% of cases and controls were white. Exposure to silica (high, medium or low) and formaldehyde (high, medium, low or none) was classified by means of a job–exposure matrix based on industrial hygiene data, walk-through surveys, job description, knowledge of the tasks performed in a job and reports in the scientific literature. [In the analysis reported, exposure to formaldehyde was dichotomized as some versus none; no data were provided on the probable levels of airborne concentrations.] Data on tobacco smoking (yes or no) were available for 75.5% of cases and 68.6% of a random subset of two controls per case and were obtained from various sources including the subject himself, his next of kin, plant medical records, hospital medical records and death certificates. Analysis was performed using conditional logistic regression with and without the inclusion of lag

periods. Overall, 25% each of cases and controls were classed as having been exposed to formaldehyde. After adjustment for tobacco smoking, birth cohort (< 1915 versus ≥ 1915) and cumulative exposure to silica (partitioned to four levels at the quartiles), the odds ratio for unlagged exposure to formaldehyde was 1.31 (95% CI, 0.83–2.07); with the incorporation of increasing lag periods, this risk estimate decreased progressively to 0.84 (95% CI, 0.44–1.60) for a 20-year lag. Risk estimates were little affected by the inclusion of tobacco smoking in the regression models, and there was no evidence of an interaction between formaldehyde and smoking. [The Working Group noted that data to support this statement were not shown.]

The relation of formaldehyde to risk for cancer was examined further in a subset of 3929 men from the full cohort who had worked in jobs that entailed potential exposure to formaldehyde for at least 6 months between January 1960 and May 1987 (Andjelkovich *et al.*, 1995). The mortality of this group was compared with that of the national population (by the person–years method), with that of an internal reference population of 2032 cohort members who had worked during the same period in jobs that did not entail exposure to formaldehyde and with that of an occupational referent population assembled by the NCI and NIOSH, using Poisson regression analysis. Cumulative exposure to formaldehyde and silica was estimated for each worker based on detailed occupational histories and evaluation of job-specific exposure levels by an occupational hygienist. Smoking status was ascertained for 65.4% of the exposed subcohort and 55.1% of the unexposed control subcohort. In the follow-up through to 1989 and in comparison with national death rates, mortality from all cancers was close to that expected in both the formaldehyde-exposed (127 deaths; SMR, 0.99; 95% CI, 0.82–1.17) and unexposed (95 deaths; SMR, 0.97; 95% CI, 0.79–1.19) populations. In both the exposed and unexposed subcohorts, a statistically non-significant excess of mortality from cancers of the buccal cavity and pharynx (exposed: six deaths; SMR, 1.31; 95% CI, 0.48–2.86; unexposed: five deaths; SMR, 1.69; 95% CI, 0.54–3.95) and lung cancer (exposed: 51 deaths; SMR, 1.20; 95% CI, 0.89–1.58; unexposed: 38 deaths; SMR, 1.19; 95% CI, 0.84–1.63) was observed. Mortality from cancers of the lung, buccal cavity and pharynx was not found to increase with cumulative exposure in the Poisson regression analysis. Mortality from laryngeal cancer (two deaths; SMR, 0.98; 95% CI, 0.11–3.53), cancer of the brain and central nervous system (two deaths; SMR, 0.62; 95% CI, 0.07–2.23) and leukaemia (two deaths; SMR, 0.43; 95% CI, 0.05–1.57) was lower than expected among the exposed.

(*g*) *Other chemical workers and plastics manufacturers*

A study of mortality among workers at a formaldehyde resin plant in Italy (Bertazzi *et al*., 1986) included 1332 male workers who had ever been employed for at least 30 days between the launch of the plant in 1959 and 1980. Follow-up for vital status was extended from 1980 to 1986 in a second study (Bertazzi *et al*., 1989). Work histories of past employees were reconstructed from interviews with retired workers, current workers and foremen. Actual or reconstructed work histories were available for all but 16.5% of the cohort. Job mobility was low, and 79% of the workers had held a single job throughout their

career. On the basis of their work histories, workers were placed into one of three categories: exposed to formaldehyde, exposed to compounds other than formaldehyde and exposure unknown. Individual exposures could not be estimated, but the mean concentrations in fixed area samples that were taken between 1974 and 1979 were 0.2–3.8 mg/m^3 [0.2–3.1 ppm]. SMRs were calculated using the person–years methods to estimate expected numbers based on national and local mortality rates, and were adjusted for age and calendar time. A deficit of lung cancer was observed among workers who had been exposed to formaldehyde; six cases of lung cancer were observed and 8.7 were expected. Excess mortality from lymphatic and haematopoietic neoplasms was observed among formaldehyde-exposed workers based on only three deaths (SMR, 1.73 [95% CI, 0.36–5.06]). During the first follow-up (Bertazzi *et al.*, 1986), no nasal cancer was recorded (0.03 expected).

Ott *et al*. (1989) evaluated data from a nested case–control study within a cohort of 29 139 men who had been employed in two chemical manufacturing facilities and a research and development centre. Cases were subjects who had died between 1940 and 1978 from non-Hodgkin lymphoma (52 cases), multiple myeloma (20 cases), non-lymphocytic leukaemia (39 cases) and lymphocytic leukaemia (18 cases); information on death certificates was used to determine cause of death. Five controls per case were selected from the total employee cohort and were frequency-matched to cases by decade of first employment and duration of survival after first employment. Potential exposure to several chemicals, including formaldehyde, was assessed based on use of the chemical in the work area or in an activity in which the subject was involved at a specific time. Because adjustment for age did not substantially change the risk estimates, crude odds ratios were presented. Odds ratios for ever versus never exposed to formaldehyde for non-Hodgkin lymphoma (two exposed cases), multiple myeloma (one exposed case), non-lymphocytic (two exposed cases) and lymphocytic (one exposed case) leukaemia were 2.0, 1.0, 2.6 and 2.6, respectively. [The Working Group noted that confidence intervals were not provided and could not be calculated because the number of exposed controls was not given.]

Dell and Teta (1995) conducted a retrospective cohort study of mortality of 5932 male employees at a plastics manufacturing and research and development facility in Bound Brook, NJ, USA. Workers who were included in the cohort had worked for at least 7 months between 1946 and 1967 at the facility where they had been exposed to a number of chemicals, including asbestos, polyvinyl chloride and formaldehyde. The cohort was followed for vital status through to 1988. Only 111 of the cohort members had held jobs that involved potential exposure to formaldehyde. Person–years methods were applied in which national and state mortality rates were used as the referent. The analysis was stratified by whether workers were paid hourly or were salaried, by duration of employment with lag intervals of 0, 10 and 15 years and by time since first employment. Mortality for all cancers was close to expected (using national rates) among hourly workers (334 deaths; SMR, 1.02; 95% CI, 0.92–1.14). Excess mortality was observed among hourly workers for cancers of the pancreas (25 deaths; SMR, 1.46; 95% CI, 0.95–2.16), lung (124 deaths; SMR, 1.10; 95% CI, 0.92–1.31) and other parts of the respiratory system (five deaths; SMR, 3.73; 95% CI, 1.21–8.70). The excess mortality from cancers of other parts of the respiratory system was

entirely due to an excess mortality from pleural mesothelioma, which was most probably attributable to exposure to asbestos. An excess of mortality from lung cancer (4 observed, 1.1 expected) was noted among 57 workers who had been exposed to formaldehyde in the hexamethylenetetramine process. No cases of nasal or nasopharyngeal cancer were observed. [The Working Group and the authors noted that, because of its small size, this study was relatively uninformative with regard to formaldehyde.]

(*h*) *Abrasives industry*

Cancer mortality and incidence among workers in the abrasives industry in Sweden was evaluated by Edling *et al*. (1987a) in plants that manufactured grinding wheels and employed abrasives bound with formaldehyde resins. The levels of formaldehyde were reported to be 0.1–1.0 mg/m^3. A cohort of 911 workers (211 women in administration and production and 700 men, of whom 521 were blue-collar workers) who had been employed for at least 5 years between 1955 and 1983 was followed for mortality through to 1983 and for cancer incidence through to 1981, yielding 79 deaths and 24 incident cancers. Deaths and morbidity that occurred at the age of 75 years or older were excluded because of concerns about diagnostic validity. Person–years methods were used to generate expected numbers based on rates for the general population, stratified for age, calendar year and sex. No significant excesses of mortality or morbidity were seen among male blue-collar workers, administrative personnel or among women. All cancer mortality (17 deaths; SMR, 0.93 [95% CI, 0.54–1.49]) and incidence (24 cases; standardized incidence ratio (SIR), 0.84 [95% CI, 0.54–1.25]) were slightly lower than expected. Lung cancer incidence was lower than expected (two cases; SIR, 0.57 [95% CI, 0.07–2.06]). No cases of leukaemia, or nasal or buccal cancer were observed. One case of nasopharyngeal cancer and one of cancer of the nervous system were reported.

(*i*) *Mixed industrial exposures*

Hansen and Olsen (1995) conducted a standardized proportionate cancer incidence study of workers in Denmark. Individuals who were born between 1897 and 1964 and had been diagnosed with cancer between 1970 and 1984 were identified from the Danish Cancer Registry. Employment histories were established through linkage to the Supplementary Pension Fund, which began in 1964. A total of 91 182 men who had cancer, who met the study criteria and who had records in the Supplementary Pension Fund were identified. The companies in which individuals worked were identified by the Fund and the use of formaldehyde by these companies was retrieved from the Danish Product Register. Cancer patients whose longest work experience after 1964 was at one of the companies that used formaldehyde and was at least 10 years before the date of diagnosis were regarded as being potentially exposed to formaldehyde. White-collar workers were assumed to have low exposure, blue-collar workers were assumed to have high exposure and workers with a missing job title were assumed to have unknown exposure to formaldehyde. [The Working Group noted that this may not be a very reliable means of classifying workers with regard to exposure.] Blue-collar cases who had worked in wood and

furniture companies and carpentry enterprises or had worked as a cabinet maker, joiner or carpenter were classified as having potential exposure to wood dust. A parallel study included 73 423 women with incident cancer and records of the Supplementary Pension Fund (Hansen & Olsen, 1996). Standardized proportionate incidence of cancer ratios (SPICR) were estimated using age-, sex- and calender period-specific proportions among all employees in Denmark as the reference. A statistically significant excess of mortality from cancer of the nasal cavity and paranasal sinuses (SPICR, 2.3; 95% CI, 1.3–4.0) was observed among male workers who were potentially exposed to formaldehyde, based on 13 cases. Among women, the SPICR was 2.4 (95% CI, 0.6–6.0), based on four cases. The excess mortality from nasal cancer observed in men was more pronounced among blue-collar workers who were exposed to formaldehyde only (nine cases; SPICR, 3.0; 95% CI, 1.4–5.7) or who had co-exposure to formaldehyde and wood dust (two cases; SPICR, 5.0; 95% CI, 0.5–13.4). The observed number of cases was close to expected for cancers of the buccal cavity and pharynx (23 cases; SPICR, 1.1; 95% CI, 0.7–1.7), nasopharynx (four cases; SPICR, 1.3; 95% CI, 0.3–3.2), brain and nervous system (54 cases; SPICR, 1.1; 95% CI, 0.9–1.5), larynx (32 cases; SPICR, 0.9; 95% CI, 0.6–1.2) and lung (410 cases; SPICR, 1.0; 95% CI, 0.9–1.1) and for leukaemia (39 cases; SPICR, 0.8; 95% CI, 0.6–1.6). No cancer site showed risk estimates that were significantly different from unity among women.

2.1.2 *Cohort and proportionate mortality studies of professional groups*

Pathologists, anatomists, embalmers and funeral directors have been studied because they use formaldehyde as a tissue preservative. Investigations of these occupations have several methodological problems. The use of national statistics to generate expected numbers may bias estimates of relative risks downwards for some cancers and upwards for others because some of these groups have a higher socioeconomic level than the general population; only a few investigations included a special referent population that was designed to diminish potential socioeconomic confounding. None of these studies presented the data necessary to adjust for tobacco use. Since anatomists and pathologists in the USA generally smoke less than the general population (Sterling & Weinkam, 1976), estimates of relative risks for smoking-related cancers will be artificially low. Without adjustments, the biases introduced by socioeconomic factors and tobacco smoking may be strong enough to preclude any possibility of detecting an excess occurrence of tobacco-related cancers. This may be less of a problem for embalmers, however, because their smoking habits may not differ from those of the general population (Sterling & Weinkam, 1976). In no study were risk estimates developed by level of exposure, and in only a few studies were risks evaluated by duration of exposure. When exposure estimates are not presented in the following text, they were not provided in the original study. Non-differential error in exposure assessment, which occurs when the measures of exposure are about equally inaccurate for study subjects who do and do not have the cancer of interest, diminishes the chances of uncovering an underlying association, as it biases estimates of

the relative risk towards the null. Key study features and findings from the cohort and proportionate mortality studies of professional groups are summarized in Table 17 by subgroups of profession.

(*a*) *Cohort of British pathologists and medical technicians*

Harrington and Shannon (1975) evaluated the mortality of pathologists and medical laboratory technicians in Great Britain in 1975. A total of 2079 members of the Royal College of Pathologists and the Pathological Society who were alive in 1955 were enrolled and followed for vital status through to 1973. The Council for Professions Supplementary to Medicine enabled the identification of 12 944 technicians. Ten of the pathologists who died and 20 of the medical technicians who died were women, but the number of women included in the cohort was not provided. Expected numbers of deaths were calculated from sex-, 5-year calendar period- and 5-year age group-specific rates for England and Wales or Scotland. A deficit in mortality from cancer was observed in both pathologists (40 observed, 66.9 expected) and medical technicians (37 observed, 59.8 expected). The SMR for lymphatic and haematopoietic cancer was significantly elevated among pathologists (eight deaths [SMR, 2.00; 95% CI, 0.86–3.94]), but not among technicians (three deaths [SMR, 0.55; 95% CI, 0.11–1.59]). No excess incidence of leukaemia was observed in either group. The SMRs for cancers at other sites were all below 1.0.

The study of British pathologists was extended and expanded by Harrington and Oakes (1984), who added new entrants and traced new and previously studied subjects from 1974 through to 1980. The population now included 2307 men and 413 women. SMRs were calculated using expected rates based on age-, sex- and calendar time-specific data from England and Wales. The SMR for all cancers among men was 0.61 (32 deaths [95% CI, 0.42–0.86] and that among women was 1.41 (seven deaths [95% CI, 0.57–2.90]). Mortality from brain cancer was significantly elevated among men (four deaths; SMR, 3.33 [95% CI, 0.91–8.53] $p < 0.05$), but not among women. No cases of nasal or nasal sinus cancer were observed, but the expected number was small (0.12). Mortality from lung cancer among men was significantly lower than expected (nine deaths; SMR, 0.41 [95% CI, 0.19–0.78]). Mortality from leukaemia and other lymphatic and hematopoetic neoplasms was close to that expected [men and women combined: three deaths; SMR, 0.92; 95% CI, 0.18–2.68].

This cohort was further evaluated by Hall *et al*. (1991), who extended follow-up of mortality from 1980 through to 1986 and added new members of the Pathological Society, which resulted in 4512 individuals available for study (3069 men and 803 women in England and Wales; 409 men in Scotland; and 231 members from Northern Ireland and women from Scotland for whom corresponding reference rates were not available). Sex-specific SMRs were based on expected rates for England and Wales or Scotland (for men only), as appropriate, and were adjusted for age (5-year groups) and calendar time. The SMRs for all causes of death were all considerably below 1.0: men from England and Wales, 0.43 (176 deaths; 95% CI, 0.37–0.50); women from England and Wales, 0.65 (18 deaths; 95% CI, 0.38–1.03); and men from Scotland, 0.50 (29 deaths; 95% CI, 0.34–0.72). The SMRs for cancers at all sites were 0.40 (44 deaths; 95% CI, 0.29–0.54) and 0.59 (nine

Table 17. Cohort and proportionate mortality studies of cancer in professionals exposed to formaldehyde

Reference, country, years of study	Study population, design (study size)	Exposure assessment	Organ site	No. of cases/ deaths	SMR[a] (95% CI)	Comments
British pathologists and medical technicians						
Hall *et al*. (1991), United Kingdom, 1974–87 (update of Harrington & Oakes, 1984, plus new members since 1973)	Pathologists, SMR (4512 men and women) [sex distribution not reported]	None	All cancers	53 deaths	0.45 (0.34–0.59)	Data presented for men and women from England and Wales (n = 3872)
			Nasopharynx	NR	NR	
			Nasal cavity	NR	NR	
			Lymphohaematopoietic	10 deaths	1.44 (0.69–2.65)	
			Leukaemia	4 deaths	1.52 (0.41–3.89)	
			Lung	9 deaths	0.19 (0.09–0.36)	
			Brain and central nervous system	6 deaths	2.18 (0.80–4.75)	
Anatomists and pathologists in the USA						
Stroup *et al*. (1986), USA, 1925–79	Anatomists, SMR (2239 men)	Duration	All cancers	118 deaths	0.64 (0.53–0.76)	
			Nasopharynx	NR	NR	
			Nasal cavity	0 deaths	(0.0–7.2)	0.5 expected
			Lymphohaematopoietic	18 deaths	1.2 (0.7–2.0)	
			Lymphoma	2 deaths	0.7 (0.1–2.5)	
			Leukaemia	10 deaths	1.5 (0.7–2.7)	
			Chronic myeloid leukaemia	3 deaths	8.8 (1.8–25.5)	Analysis limited to 1969–79
			Other lymphatic tissue	6 deaths	2.0 (0.7–4.4)	
			Buccal cavity/pharynx	1 death	0.2 (0.0–0.8)	
			Lung	12 deaths	0.3 (0.1–0.5)	No trend with duration
			Brain and central nervous system	10 deaths	2.7 (1.3–5.0)	Trend with duration
Logue *et al*. (1986), USA, 1962–77	Pathologists, SMR (5585 men)	None	Nasopharynx	NR	NR	Rate of buccal cavity/pharyngeal cancer was twice as high among pathologists than among radiologists.
			Nasal cavity	NR	NR	
			Lymphohaematopoietic	NR	0.48 (NR)	
			Leukaemia	NR	1.06 (NR)	
			Buccal cavity/pharynx	NR	0.71 (NR)	
			Respiratory system	NR	0.24 ($p < 0.01$)	

Table 17 (contd)

Reference, country, years of study	Study population, design (study size)	Exposure assessment	Organ site	No. of cases/ deaths	SMR[a] (95% CI)	Comments
Embalmers and funeral directors						
Walrath & Fraumeni (1983), New York, USA, 1925–80	Embalmers and embalmers/funeral directors, PMR/PCMR (1132 white men)	Time since first licence, age at first licence	All cancers	243 deaths	1.00	PCMR
			Nasopharynx	NR	NR	
			Nasal cavity	0 deaths	NA	0.5 expected
			Lymphohaematopoietic	25 deaths	1.21	PMR
			Lympho- and reticulosarcoma	5 deaths	0.82	PCMR
			Other lymphatic cancers	6 deaths	1.23	PMR
			Leukaemia	12 deaths	1.19	PCMR
			Myeloid leukaemia	6 deaths	[1.5]	PMR
			Buccal cavity/pharynx	8 deaths	1.03	PCMR; 0 deaths from nasopharyngeal cancer
				7 deaths	2.01	PMR, embalmers only
				1 death	0.28	PMR, funeral directors
			Lung	70 deaths	1.11	PCMR (+ two deaths from pleural cancer)
			Brain and central nervous system	9 deaths	1.38	PCMR
				6 deaths	2.34	PMR, embalmers only, $p < 0.05$
				3 deaths	0.93	PMR, funeral directors
Walrath & Fraumeni (1984), California, USA, 1925–80	Embalmers, PMR/PCMR (1007 white men)	Duration	All cancers	205 deaths	1.00	PCMR; $p < 0.05$ for PMR
			Nasopharynx	NR	NR	
			Nasal cavity	0 deaths	NA	0.6 expected
			Lymphohaematopoietic	19 deaths	1.22	PMR
			Lympho- and reticulosarcoma	3 deaths	[1.0]	PMR
			Leukaemia	12 deaths	1.40	PCMR; $p < 0.05$ for PMR; trend with duration
			Myeloid leukaemia	6 deaths	[1.50]	PMR
			Buccal cavity/pharynx	8 deaths	0.99	PCMR, inverse trend with duration;
			Lung	41 deaths	0.87	0 deaths from nasopharyngeal cancer
			Brain	9 deaths	1.68	PCMR, no trend with duration
						PCMR; $p < 0.05$ for PMR; no trend with duration

Table 17 (contd)

Reference, country, years of study	Study population, design (study size)	Exposure assessment	Organ site	No. of cases/ deaths	SMR[a] (95% CI)	Comments
Levine *et al*. (1984), Canada, 1950–77	Embalmers, SMR (1413 men)	None	All cancers	58 deaths	0.87 [0.66–1.12]	
			Nasopharynx	NR	NR	
			Nasal cavity	0 deaths	NA	0.2 expected
			Lymphohaematopoietic	8 deaths	1.23 [0.53–2.43]	
			Leukaemia	4 deaths	[1.60] [0.44–4.10]	Histological type not mentioned
			Buccal cavity/pharynx	1 death	[0.48] [0.01–2.65]	
			Lung	19 deaths	0.94 [0.57–1.47]	
			Brain and central nervous system	3 deaths	[1.15] [0.24–3.37]	
Hayes *et al*. (1990), USA, 1975–85	Embalmers/funeral directors, PMR (3649 white men, 397 non-white men)	None	All cancers	900 deaths	1.07 (1.01–1.15)	White
				102 deaths	1.08 (0.87–1.31)	Non-white
			Nasopharynx	3 deaths	1.89 (0.39–5.48)	White
				1 death	4.00 (0.10–22.3)	Non-white
			Nasal cavity	0 deaths	NA	White and non-white, 1.7 expected
			Lymphohaematopoietic	100 deaths	1.31 (1.06–1.59)	White
				15 deaths	2.41 (1.35–3.97)	Non-white
			Lympho- and reticulosarcoma	11 deaths	1.08 (0.54–1.93)	White
				1 death	1.89 (0.05–10.5)	Non-white
			Lymphatic leukaemia	5 deaths	0.57 (0.19–1.33)	White
				2 deaths	2.99 (0.36–10.7)	Non-white
			Myeloid leukaemia	23 deaths	1.61 (1.02–2.41)	White
				1 death	1.06 (0.02–5.93)	Non-white
			Other and unspecified leukaemia	17 deaths	2.08 (1.21–3.34)	White
				3 deaths	4.92 (1.01–14.36)	Non-white
			Buccal cavity/pharynx	26 deaths	1.19 (0.78–1.74)	White
				4 deaths	1.25 (0.34–3.20)	Non-white
			Lung	285 deaths	0.97 (0.86–1.09)	White
				23 deaths	0.75 (0.47–1.13)	Non-white men
			Brain and central nervous system	24 deaths	1.23 (0.80–1.84)	White
				0 deaths	NA	Non-white, 0.8 expected

CI, confidence interval; NA, not applicable; NR, not reported; PCMR, proportionate cancer mortality ratio; PMR, proportionate mortality ratio; SMR, standardized mortality ratio

[a] Unless otherwise stated

deaths; 95% CI, 0.27–1.12) among men from England and Wales and Scotland, respectively, and 0.95 (nine deaths; 95% CI, 0.43–1.80) among women from England and Wales. No significant excess was seen for cancer at any site. Non-significant excess mortality occurred for brain cancer (six deaths; SMR, 2.40; 95% CI, 0.88–5.22) and lymphatic and haematopoietic cancer (nine deaths; SMR, 1.42; 95% CI, 0.65–2.69) among men from England and Wales, breast cancer (four deaths; SMR, 1.61; 95% CI, 0.44–4.11) among women from England and Wales and prostatic cancer (two deaths; SMR, 3.30; 95% CI, 0.39–11.8) among men from Scotland.

(*b*) *Anatomists and pathologists in the USA*

Stroup *et al*. (1986) evaluated mortality among members of the American Association of Anatomists. A total of 2317 men had joined the Association between 1888 and 1969; because only 299 women had joined during this period, they were not included. Ninety-eight of the men were excluded because they had died, moved or were lost to follow-up before 1925, which resulted in a final study size of 2239. Follow-up of the cohort for vital status was accomplished from the date the person joined the association until 1979. The expected numbers of deaths were calculated from age-, race-, sex- and calendar time-specific rates for the general population of the USA for the period 1925–79 or for male members of the American Psychiatric Association, a population that should be similar to anatomists with regard to socioeconomic status, in 1900–69. In comparison with the general population, the cohort showed a very large 'healthy worker effect', with SMRs of 0.65 for all causes (738 deaths) and 0.64 (118 deaths; 95% CI, 0.53–0.76) for cancer at all sites. Excess mortality was observed for cancers of the brain and central nervous system (10 deaths; SMR, 2.7; 95% CI, 1.3–5.0), leukaemia (10 deaths; SMR, 1.5; 95% CI, 0.7–2.7) and lymphatic tissues other than lymphosarcoma, reticulosarcoma, Hodgkin disease and leukaemia (six deaths; SMR, 2.0; 95% CI, 0.7–4.4). The risk for brain cancer increased with duration of membership, from 2.0 for < 20 years to 2.8 for 20–39 years and to 7.0 for ≥ 40 years; no such pattern was seen for lung cancer or leukaemia. Of the 10 deaths from leukaemia, five were myeloid and the SMR for chronic myeloid leukaemia was statistically significantly elevated (three deaths; SMR, 8.8; 95% CI, 1.8–25.5) in the period 1969–79 for which cell type-specific mortality rates were available. The SMRs were below 1.0 for lung cancer (12 deaths; SMR, 0.3; 95% CI, 0.1–0.5) and oral and pharyngeal cancer (one death; SMR, 0.2; 95% CI, 0.0–0.8). No death from nasal cancer occurred (0.5 expected). When compared with members of the American Psychiatric Association, anatomists had deficits in mortality from lung cancer (seven deaths; SMR, 0.5; 95% CI, 0.2–1.1) and leukaemia (three deaths; SMR, 0.8; 95% CI, 0.2–2.9), but they still had an excess mortality from brain cancer (nine deaths; SMR, 6.0; 95% CI, 2.3–15.6).

Logue *et al*. (1986) evaluated mortality among 5585 members of the College of American Pathologists listed in the Radiation Registry of Physicians. The cohort was established by enrolling members between 1962 and 1972 and following them up through to 1977. Direct comparisons were made between the mortality rates of pathologists and a cohort of 4418 radiologists and used the Mantel-Haenszel procedure with adjustment for

age and calendar time for large categories of death (e.g. all cancers). Indirect comparisons that used mortality rates for white men in the USA in 1970 as the referent were also performed to compute SMRs. The age-adjusted mortality rate for all cancers was found to be slightly lower in pathologists than in radiologists (1.37 versus 1.51 per 1000 person–years). Based on comparisons with the national population, a deficit in mortality was observed among pathologists for cancers of the buccal cavity and pharnyx (SMR, 0.71) and respiratory system (SMR, 0.24) and for lymphatic and haematopoietic neoplasms other than leukaemia (SMR, 0.48). Mortality from leukaemia was slightly elevated (SMR, 1.06) among pathologists. [The number of deaths for each cancer site was not reported.] However, the age-adjusted mortality rate for leukaemia was higher among radiologists than among pathologists (0.15 versus 0.10 per 1000 person–years). [Confidence intervals were not reported and could not be estimated since observed and expected numbers of deaths were not reported.]

(*c*) *Embalmers and funeral directors*

Walrath and Fraumeni (1983) used licensing records from the New York State (USA) Department of Health, Bureau of Funeral Directing and Embalming to identify 1678 embalmers who had been licensed between 1902 and 1980 and who had died between 1925 and 1980. Death certificates were obtained for 1263 (75%) decedents (1132 white men, 79 non-white men, 42 men of unknown race and 10 women); proportionate mortality ratios (PMRs) and proportionate cancer mortality ratios (PCMRs) were calculated for white men and non-white men on the basis of age-, race-, sex- and calendar time-specific proportions in the general population. Observed and expected numbers were generally not provided for non-white men, but it was indicated that there was a significant excess mortality from cancers of the larynx (two deaths) and lymphatic and haematopoietic system (three deaths) in this group. Among white men, the PCMR was 1.00 (243 deaths) for all cancers combined. PCMRs for specific cancers were 1.03 (eight deaths) for buccal cavity and pharynx, 1.11 (70 deaths) for lung, 1.38 (nine deaths) for brain, 1.21 (PMR; 25 deaths) for lymphatic and haematopoietic system, 0.82 (five deaths) for lymphosarcoma and reticulosarcoma (ICD-8 200) and 1.19 (12 deaths) for leukaemia. Six of the leukaemia deaths (4.1 expected) were from myeloid leukaemia [PMR, 1.5]. No deaths occurred from cancer of the nasal sinuses or nasopharynx. There was little difference in PMRs by time since first licence. The subjects who were recruited had been licensed as either embalmers or as both embalmers and funeral directors. Mortality patterns were analysed separately for the two groups because the authors assumed that persons who were licensed only as embalmers would have had more exposure to formaldehyde than embalmers who were also funeral directors. The PMR for cancer of the brain and central nervous system was significantly increased among people who were licensed only as embalmers (six deaths; PMR, 2.34; $p < 0.05$) but not among those who also were licensed as a funeral director (three deaths; PMR, 0.93). A difference was also observed for mortality from cancer of the buccal cavity and pharynx: the PMR for embalmers was 2.01 (seven deaths) and that for embalmers/funeral directors was 0.28 (one death). Neoplasms of the lymphatic and haematopoietic system were only

elevated among individuals who were licensed as both an embalmer and funeral director (16 deaths; PMR, 1.39).

Walrath and Fraumeni (1984) used the records of the California (USA) Bureau of Funeral Directing and Embalming to examine proportionate mortality among embalmers who had first been licensed in California between 1916 and 1978. They identified 1109 embalmers who died between 1925 and 1980, comprised of 1007 white men, 39 non-white men, 58 white women and five non-white women. Only mortality of white men was analysed. PMRs and PCMRs were calculated using age-, race-, sex- and calendar year-specific proportions from the general population of the USA. Total cancer mortality was significantly greater than that expected (205 deaths; PMR, 1.21 for all cancers combined). Also, a statistically significant excess of proportionate mortality was observed for cancers of the colon (30 deaths; PMR, 1.87), prostate (23 deaths; PMR, 1.75), brain and central nervous system (nine deaths; PMR, 1.94) and leukaemia (12 deaths; PMR, 1.75). The magnitude of these excesses was reduced and no longer statistically significant in the PCMR analyses (Table 17). Mortality from cancers of the buccal cavity and pharynx was slightly elevated in the PMR analysis (eight deaths; PMR, 1.31) but not in the PCMR analysis (PCMR, 0.99). Mortality from lung and pleural cancers was close to expected in both the PMR (41 observed, 42.9 expected; PMR, 0.96) and PCMR (0.87) analyses. There was no death from cancer of the nasal passages (0.6 expected). Mortality from leukaemia was found to be increased predominantly among embalmers who had had a licence for 20 or more years (eight deaths; PMR, 2.21). Six of the 12 cases of leukaemia were of the myeloid type [PMR, 1.5].

Mortality among 1477 male embalmers who had been licensed by the Ontario (Canada) Board of Funeral Services between 1928 and 1957 was evaluated by Levine *et al*. (1984). The cohort was followed for mortality from the date of first licence through to 1977. Expected numbers of deaths were derived from the mortality rates for men in Ontario in 1950–77, adjusted for age and calendar year. Since mortality rates for Ontario were not available before 1950, person–years and deaths in the cohort before that time were excluded from the analysis, which left 1413 men known to be alive in 1950. Mortality from all cancers was observed to be slightly lower than expected (58 deaths; SMR, 0.87 [95% CI, 0.66–1.12]). A small and statistically non-significant excess in mortality was observed for cancers of the lymphatic and haematopoietic system (eight deaths; SMR, 1.23 [95% CI, 0.53–2.43]) and leukaemia (four deaths [SMR, 1.60; 95% CI, 0.44–4.10]). Mortality from cancers of the buccal cavity and pharynx (one death [SMR, 0.48; 95% CI, 0.01–2.65]), lung (19 deaths; SMR, 0.94 [95% CI, 0.57–1.47]) and brain (three deaths [SMR, 1.15; 95% CI, 0.24–3.37]) was close to or lower than expected. No death from cancer of the nose, middle ear or sinuses was observed (0.2 expected).

Hayes *et al*. (1990) identified 6651 deceased embalmers/funeral directors from the records of licensing boards and state funeral directors' associations in 32 states and the District of Columbia and from the vital statistics offices of nine states and New York City in the USA between 1975 and 1985. Death certificates were received for 5265. Exclusion of 449 decedents included in previous studies of embalmers in New York (Walrath &

Fraumeni, 1983) and California (Walrath & Fraumeni, 1984), 376 subjects who probably did not work in the funeral industry, eight subjects of unknown race or age at death and 386 women left 4046 male decedents available for analysis (3649 whites and 397 non-whites). PMRs and PCMRs were calculated on the basis of expected numbers from race- and sex-specific groups of the general population, adjusted for 5-year age and calendar-time categories. The PMR for all cancers was 1.07 (900 deaths; 95% CI, 1.01–1.15) for whites and 1.08 (102 deaths; 95% CI, 0.87–1.31) for non-whites. The PMRs for specific cancers were: buccal cavity and pharynx (whites: 26 deaths; PMR, 1.19; 95% CI, 0.78–1.74; non-whites: four deaths; PMR, 1.25; 95% CI, 0.34–3.20), nasopharynx (whites: three deaths; PMR, 1.89; 95% CI, 0.39–5.48; non-whites: one death; PMR, 4.00; 95% CI, 0.10–22.3), nasal sinuses (whites and non-whites: 0 observed, 1.7 expected), lung (whites: 285 deaths; PMR, 0.97; 95% CI, 0.86–1.09; non-whites: 23 deaths; PMR, 0.75; 95% CI, 0.47–1.13), brain and central nervous system (whites: 24 deaths; PMR, 1.23; 95% CI, 0.80–1.84; non-whites: 0 observed, 0.8 expected) and lymphatic and haematopoietic system (whites: 100 deaths; PMR, 1.31; 95% CI, 1.06–1.59; non-whites: 15 deaths; PMR, 2.41; 95% CI, 1.35–3.97). The risks for cancers of the lymphatic and haematopoietic system and brain and central nervous system did not vary substantially by licensing category (embalmer versus funeral director), by geographical region, by age at death or by source of data on mortality. Among the lymphatic and haematopoietic cancers, the PMRs were significantly elevated for myeloid leukaemia (both groups combined: 24 deaths; PMR, 1.57; 95% CI, 1.01–2.34) and other and unspecified leukaemia (both groups combined: 20 deaths; PMR, 2.28; 95% CI, 1.39–3.52); non-significant excesses of mortality were observed for several other histological types.

2.1.3 *Other cohort studies*

In a study of users of various medicinal drugs based on computer-stored hospitalization records of the outpatient pharmacy at the Kaiser–Permanente Medical Center in San Francisco (CA, USA), Friedman and Ury (1983) evaluated cancer incidence in a cohort of 143 574 pharmacy users from July 1969 through August 1973 and followed them up to the end of 1978. The number of cases among users of specific drugs was compared with the number expected on the basis of rates for all pharmacy users, adjusted for age and sex. Since many analyses were performed (56 cancers and 120 drugs, for 6720 combinations), chance findings would be expected. Five cancers were associated with use of formaldehyde solution (topically for warts) (morbidity ratio, 0.8 [95% CI, 0.3–2.0]). The morbidity ratio for lung cancer was significantly elevated (four cases; morbidity ratio, 5.7 [95% CI, 1.6–15]) for people who used formaldehyde. Information on tobacco smoking was not provided. [The Working Group noted the short period of follow-up, the small number of cases and the lack of detailed information on exposure that made this study largely uninformative.]

Several studies have evaluated risk for cancer in haemodialysis patients who may have been potentially exposed to formaldehyde (see Section 1.3.2). [The Working Group

considered these studies to be largely uninformative since some patients with chronic renal failure receive immunosuppressive drugs, which are known to increase their risk for cancer, and because these studies are generally small, have short follow-up and provide limited or no information on exposures to formaldehyde.]

2.2 Case–control studies

Case–control studies have been used to examine the association between exposure to formaldehyde and various cancers. For rare tumours such as sinonasal and nasopharyngeal cancer, they have the potential to provide greater statistical power than can normally be achieved in cohort studies. Against this advantage, however, must be set the difficulties in assessing exposure to formaldehyde retrospectively in community-based studies. This requirement is usually addressed through expert evaluation of job histories by an occupational hygienist, or through the use of a job–exposure matrix. For a chemical such as formaldehyde, however, these methods tend to lack specificity when applied to the general population. Thus, the subjects who are classed as having been exposed to formaldehyde in community-based case–control studies usually have lower exposures on average than those in occupational cohorts that are specially selected for investigation because they are known to experience high exposures. Exposures to formaldehyde were assessed in some studies by asking study subjects whether they had been exposed to formaldehyde. This use of self-reported exposures is of questionable validity and in particular may lead to recall bias.

2.2.1 *Cancers of the nasal cavity and paranasal sinuses*

The study design of and results from case–control studies on cancers of the nasal cavity, paranasal sinuses, nasopharynx and hypopharynx associated with exposure to formaldehyde are summarized in Table 18.

With the purpose of investigating the carcinogenic effects of exposure to wood dust, Hernberg *et al.* (1983a) conducted a joint Nordic case–control study of 167 patients in Finland, Sweden and most of Denmark in whom primary malignant tumours of the nasal cavity and paranasal sinuses had been diagnosed between July 1977 and December 1980 and 167 country-, age- and sex-matched controls who had been diagnosed with cancers of the colon and rectum. The study subjects represented 58% of all cancers identified at these anatomical sites; the exclusions were due to early deaths or to non-responding or missing controls. Information on the occupations and tobacco smoking habits of the study subjects was obtained by standardized telephone interview. None of the cases or controls had worked in the particle-board or plywood industry or in the production of formaldehyde or formaldehyde-based glues. No association was found between sinonasal cancer and other occupations in which exposure to formaldehyde was considered to be most probable. A total of 18 cases and six controls had worked in ‘painting, lacquering and glueing’, a category that the authors considered may have entailed minimal exposure to

Table 18. Case–control studies of cancers of the nasal cavity, paranasal sinuses, nasopharynx and hypopharynx

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hernberg *et al.* (1983a), Denmark, Finland, Sweden, 1977–80	Nasal cavity and parasinuses (160.0–160.9; ICD revision not given)	167 patients [sex distribution not reported] with primary malignant tumours	167 patients with cancer of the colon and rectum, matched by country, sex and age	Employment in particle-board or plywood industry	Yes/no	0 cases, 0 controls		
				Painting, lacquering and glazing	Yes/no	18 cases, 6 controls		Concomitant exposure of 15 cases to wood dust
Brinton *et al.* (1984), USA, 1970–80	Nasal cavity and parasinuses (ICD-8 160.0, 160.2–160.5, 160.8–160.9)	160 (93 men, 67 women), including 86 squamous-cell carcinomas and 24 adenocarcinomas or adenoid cystic carcinomas; 61 in nasal cavity, 71 in maxillary sinus and 28 other sinus or overlapping sites	290 (178 hospital controls, 112 death certificate controls); hospital controls were required to be alive for living cases; death certificate controls were identified for deceased cases; matched on age, sex, race and county of residence	Telephone interviews with subjects or next of kin included a checklist of industries and self-reported exposures including formaldehyde.	*Men and women combined* Unexposed Exposed	 1.0 0.35 (0.1–1.8)	Adjusted for sex; control for tobacco use did not change results.	Formaldehyde exposure assessment was self-reported; only 33% of cases and 39% of controls were interviewed directly; for the remainder, exposures relied on recall of next of kin.
Olsen *et al.* (1984), Denmark, 1970–82	Nasal cavity, nasal sinuses (160.0, 160.2, 160.9) and nasopharynx (146) (ICD revision not given)	754 incident patients [sex distribution not reported] selected from the Danish Cancer Registry including 488 carcinomas of the nasal cavity and sinuses and 266 carcinomas of the nasopharynx	2465 patients with cancers of the colon, rectum, prostate and breast; frequency-matched by sex, age (± 5 years) and year of diagnosis (± 5 years); 4.2% of men and 0.1% of women exposed to formaldehyde	Record linkage with pension fund with compulsory membership; job title from Central Pension Registry; exposure assessed blindly as certain, probable, unlikely, unknown	*Industries and occupations with certain exposure to formaldehyde* Ever exposed Unexposed to wood dust Exposed to wood dust Exposure for > 10 years before diagnosis Unexposed to wood dust Exposed to wood dust Adjusted for wood dust *Industries and occupations with certain or possible exposure* Men Women	*Sinonasal* 2.8 (1.8–4.3) 1.8 (0.7–4.9) 3.5 (2.2–5.6) 3.1 (1.8–5.4) 1.5 (0.4–5.3) 4.1 (2.3–7.3) 1.6 (0.7–3.6) *Nasopharynx* 0.7 (0.3–1.7) 2.6 (0.3–21.9)	Unadjusted Unadjusted	Data for sinonasal cancer reported for men only

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hayes *et al.* (1986a), Netherlands, 1978–81	Nasal cavity and accessory sinuses (ICD-9 160.0, 160.2–160.5)	91 male patients histologically confirmed, alive or deceased	195 age-stratified random sample of living men resident in the Netherlands in 1982 or deceased in the Netherlands in 1980	Taking into account job history, time period and potential frequency of exposure, exposure was classified into 10 groups independently by two occupational hygienists (assessment A and B)	*Any exposure to formaldehyde* Assessment A Assessment B *No or little exposure to wood dust* Assessment A Assessment B *Moderate to high exposure to wood dust* Assessment A Assessment B *Squamous-cell carcinoma only* Assessment A Assessment B	 2.5 (1.5–4.3)[a] 1.9 (1.2–3.0)[a] 2.5 [1.0–5.9] 1.6 [0.8–3.1] 1.9 [0.6–6.5] NR 3.0 [1.2–7.8] 1.9 [0.9–4.1]	Standardized for age in 10-year groups; control for usual number of cigarettes smoked did not modify the results. No or little exposure to wood dust	Relative risk for adenocarcinoma for those ever employed in the wood and paper industry, 11.3 (90% CI, 4.0–35.1); moderate increase associated with increase in level of exposure to formaldehyde with no concomitant exposure to wood dust
Olsen & Asnaes (1986), Denmark, 1970–82	Nasal cavity, paranasal sinuses (160.0, 160.2–160.9) and nasopharynx (146) (ICD revision not given)	759 (509 men, 250 women) histologically confirmed cancers of the nasal cavity and paranasal sinuses (466 cases; 310 men, 156 women) and nasopharynx (293 cases; 199 men, 94 women)	2465 patients with cancers of the colon, rectum, prostate and breast frequency-matched by sex, age (± 5 years) and year of diagnosis (± 5 years); 4.2% of men and 0.1% of women exposed to formaldehyde	Record linkage with pension fund with compulsory membership; job title from Central Pension Registry; exposure assessed blindly as certain, probable, unlikely, unknown	*Likely or possible exposure to formaldehyde ≥ 10 years before diagnosis* Squamous-cell carcinoma (215) Adenocarcinoma (39)	 2.4 (0.8–7.4) 1.8 (0.5–6.0)	Adjusted for exposure to wood dust	Data presented for men for cancer of the nasal cavity and paranasal sinuses; no association observed with nasopharyngeal cancer

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Vaughan *et al.* (1986a), USA, 1979–83	Nasal cavity (160) and pharynx (146–149) (ICD revision not given)	285 incident cases [sex distribution not reported] identified by the local Cancer Surveillance System, aged 20–74 years, including oro- and hypopharynx (205), nasopharynx (27) and sinuses (53)	552 identified by random-digit dialling	Job–exposure linkage system, resulting in four categories: high, medium, low and background		*Sinonasal*	Age, sex, cigarette smoking and alcohol consumption	
					Low exposure	0.8 (0.4–1.7)		
					Medium or high exposure	0.3 (0.0–1.3)		
					Highest exposure score	0.3 (0.0–2.3)		
						Nasopharynx		
					Low exposure	1.2 (0.5–3.3)		
					Medium or high exposure	1.4 (0.4–4.7)		
					Highest exposure score	2.1 (0.6–7.8)		
						Oro-/hypopharynx		
					Low exposure	0.8 (0.5–1.4)		
					Medium exposure	0.8 (0.4–1.7)		
					High exposure	0.6 (0.1–2.7)		
					Highest exposure score	1.5 (0.7–3.0)		
Vaughan *et al.* (1986b), USA, 1979–83	Nasal cavity (160) and pharynx, (146–149) (ICD revision not given)	285 incident cases [sex distribution not reported] identified by the local Cancer Surveillance System, aged 20–74 years, including oro- and hypopharynx (205), nasopharynx (27) and sinuses (53)	552 identified by random-digit dialling	Residential exposure: residential history since 1950		*Sinonasal*	Sex, age, cigarette smoking and alcohol consumption	
					Mobile home	0.6 (0.2–1.7)		
					Particle-board at home			
					1–9 years	1.8 (0.9–3.8)		
					≥ 10 years	1.5 (0.7–3.2)		
						Nasopharynx		
					Mobile home		Cigarette smoking and race	
					1–9 years	2.1 (0.7–6.6)		
					≥ 10 years	5.5 (1.6–19.4)		
					Particle-board at home			
					1–9 years	1.4 (0.5–3.4)		
					≥ 10 years	0.6 (0.2–2.3)		
						Oro-/hypopharynx		
					Mobile home		Sex, age, cigarette smoking and alcohol consumption	
					1–9 years	0.9 (0.5–1.8)		
					≥ 10 years	0.8 (0.2–2.7)		
					Particle-board at home			
					1–9 years	1.1 (0.7–1.9)		
					≥ 10 years	0.8 (0.5–1.4)		

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Rousch *et al.* (1987), USA, 1935–75	Nasal cavity and sinuses, and naso-pharynx (ICD code not given)	198 men with sinonasal cancer and 173 with nasopharyngeal cancer registered at the Connecticut Tumor Registry	605 men who died during the same period, selected by random sampling without matching or stratification	Job title, industry, specific employment, year of employment, obtained from death certificates and city directories		*Sinonasal*	Age and calendar period	
					Probably exposed for most of working life	0.8 (0.5–1.3)		
					Plus exposure ≥ 20 years before death	1.0 (0.5–1.8)		
					Plus exposure to high level for some years	1.0 (0.5–2.2)		
					Plus exposure to high level ≥ 20 years before death	1.5 (0.6–3.9)		
						Nasopharynx		
					Probably exposed for most of working life	1.0 (0.6–1.7)		
					Plus exposure ≥ 20 years before death	1.3 (0.7–2.4)		
					Plus exposure to high level for some years	1.4 (0.6–3.1)		
					Plus exposure to high level ≥ 20 years before death	2.3 (0.9–6.0)		

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Luce *et al.* (1993), France, 1986–88	Nasal cavity and parasinuses (ICD-9 160.0, 160.2–160.9)	207 cases (167 men, 40 women): 59 men and 18 women with squamous-cell carcinomas, 82 men and five women with adenocarcinomas and 25 men and 17 women with other histology	409 from two sources: 323 hospital cancer controls (15 sites) frequency-matched by age and sex; 86 proposed by cases, matched by age (± 10 years), sex and residence	Industrial hygienist review of structured job interview, classifying exposure by frequency, concentration and duration; computation of cumulative exposure level and lifetime average level	*Squamous-cell carcinoma* Possibly exposed Probably or definitely Average level ≤ 2 Average level > 2 Duration ≤ 20 years Duration > 20 years Cumulative level ≤ 30 > 30	**Men** 0.96 (0.38–2.42) 0.70 (0.28–1.73) 1.32 (0.54–3.24) 1.09 (0.48–2.50) 0.76 (0.29–2.01) 1.26 (0.54–2.94) 0.68 (0.27–1.75)	Adjusted for age, exposure to wood dust and exposure to glues and adhesives	Adjustment for usual cigarette use or for smoking history did not change results.
					Adenocarcinoma Possibly exposed Probably or definitely Average level ≤ 2 Average level > 2 Duration ≤ 20 years Duration > 20 years Cumulative level ≤ 30 30–60 > 60	 1.28 (0.16–10.42) 4.15 (0.96–17.84) 5.33 (1.28–22.20) 1.03 (0.18–5.77) 6.86 (1.69–27.80) 1.13 (0.19–6.90) 2.66 (0.38–18.70) 6.91 (1.69–28.23)		Most cases of adenocarcinomas exposed to both formaldehyde wood dust; very large odds ratio (288) for wood dust; therefore, there is concern about the possibility of incomplete adjustment for wood dust in these results.
					Other histology Possibly exposed Probably or definitely Average level ≤ 2 Average level > 2 Duration ≤ 20 years Duration > 20 years Cumulative level ≤ 30 > 30	 0.81 (0.15–4.36) 1.67 (0.51–5.42) 3.04 (0.95–9.70) 2.82 (0.94–8.43) 1.62 (0.48–5.51) 2.18 (0.65–7.31) 2.21 (0.73–6.73)		

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
West *et al.* (1993), Philippines [study years not reported]	Nasopharynx (ICD code not given)	104 incident cases (76 men, 28 women) histologically confirmed	104 hospital controls matched for sex, age and hospital ward type; 101 community controls matched for sex, age and neighbourhood	Occupation classified as likely or unlikely to involve exposure to formaldehyde; duration of exposure; 10-year lag period; years since first exposure; age at start of exposure	< 15 years ≥ 15 years < 15 years (10-year lag) ≥ 15 years (10-year lag) Age ≥ 25 years at first exposure Age < 25 years at first exposure First exposure < 25 years before diagnosis First exposure ≥ 25 years before diagnosis	2.7 (1.1–6.6) 1.2 (0.5–3.2) 1.6 (0.6–3.8) 2.1 (0.7–6.2) 1.2 (0.5–3.3) 2.7 (1.1–6.6) 1.3 (0.6–3.2) 2.9 (1.1–7.6)	Years since first exposure to dust and/or exhaust fumes	
Gustavsson *et al.* (1998), Sweden, 1988–91	Oro- and hypopharynx (ICD-9 146, 148)	545 incident male cases among residents of two regions, aged 40–79 years [including at least 124 cases of pharyngeal cancer]	641 selected by stratified random sampling; frequency-matched to cases by age (10–15-year groups) and region	Work history reviewed by occupational hygienist; occupations coded by intensity and probability of exposure	Ever exposed	1.01 (0.49–2.07)	Age, region, alcohol, consumption and smoking habits	
Armstrong *et al.* (2000), Malaysia, (Selagor and Federal Territory), 1987–92	Nasopharyngeal squamous-cell carcinoma (ICD code not given)	282 Chinese men and women from four centres (prevalent and incident cases) [no information on age distribution]	One Chinese control selected by multistage area sampling per case; matched by age and sex	Structured in-home interviews; occupational exposures assessed by a job–exposure matrix	Any (unadjusted) Any (adjusted)	1.24 (0.67–2.32) 0.71 (0.34–1.41)	Diet and tobacco use	Mixture of prevalent (42%) and incident (58%) cases

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Laforest *et al.* (2000), France, 1989–91	Hypopharynx (squamous-cell) (ICD code not given)	201 men with confirmed histology from 15 hospitals [no information on age]	296 male patients with other (selected) primary tumours from the same or nearby hospitals; recruited 1987–91; matched by age	Structured in-person interviews; occupational exposures assessed with a job–exposure matrix earlier developed	Ever exposed	1.35 (0.86–2.14)	Age, tobacco smoking, alcohol consumption, coal dust and asbestos	
					Probability of exposure (%)			
					< 10	1.08 (0.62–1.88)		
					10–50	1.01 (0.44–2.31)		
					> 50	3.78 (1.50–9.49)		
					Duration (years)			
					< 7	1.09 (0.50–2.38)		
					7–20	1.39 (0.74–2.62)		
					> 20	1.51 (0.78–2.92)		
					Cumulative level			
					Low	1.03 (0.51–2.07)		
					Medium	1.57 (0.81–3.06)		
					High	1.51 (0.74–3.10)		
					Exclusion of subjects with exposure probability < 10%			
					Ever exposed	1.74 (0.91–3.34)		
					Duration (years)			
					< 7	0.74 (0.20–2.68)		
					7–20	1.65 (0.67–4.08)		
					> 20	2.70 (1.08–6.73)		
					Cumulative level			
					Low	0.78 (0.11–5.45)		
					Medium	1.77 (0.65–4.78)		
					High	1.92 (0.86–4.32)		

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Vaughan *et al.* (2000), USA (Connecticut, metropolitan Detroit, Iowa, Utah, Washington), 1987–93	Epithelial nasopharyngeal carcinoma: epithelial NOS (801x–804x), undifferentiated or non-keratinizing (8020–1, 8072–3, 8082) and squamous-cell (805x–808x, except 8072–3)	196 men and women [sex distribution not reported] from five cancer registries, aged 18–74 years	244 population-based selected by random digit dialling; frequency-matched by sex, cancer registry and age (5-year groups)	Structured telephone interviews; occupational exposures assessed by a job–exposure matrix	Ever exposed *Max. exposure (ppm)* < 0.1 0.1–0.5 > 0.5 *p* for trend *Duration (years)* 1–5 6–17 ≥ 18 *p* for trend *Differentiated squamous-cell and epithelial NOS only* Ever exposed *Duration (years)* 1–5 6–17 ≥ 18 *p* for trend *Cumulative exposure (ppm–years)* 0.05–0.4 > 0.4–1.10 > 1.10 *p* for trend	1.3 (0.8–2.1) 1.4 (0.8–2.4) 0.9 (0.4–2.3) 1.6 (0.3–7.1) 0.57 0.8 (0.4–1.6) 1.6 (0.7–3.4) 2.1 (1.0–4.5) 0.070 1.6 (1.0–2.8) 0.9 (0.4–2.1) 1.9 (0.9–4.4) 2.7 (1.2–6.0) 0.014 0.9 (0.4–2.0) 1.8 (0.8–4.1) 3.0 (1.3–6.6) 0.033	Age, sex, race, centre, cigarette use, proxy status and education	Data presented for any potential exposure (possible, probable or definite); not influenced by a 10-year lag period or adding wood dust exposure to models

Table 18 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hildesheim *et al.* (2001) Taiwan, China, 1991–94	Nasopharynx; > 90% non-keratinizing and undifferentiated and remainder squamous-cell carcinomas (ICD code not given)	375 histologically confirmed hospital cases (31% women), aged < 75 years	325 community controls, individually matched on sex, age (5 years) and district of residence	Structured in-person interviews; occupational exposures assessed by an industrial hygienist; blood specimen was tested for anti-EBV antibodies.	Ever exposed *Duration* 1–10 years >10 years *p* for trend *Cumulative exposure* < 25 ≥ 25 *p* for trend	1.4 (0.93–2.2) 1.3 (0.69–2.3) 1.6 (0.91–2.9) 0.08 1.3 (0.70–2.4) 1.5 (0.88–2.7) 0.10	Age, sex, education and ethnicity	Observations were not influenced by adding wood dust exposure to models; in a sub-analysis restricted to 360 cases and 94 controls seropositive for at least one type of antibody against EBV, the association between exposure to formaldehyde and nasopharyngeal cancer appeared somewhat stronger.
Berrino *et al.* (2003), France, Italy, Spain, Switzerland, 1979–82	Hypopharynx and epilarynx (ICD code not given)	100 men, incident cases histologically confirmed from six centres, aged ≤ 55 years	819 men from the general local population of each centre; age- and sex-stratified	Structured in-person interviews; occupational exposures assessed by an expert panel using a previously established job–exposure matrix	*Probability of exposure* Possible Probable and certain	 1.3 (0.6–2.6) 0.5 (0.1–1.8)	Age, centre, tobacco use, alcohol consumption, diet, socioeconomic status, asbestos, PAHs, chromium, arsenic, wood dust, solvents, other dusts and gases	[The credibility of the negative finding is limited because formaldehyde was the agent for which the validity of the job–exposure matrix was lowest.]

CI, confidence interval; EBV, Epstein-Barr virus; ICD, international code of diseases; NOS, not otherwise specified; PAHs, polycyclic aromatic hydrocarbons

[a] 90% confidence interval

formaldehyde; when workers exposed to wood dust were excluded, more controls than cases had been exposed (three cases, six controls). [The Working Group noted that the study was not designed to address exposure to formaldehyde and that all the cases in Denmark were also included in the study of Olsen *et al*. (1984).]

In a case–control study conducted in four hospitals in North Carolina and Virginia, USA, in 1970–80, 193 men and women who had primary malignancies of the nasal cavity and sinuses were identified (Brinton *et al.*, 1984). Two hospital controls who were alive at the date of the interview were selected for each living patient and matched on hospital, year of admission, age, sex, race and administrative area; for deceased patients, two similarly matched controls were chosen: one patient who had attended the same hospital but who was not necessarily alive at the date of the interview, and one deceased person who was identified from records of the state vital statistics offices. Patients who had cancer of the buccal cavity and pharynx, nasal cavity, middle ear and accessory sinuses, larynx and oesophagus and patients who had various nasal disorders were excluded from the control group. Telephone interviews were completed for 160 of the nasal cancer patients (83%) and 290 of the controls (78%), either directly with the patients themselves (33% of cases and 39% of controls) or with their next of kin. Occupational exposures were assessed by the interviewee's recall in response to a checklist of exposures, including formaldehyde. Exposure to formaldehyde was reported for two nasal cancer patients (one man and one woman), to yield an odds ratio of 0.35 (95% CI, 0.1–1.8). [The Working Group noted that the exposure assessment was limited as it relied on self-reports and, furthermore, that a high proportion of interviews were with next of kin. The informativeness of the study was further limited by the small number of exposed subjects.]

In a population-based study in Denmark (Olsen *et al.*, 1984), 488 men and women in whom cancer of the sinonasal cavities had been diagnosed during the period 1970–82 and reported to the national cancer registry were matched to 2465 controls for sex, age and year of diagnosis, who were selected from all patients in whom cancer of the colon, rectum, prostate or breast had been diagnosed during the same period. Histories of exposure to formaldehyde, wood dust and 10 other specified compounds or industrial procedures were assessed by industrial hygienists who were unaware of the case or control status of the study subjects, on the basis of individual employment histories obtained from a national pension scheme in operation since 1964. The industrial hygienists classified subjects according to whether they had definitely or probably been exposed, had not been exposed or had undetermined exposure to individual compounds during 1964–82. Of the controls, 4.2% of men and 0.1% of women had held occupations that presumably entailed exposure to formaldehyde. The odds ratios for definite exposures to formaldehyde (unadjusted for any other occupational exposure and using the no exposure category as the reference level) were 2.8 (95% CI, 1.8–4.3) for men and 2.8 (95% CI, 0.5–14) for women. Further results were not presented for women. Adjustment for exposure to wood dust reduced the risk estimate for men to 1.6, which was no longer significant. Only five men in the group of 33 workers with definite exposure to formaldehyde had not been exposed to wood dust. Probable exposure to formaldehyde was associated with a slightly increased

risk for sinonasal cancer in men (odds ratio, 1.2; 95% CI, 0.8–1.7). [The Working Group noted that the employment histories of study subjects were restricted to 1964 or later and that the study was limited by the fact that the industries that used formaldehyde in Denmark in this study seemed to be dominated by exposure to wood dust, which makes assessment of the separate effect of exposure to formaldehyde on the risk for sinonasal cancer difficult.]

A re-analysis was performed (Olsen & Asnaes, 1986) in which data on 215 men with squamous-cell carcinoma and 39 with adenocarcinoma of the sinonasal cavities were examined separately. An odds ratio (adjusted for exposure to wood dust) of 2.3 (95% CI, 0.9–5.8) for squamous-cell carcinoma was found for 13 cases who had ever been exposed to formaldehyde; of these, four had not been exposed to wood dust, which gave an odds ratio of 2.0 (95% CI, 0.7–5.9). Introduction of a 10-year lag period into the analysis yielded odds ratios of 2.4 (95% CI, 0.8–7.4) and 1.4 (95% CI, 0.3–6.4), respectively. The analysis revealed an association between exposure to wood dust and adenocarcinoma (odds ratios for any exposure, 16.3; 95% CI, 5.2–50.9) but only a weak association with squamous-cell carcinoma (odds ratio, 1.3; 95% CI, 0.5–3.6). For the 17 cases of adenocarcinoma in men who had ever been exposed to formaldehyde, the odds ratio, after adjustment for exposure to wood dust, was 2.2 (95% CI, 0.7–7.2), and that among men who had been exposed 10 or more years before diagnosis was 1.8 (95% CI, 0.5–6.0); however, only one man who had an adenocarcinoma had been exposed to formaldehyde alone. [The Working Group noted a concern that possibly incomplete adjustment for confounding from exposure to wood dust in the assessment of the risk for adenocarcinoma could explain the weak association observed with exposure to formaldehyde, but also noted that the assessment of risk for squamous-cell carcinoma was unlikely to have been affected because squamous-cell carcinoma was not clearly associated with exposure to wood dust.]

From an examination of medical records in the six major institutions in the Netherlands for surgical and radiographic treatment of tumours of the head and neck, Hayes *et al.* (1986a) identified 116 men, aged 35–79 years, in whom a histologically confirmed epithelial cancer of the nasal cavity or paranasal sinuses had been diagnosed during 1978–81. The cases were frequency-matched on age with 259 population controls who were chosen randomly from among living male residents of the Netherlands in 1982 (in a ratio of 2:1 for all patients) and from among deceased men in 1980 (in an approximate ratio of 1:1 for dead cases). Detailed histories, including information on exposure to a selected list of substances in the workplace and subjects' tobacco smoking habits, were obtained by personal interview of study subjects or their next of kin, with a participation of 78% for 91 case patients and 75% for 195 controls. Independently of one another, two industrial hygienists (A and B) reviewed job histories and graded possible exposure to formaldehyde. Exposure to wood dust was assessed similarly by one hygienist. At least some potential occupational exposure to formaldehyde was considered to have occurred for 23% of all study subjects by assessment A and for 44% by assessment B; among 224 subjects with little or no exposure to wood dust, exposure to formaldehyde was considered by assessments A and B to have occurred in 15 and 30%, respectively. For 62 subjects who were classed as having moderate or high

exposure to wood dust, there was a weak association with exposure to formaldehyde as assessed by hygienist A (odds ratio, 1.9 [95% CI, 0.6–6.5]), but no odds ratio could be derived for exposure as assessed by hygienist B. For the 224 subjects who had little or no exposure to wood dust, the odds ratios for exposure to formaldehyde were 2.5 [95% CI, 1.0–5.9] (hygienist A) and 1.6 [95% CI, 0.8–3.1] (hygienist B). When the analysis was restricted to 45 cases of squamous-cell carcinoma of the paranasal sinuses who had little or no exposure to wood dust, the odds ratios for high exposure to formaldehyde were 3.1 [95% CI, 0.7–13.5] (hygienist A) and 2.4 [95% CI, 0.9–6.1] (hygienist B). [The Working Group noted that a greater proportion of case patients than controls were deceased (36% versus 14%) and variable numbers of next of kin were interviewed; furthermore, 10% of controls but none of the case patients were interviewed by telephone. The Group noted, however, that, although assessments A and B differed, both gave positive results.]

Vaughan *et al*. (1986a) conducted a population-based case–control study in a 13-county area in western Washington State, USA. The study included incident cases of sinonasal and pharyngeal cancer that were identified from a cancer registry that was reported to identify 98–99% of the cancers in the study area. Cases eligible for study were between the ages of 20 and 74 years and had a date of diagnosis between 1979 and 1983 for sinonasal cancer, and from 1980 to 1983 for pharyngeal cancer. Control subjects were identified by random-digit dialling and were frequency-matched to be similar in age and sex as the cases. Medical, tobacco smoking, alcohol use, residential and occupational histories were collected in a telephone interview with study subjects or their next of kin. Of the 415 cases eligible for study, 59 could not be located or were deceased with no known next of kin and 61 were not interviewed due to physician or subject refusal. Of the 295 cases who were successfully interviewed, 10 did not meet the eligibility requirements of the study, resulting in 285 cases being included in the analysis (53 sinonasal, 27 nasopharyngeal and 205 oro- or hypopharyngeal cancers). Approximately half of the case interviews were with their next of kin. Of a total of 690 persons eligible as controls, 573 were interviewed; 21 of these were excluded because they did not meet the eligibility requirements of the study, which resulted in 552 controls being available for analysis. [Although not explicitly stated, it appears that none of the interviews of the controls were by proxy.] Occupational exposure to formaldehyde was assessed by means of a job–exposure linkage system in which each job within each industry was classified according to the likelihood of exposure (unlikely, possible or probable). Those jobs that were defined as probably exposed were further classified into high or low exposure intensity. These two measures of exposure were then combined into a summary variable that resulted in the following four levels: (1) high (probable exposure to high levels), (2) medium (probable exposure to low levels), (3) low (possible exposure at any level) and (4) background. For the analysis, an estimate of the duration of exposure and the maximum exposure level (low, medium or high) reached in any job was developed for each individual. A cumulative exposure score was also developed by combining the information on duration and level of exposure. Unconditional logistic regression was used for the analysis in which age, sex and other potential confounders were controlled for when necessary. The odds ratios for sinonasal cancer,

adjusted for sex, age, cigarette smoking and alcohol consumption, decreased with increasing exposure by all of the measures. The odds ratios observed were: 0.8 (95% CI, 0.4–1.7) for low and 0.3 (95% CI, 0.0–1.3) for medium or high maximum exposure level attained; 0.7 (95% CI, 0.3–1.4) for 1–9 years and 0.4 (95% CI, 0.1–1.9) for ≥ 10 years of exposure; and 0.5 (95% CI, 0.1–1.6) for 5–19 and 0.3 (95% CI, 0.0–2.3) for ≥ 20 units of the exposure score. [The number of exposed cases could not be determined for these analyses.] An analysis was also performed in which the exposure score was estimated at 16 years before the date of diagnosis for the case and 16 years before the date of interview for the controls (i.e. lagged by 16 years). Lagging the exposures in this way resulted in no cases in the high exposure group, and did not produce interpretable findings. [The Working Group noted that the different proportions of interviews conducted with next of kin of cases and controls may have affected the odds ratios.]

Vaughan *et al.* (1986b) also explored the relationships between these types of tumour and residential exposure to formaldehyde. Living in a mobile home and the presence of urea–formaldehyde foam insulation, particle-board or plywood in residences were taken as indirect measures of residential exposure. Five of the patients with sinonasal cancer had lived in a mobile home (odds ratio, 0.6; 95% CI, 0.2–1.7), all for fewer than 10 years; 25 had lived in residences constructed with particle-board or plywood, which yielded odds ratios of 1.8 (95% CI, 0.9–3.8) for periods of < 10 years and 1.5 (95% CI, 0.7–3.2) for ≥ 10 years. The risks associated with exposure to formaldehyde foam insulation could not be estimated, because of low exposure frequencies.

Roush *et al*. (1987) reported on a population-based case–control study of 371 men registered at the Connecticut (USA) Tumor Registry with a diagnosis of sinonasal cancer (198 cases) or nasopharyngeal cancer (173 cases), who had died of any cause in Connecticut in 1935–75, and 605 male controls who had died during the same period and were selected randomly from the files of Connecticut death certificates, without stratification or matching. Information on the occupations of the study subjects was derived from death certificates and from annual city directories; the latter were consulted 1, 10, 20, 25, 30, 40 and 50 years before death, when available. Odds ratios for occupation–cancer relationships based on occupational information obtained from death certificates were similar to the corresponding odds ratios based on city directory information in two previous studies. Each occupation held by case patients and controls was assessed by an industrial hygienist (blinded to case–control status) with regard to the likelihood (none, possibly, probably, definitely) and level (0, < 1 ppm, ≥ 1 ppm) of workplace exposure to formaldehyde, and study subjects were subsequently categorized into one unexposed and four exposed groups according to degrees of probable exposure to formaldehyde. For sinonasal cancer, the odds ratio, adjusted for age at death, year of death and number of jobs reported, was 0.8 (95% CI, 0.5–1.3) for those who had probably been exposed to some level of formaldehyde for most of their working life compared with all others. In order to evaluate high short-term exposures, the odds ratio for those who fulfilled the more restricted exposure criteria of being probably exposed to some level for most of their working life and probably exposed to high levels for some years was 1.0 (95% CI, 0.5–2.2) and, for those who had probably been exposed to some level for most

of their working life and probably exposed to high levels at some point 20 or more years before death, the odds ratio was 1.5 (95% CI, 0.6–3.9).

Luce *et al.* (1993) conducted a case–control study of men and women who had primary malignancies of the nasal cavities and paranasal sinuses and were diagnosed in one of 27 hospitals in France between January 1986 and February 1988. Three hundred and three cases were identified; 57 had died and, of the remaining 246 cases, 32 could not be located or were too ill and seven refused to participate. Histological confirmation was available in the medical records of all but one of the remaining 207 case patients. Four hundred and forty-three control subjects were selected by frequency matching for age and sex among patients in whom another cancer had been diagnosed during the same period at the same or a nearby hospital (340 subjects) or from a list of names of healthy individuals provided by the cases (103 subjects). Sixteen could not be located or were too ill and 18 declined to participate, which left 409 controls for analysis. Occupational exposures to formaldehyde and 14 other substances or groups of substances were assessed by an industrial hygienist on the basis of information that was obtained during a personal interview at the hospital (for the cancer patients) or at home (for the healthy controls) on job histories, a number of pre-defined occupational exposures, socioeconomic variables and tobacco smoking habits. Study subjects were classified according to the likelihood of exposure to each of the suspected determinants of sinonasal cancer and were grouped into one of four categories: none, possible, probable or definite exposure; the latter two were further split into a number of subgroups according to three levels and calendar periods of exposure and combinations thereof. For formaldehyde, a cumulative index was calculated from the levels and duration of exposure, as well as lifetime occupational exposure. Among men, 36% of the controls and 55% of the cases were classified as potentially exposed to formaldehyde. The risks associated with exposure to formaldehyde were reported for men only. For the 59 cases who had squamous-cell carcinoma, odds ratios (adjusted for age and exposure to wood and glue) were 1.26 (95% CI, 0.54–2.94) and 0.68 (95% CI, 0.27–1.75) for the index categories of lower and higher cumulative exposure among the probable/definite exposure group. Similar patterns were evident by lifetime average level and duration of exposure. Among the 82 cases of adenocarcinoma, 67 were in the probable/definite exposure group. Odds ratios (adjusted for age and exposure to wood and glue) categorized into three levels of the cumulative exposure index were 1.13 (95% CI, 0.19–6.90), 2.66 (95% CI, 0.38–18.70) and 6.91 (95% CI, 1.69–28.23), respectively. However, most (71/82) of the formaldehyde-exposed cases of adenocarcinoma had also been exposed to wood dust, and the odds ratio for being exposed to wood dust and formaldehyde versus neither was very large (odds ratio, 692; 95% CI, 91.9–5210). Only four cases of adenocarcinoma were classified as exposed to formaldehyde but not wood dust (odds ratio, 8.1; 95% CI, 0.9–72.9). [The Working Group noted that residual confounding by exposure to wood dust may have occurred.]

2.2.2 *Nasopharyngeal carcinoma*

The study design of and results from case–control studies of the association of exposure to formaldehyde with cancer of the nasopharynx are summarized in Table 18.

The study by Olsen *et al*. (1984) (described in detail in Section 2.2.1) also evaluated the risk of exposure to formaldehyde among 266 men and women who had been diagnosed with nasopharyngeal cancer. The odds ratio, unadjusted for other occupational exposures, for exposure to formaldehyde was 0.7 (95% CI, 0.3–1.7) for men and 2.6 (95% CI, 0.3–21.9) for women.

The association between nasopharyngeal carcinoma and exposure to formaldehyde was also examined in the population-based case–control study in 13 counties of Washington State conducted by Vaughan *et al*. (1986a,b) (described in Section 2.2.1). The odds ratios increased slightly with all of the measures of occupational exposure examined in this study. The observed odds ratios in the analysis of the maximum exposure level achieved were: 1.2 (seven exposed cases; 95% CI, 0.5–3.3) for low exposure and 1.4 (four exposed cases; 95% CI, 0.4–4.7) for medium or high exposures; 1.2 (eight exposed cases; 95% CI, 0.5–3.1) for 1–9 years and 1.6 (three exposed cases; 95% CI, 0.4–5.8) for ≥ 10 years of exposure; and 0.9 (three exposed cases; 95% CI, 0.2–3.2) for 5–19 units and 2.1 (three exposed cases; 95% CI, 0.6–7.8) for ≥ 20 units of the cumulative exposure score. When a lag period of 15 years or more was introduced into the analysis, the odds ratio associated with the highest cumulative exposure score to formaldehyde was unchanged (two exposed cases; odds ratio, 2.1; 95% CI, 0.4–10). An association was found between living in a mobile home and risk for nasopharyngeal cancer, with odds ratios of 2.1 (four exposed cases; 95% CI, 0.7–6.6) for < 10 years and 5.5 (four exposed cases; 95% CI, 1.6–19.4) for ≥ 10 years of residence. An analysis was performed that considered the joint effect of occupational exposure and residence in a mobile home. Subjects were considered to be occupationally exposed in this analysis if they had a cumulative exposure score of 5 or more. A relatively strong association was observed among individuals who were exposed occupationally and had ever lived in a mobile home compared with those who had neither exposure (odds ratio, 6.7; 95% CI, 1.2–38.9), although this finding was based on only two cases and seven controls with joint exposure.

In the study by Roush *et al*. (1987) (described in Section 2.2.1), the odds ratios for men with nasopharyngeal cancer were presented in the following categories: those who had probably been exposed to some level for most of their working life; those who had probably been exposed to some level for most of their working life and probably been exposed to high levels for some years; and those who had probably been exposed to some level for most of their working life and probably been exposed to high levels at some point 20 or more years before death. The odds ratios were, respectively, 1.0 (95% CI, 0.6–1.7), 1.4 (95% CI, 0.6–3.1) and 2.3 (95% CI, 0.9–6.0).

The etiology of nasopharyngeal carcinoma was studied in the Philippines; both viral (Hildesheim *et al*., 1992) and non-viral (West *et al*., 1993) risk factors were addressed. West *et al.* (1993) conducted a case–control study of 104 histologically confirmed cases of

nasopharyngeal carcinoma in Rizal Province, where the incidence rates of this tumour (4.7/100 000 men and 2.6/100 000 women) were intermediate between those in China and those in western countries. The cases (100% response rate) were identified at the Philippines General Hospital, as were 104 hospital controls (100% response rate), who were matched to cases on sex, age and type of hospital ward; 101 community controls (77% response rate), who were matched on sex, age and neighbourhood, were also available. Hospital controls were selected from the rosters of patients who were present on the same day that a suspected case was confirmed by biopsy; patients who had disorders that were possibly linked to dietary patterns were excluded (gastrointestinal cancer, peptic ulcer, chronic cirrhosis, gallbladder disease). Community controls were asked to participate on the basis of their living in a house close to that of their matched case. A personal interview included questions on tobacco smoking and areca nut habits, diet, sociodemographic variables and occupational history. An industrial hygienist classified each job held by the study subjects as likely or unlikely to involve exposure to formaldehyde, solvents, exhaust fumes, wood dust, dust in general and pesticides, and combined the classification with information on period and duration of employment in such occupations. Since the findings on occupational exposures did not differ when hospital and community controls were considered separately, only results from the comparison of cases versus all controls are shown. Four exposure indices were established for each subject: total duration, duration lagged by 10 years, number of years since first exposure and age at first exposure. The risk for nasopharyngeal carcinoma was associated with exposure to formaldehyde; the odds ratios, adjusted for the effects of dusts and exhaust fumes and other suspected risk factors, were 1.2 (12 exposed cases; 95% CI, 0.41–3.6) for subjects who were first exposed < 25 years before diagnosis and 4.0 (14 exposed cases; 95% CI, 1.3–12.3) for those who were first exposed ≥ 25 years before diagnosis. In the subgroup of subjects who were first exposed to formaldehyde ≥ 25 years before diagnosis and first exposed to dust and/or exhaust fumes ≥ 35 years before diagnosis, an odds ratio of 15.7 (95% CI, 2.7–91.2) was found relative to people who were not exposed to either factor [numbers exposed not given]. The odds ratio for an overall exposure of ≥ 15 years (eight exposed cases; odds ratio, 1.2; 95% CI, 0.48–3.2) was lower than that for a duration of < 15 years (19 exposed cases; odds ratio, 2.7; 95% CI, 1.1–6.6). However, when exposure was lagged by 10 years, those exposed for ≥ 15 years showed an odds ratio of 2.1 (eight exposed cases; 95% CI, 0.70–6.2). Subjects who were first exposed before the age of 25 years had an odds ratio of 2.7 (16 exposed cases; 95% CI, 1.1–6.6), while the odds ratio for those who were first exposed at age 25 or more years was 1.2 (11 exposed cases; 95% CI, 0.47–3.3). Subjects who reported daily use of anti-mosquito coils had a 5.9-fold (95% CI, 1.7–20.1) increase in risk compared with those who reported never using coils in a model that adjusted for potential confounders (West *et al.*, 1993). [The Working Group noted that formaldehyde has been reported to occur in the smoke released from anti-mosquito coils (see Section 1), and that the authors did not control for the presence of Epstein-Barr viral (EBV) antibodies, which showed a strong association with nasopharyngeal cancer (odds ratio, 21) in the study of Hildesheim *et al.* (1992).]

A study from Malaysia investigated nasopharyngeal cancer based on cases that were ascertained through records of histologically confirmed diagnoses at four centres that had a radiotherapy unit (Armstrong *et al*., 2000). In total, 530 Chinese cases of squamous-cell carcinomas of the nasopharynx who had resided in the study area for at least 5 years were diagnosed between 1 January 1987 and 30 June 1992. Among these, only 282 (53%) were included in the study (69% men), since 121 (23%) had died, 63 (12%) could not be located, four (1%) were too ill to participate and 60 (11%) refused to participate. One control with no history of cancer of the head, neck or the respiratory system was selected from the Chinese population who had resided for at least 5 years in the study area and matched to each case by sex and age (within 3 years). Information on exposures (complete residential and occupational history, alcohol and tobacco use and consumption of 55 food items at age 10 and 5 years before diagnosis) of cases and controls was obtained by structured in-home interviews by trained interviewers. Occupational history included job description, work performed, calendar time, machines, tools and substances used, size and type of workplace, and exposure to dusts, smoke, gases and chemicals. [It appears that additional questionnaires that collected more detailed information on some jobs were also used.] Exposure to 22 agents, which were selected for their ability to deposit on or be absorbed into the nasopharynx, was identified by job, calendar years, frequency (days per week) and duration (hours per day). Jobs were coded using the official Malaysian classification scheme. Four levels of exposure (none, low, medium and high) were established. [It was not clear whether the exposure assessment was made using a job–exposure matrix approach or on an individual level, because both approaches are referenced.] Dermal exposure was considered. The proportion of study participants with exposure to formaldehyde was 9.9% of cases and 8.2% of controls. For any versus no occupational exposure to formaldehyde, the odds ratio for both sexes combined was 1.24 (95% CI, 0.67–2.32) and 0.71 (95% CI, 0.34–1.43) after adjustment for diet and tobacco use. No dose–response relationship appeared with increasing duration of formaldehyde exposure.

In a multicentred, population-based case–control study from five cancer registries in the USA, associations between occupational exposure to formaldehyde and wood dust and nasopharyngeal cancer were investigated (Vaughan *et al*., 2000). At four of the five registries, the investigators identified cases diagnosed between 1 April 1987 and 30 June 1991, while case ascertainment at the fifth registry was extended for an additional 2 years. Eligible cases were men and women aged 18–74 years who had any histological type of nasopharyngeal cancer. Interviews were completed for 231 of the 294 eligible cases identified, and included 44 (19%) that were conducted with the next of kin (usually the spouse). The 196 cases who had epithelial cancers were further classified into three histological subgroups: differentiated squamous-cell (118 cases), undifferentiated or non-keratinizing (54 cases) or epithelial not otherwise specified (24 cases). Controls were identified by random-digit dialling and were frequency-matched by age (5-year age groups), sex and cancer registry. Among 324 eligible controls, 246 were interviewed (76%), two of whom were excluded because they had no telephone, which left 244 controls for analysis; for three controls, the interview was conducted with the next of kin. Experienced interviewers from

each of the five cancer registries conducted structured telephone interviews with the study subjects, which included questions on demographic background, previous medical conditions and use of medication, family history of cancer, use of alcohol and tobacco, and a lifetime history of occupational and chemical exposures, including those to formaldehyde and wood dust. For each job that had been held for at least 6 months, information was collected on job title, typical activities within the job, the type of industry and the dates at which employment began and ended. Industrial hygienists blindly assessed exposure to formaldehyde and wood dust on a job-by-job basis for each subject, based on all the available information. For each job held, both the probability (none or unlikely, possible, probable, definite) of exposure to formaldehyde and a related estimated concentration of exposure to formaldehyde (low, moderate, high) which represented an 8-h TWA were assigned. Cut-off points for analyses by duration and cumulative exposure were based on the 50th and 75th percentiles among exposed controls. The proportion of subjects who were potentially exposed to formaldehyde was 40.3% of cases compared with 32.4% of controls. For persons who were ever exposed occupationally to formaldehyde versus those who were unexposed, the odds ratio adjusted for age, sex, race, cancer registry, cigarette use, next-of-kin status and education for all epithelial nasopharyngeal cancer was 1.3 (95% CI, 0.8–2.1); for the histological subcategories of undifferentiated and non-keratinizing, differentiated squamous-cell and epithelial not otherwise specified, the odds ratios were 0.9 (95% CI, 0.4–2.0), 1.5 (95% CI, 0.8–2.7) and 3.1 (95% CI, 1.0–9.6), respectively. There was no consistent pattern of association or trend in risk with estimated maximum exposure concentration for all histological types combined. A trend of increasing risk was seen with increasing duration of exposure ($p_{trend} = 0.07$). The odds ratio for persons who had worked at least 18 years in jobs with potential exposure was 2.1 (95% CI, 1.0–4.5). Further analyses were conducted that excluded cancers of undifferentiated and non-keratinizing histology. The adjusted odds ratio by estimated probability of exposure to formaldehyde was 1.6 (95% CI, 1.0–2.8) for ever having held a job classified as 'possible, probable or definite', 2.1 (95% CI, 1.1–4.2) for 'probable or definite' and 13.3 (95% CI, 2.5–70) for 'definite'. Within the group classified with 'possible, probable or definite' exposure to formaldehyde, the subgroups with duration of exposure of 1–5 years, 6–17 years and over 18 years had odds ratios of 0.9 (95% CI, 0.4–2.1), 1.9 (95% CI, 0.9–4.4) and 2.7 (95% CI, 1.2–6.0), respectively, and the p_{trend} value for a dose–response relationship was 0.014. A similar dose–response pattern within this group was seen for estimated cumulative exposure ($p_{trend} = 0.033$). When the group was restricted to subjects with probable or definite exposure, the significance of trends lessened with respect to duration of exposure ($p = 0.069$) and cumulative exposure ($p = 0.13$). When a 10-year lag period was included, the overall findings remained similar. Moreover, the odds ratios for exposure to formaldehyde were essentially unaffected by adding exposure to wood dust to the models.

Hildesheim *et al*. (2001) investigated the associations between occupational exposure to formaldehyde, wood dust and organic solvents and risk for nasopharyngeal cancer. Incident cases (< 75 years) with histologically confirmed diagnoses were identified from two hospitals in Taipei, China (Province of Taiwan). Of 378 eligible cases that were identified,

375 agreed to participate in the study. About one third (31%) of the cases were women. One control with no history of nasopharyngeal cancer was matched to each case with respect to age (5 years), sex and district of residence. In total, 87% of eligible controls agreed to participate, which left 325 controls for the analysis. All study participants were interviewed by trained interviewers (nurses). Cases were interviewed at the time of biopsy and before treatment. The interviews obtained information on sociodemographic characteristics, diet, cigarette smoking and betel-quid chewing, residential and medical history and a complete occupational history for all jobs that had been held for at least 1 year since the age of 16 years. Living mothers were interviewed about the childhood diet of study participants. Data on occupational history were reviewed blindly by an industrial hygienist. Standard industrial and occupational classification codes were assigned to each job. Each code was assigned a classification (10 levels) for probability and intensity of exposure to formaldehyde, wood dust and organic solvents. In total, 156 of 2034 jobs (7.7%) were classified as entailing exposure to formaldehyde. Blood specimens were collected from 369 cases and 320 controls, and serum was tested for various antibodies against EBV, which is known to be associated with nasopharyngeal cancer. After adjustment for age, sex, education and ethnicity, the odds ratio (both sexes combined) for ever exposure to formaldehyde was 1.4 (95% CI, 0.93–2.2). The odds ratios for ≤ 10 years and > 10 years of exposure to formaldehyde were 1.3 (95% CI, 0.69–2.3) and 1.6 (95% CI, 0.91–2.9), respectively. Those exposed for > 20 years had an odds ratio of 1.7 (95% CI, 0.77–3.5), but the trend for ≤ 10, 10–20, and > 20 years of exposure did not reach statistical significance. The odds ratios by estimated cumulative exposure (intensity × duration) gave a similar pattern. The observed associations were not substantially affected by additional adjustment for exposure to wood dust or organic solvent. In the sub-analyses that were restricted to 360 cases and 94 controls who were seropositive for at least one of five antibodies against EBV, the association between exposure to formaldehyde and nasopharyngeal cancer appeared to be stronger to some extent. Thus, the odds ratio of ever versus never having been exposed was 2.7 (95% CI, 1.2–6.2). However, no clear dose–response pattern was observed with increasing duration of exposure or estimated cumulative exposure.

2.2.3 *Cancers of the oro- and hypopharynx*

The study design of and results from case–control studies of the association of exposure to formaldehyde with cancer of the oro- and hypopharynx are summarized in Table 18.

The association between oro- and hypopharyngeal cancer and exposure to formaldehyde was examined in the population-based case–control study by Vaughan *et al*. (1986a,b) (described in detail in Section 2.2.1). Evidence for a weak trend in the odds ratios was observed with the number of years of occupational exposure to formaldehyde (odds ratio, 0.6; 95% CI, 0.3–1.0 for 1–9 years; odds ratio, 1.3; 95% CI, 0.7–2.5 for ≥ 10 years) and the exposure score (odds ratio, 0.6; 95% CI, 0.3–1.2 for 5–19 units; odds ratio, 1.5; 95% CI, 0.7–3.0 for ≥ 20 units), but not with the maximum exposure level

attained (odds ratio, 0.8; 95% CI, 0.5–1.4 for low; odds ratio, 0.8; 95% CI, 0.4–1.7 for medium; odds ratio, 0.6; 95% CI, 0.1–2.7 for high). No association was observed between risk for oro- and hypopharyngeal cancer and living in a mobile home (odds ratio, 0.9; 95% CI, 0.5–1.8 for 1–9 years; odds ratio, 0.8; 95% CI, 0.2–2.7 for ≥ 10 years), or duration of living in residences with internal construction or renovation using particle-board or plywood (odds ratio, 1.1; 95% CI, 0.7–1.9 for 1–9 years; odds ratio, 0.8; 95% CI, 0.5–1.4 for ≥ 10 years).

Gustavsson *et al*. (1998) carried out a case–control study of histologically verified squamous-cell carcinoma of the oral cavity, pharynx, larynx and oesophagus among men aged 40–79 years who were born in Sweden and were resident in two regions of the country. Between 1 January 1988 and 31 January 1991, the investigators sought to identify all incident cases of these tumours in the study population through weekly reports from departments of otorhinolaryngology, oncology and surgery, supplemented by information from regional cancer registries. Cases identified incidentally at autopsy were excluded. The referents were selected by stratified random sampling from population registers, and were frequency-matched to the cases for region and age in 10- or 15-year age groups. All subjects were interviewed by one of two nurses (the cases were mostly interviewed in hospital and the referents mainly at home), who used a structured questionnaire to obtain information on smoking, oral snuff use, alcohol consumption and lifetime history of jobs held for > 1 year. The work histories were reviewed by an occupational hygienist who was blind to the case or referent status of the subject, and were coded for intensity and probability of exposure to 17 agents, including formaldehyde; 9.4% of the referents were classed as exposed. An index of cumulative exposure was derived from the product of the probability, intensity and duration of exposure across the entire work history. Exposure histories were available for 90% of the 605 cases identified (including 138 who had pharyngeal cancer) and for 85% of the 756 referents. [The exact number of cases of pharyngeal cancer included in study was not reported.] Unconditional logistic regression was used to estimate incidence rate ratios adjusted for region, age (in 10- or 15-year bands), average alcohol intake over the past 5 years (four levels) and smoking status (current, former or never). The incidence rate ratio for pharyngeal cancer and formaldehyde was 1.01 (95% CI, 0.49–2.07) based on 13 exposed cases.

A case–control study of incident male cases of hypopharyngeal and laryngeal squamous-cell cancers was conducted at 15 hospitals in France between 1 January 1989 and 30 April 1991 (Laforest *et al*., 2000). Initially, 664 such patients were identified, but 21% of cases from the combined group were excluded due to health problems, death before interview, refusal, being non-alcohol drinkers or because they could not be contacted, which left 201 cases of hypopharyngeal cancer for analysis. Potential controls were male patients with primary cancers at other sites who were selected from the same or nearby hospitals as the cases, were recruited between 1987 and 1991 and were frequency-matched to the cases by age. Of the 355 controls who were initially identified, 59 [17%] were excluded for similar reasons as the cases. Specially trained occupational physicians interviewed the study subjects on demographic characteristics, alcohol consumption, use of tobacco and lifetime

occupational history. Each job was coded with respect to occupation and industry, and occupational exposures, including formaldehyde, were assessed using a previously developed job–exposure matrix to estimate the probability and level of exposure. An index of cumulative exposure was derived for each subject based on the product of probability, level and duration of exposure in each job. Altogether, [29%] of controls and [41%] of the cases of hypopharyngeal cancer were classified as ever having been exposed to formaldehyde. The age-, asbestos-, coal dust-, alcohol- and smoking-adjusted odds ratio for ever versus never exposure to formaldehyde was 1.35 (95% CI, 0.86–2.14). There was a trend of increasing odds ratios with increasing probability of exposure to formaldehyde ($p_{trend} < 0.005$); a probability of exposure of over 50% showed an odds ratio of 3.78 (95% CI, 1.50–9.49). No significant trends were noted by duration of exposure or estimated cumulative exposure. After exclusion of study subjects who had a probability of exposure to formaldehyde of less than 10%, the odds ratio increased with duration of exposure ($p_{trend} < 0.04$) and with cumulative level of exposure ($p_{trend} < 0.14$). [The Working Group noted that the controls were interviewed at a later date than cases and did not necessarily come from the same hospital, and that interviewers were not blind to the case–control status, although they were not aware of the study hypotheses.]

A case–control study of incident laryngeal and hypopharyngeal cancer was conducted during 1979–82 in six centres in four European countries (Berrino *et al*., 2003). An attempt was made to include all incident cases from the centres, and 304 cases of hypopharyngeal cancer (including the epilarynx) were included. The participation rate varied by centre from 70 to 92%. Initially, the purpose of the study was to investigate the association between alcohol consumption, use of tobacco and diet and cancer at the two sites. An age- and sex-stratified random sample of controls was selected from the general population from each centre with an average participation rate of 74%. Information on alcohol consumption, tobacco smoking, diet and all jobs held for at least 1 year after 1944 was obtained by in-person interviews at the hospital before the treatment of cases; controls were interviewed at home. A panel of occupational physicians, industrial hygienists and chemical engineers assessed blindly the probability of exposure to 16 industrial chemicals, including formaldehyde. Among persons younger than 55 years [for whom a lifelong complete job history was available], the odds ratio for hypopharyngeal cancer (100 cases) adjusted for age, centre, tobacco use, alcohol consumption, socioeconomic status, diet and exposure to potential chemical confounders was 1.3 (95% CI, 0.6–2.6) in the group that was possibly exposed versus those who were never exposed and 0.5 (95% CI, 0.1–1.8) in the group that was probably and certainly exposed versus those who were never exposed to formaldehyde. [It is unclear whether controls were all from the catchment populations of the hospitals at which the cases were diagnosed. In research outside this study to evaluate the job–exposure matrix used, it was found that its performance for formaldehyde was poor. Any resultant misclassification of exposures would be expected to bias risk estimates towards unity.]

2.2.4 *Cancers of the lung and larynx*

The study design of and results from case–control studies of the association of cancers of the lung and larynx with exposure to formaldehyde are summarized in Table 19.

Andersen *et al*. (1982) conducted a case–control study in Denmark of doctors (79 men and five women) for whom a notification of lung cancer had been made in the files of the nationwide Danish Cancer Registry during the period 1943–77. Three control subjects per case, matched individually on sex and age, were selected at random from among individuals on official lists of Danish doctors. Information on postgraduate specialization and places of work during the professional career of cases and controls was obtained from medical directories and supplementary files at the Danish Medical Society. Potential exposure to formaldehyde was assumed to be associated with working in pathology, forensic medicine and anatomy. None of the doctors who had lung cancer had specialized in any of these fields, but one control doctor was a pathologist. Eight male case patients and 23 controls had been employed at some time in pathology, forensic medicine or anatomy, to give an odds ratio of 1.0 (95% CI, 0.4–2.4).

Fayerweather *et al.* (1983) reported on a case–control study of mortality from cancer among chemical workers in eight plants in the USA where formaldehyde was manufactured or used. A total of 493 active or pensioned men were known to have died from cancer during 1957–79, but 12 were excluded from the study because their work histories were unavailable. The remaining 481 men were individually matched on age, pay class, sex and date of first employment to 481 controls selected from among employees who had been on the company's active pay rolls during the last year of employment of the corresponding case. The cases included 181 lung cancers and eight laryngeal cancers. The work histories of both case and control subjects were ascertained principally from personnel records, but also from medical records and interviews with colleagues; a job–exposure matrix was used to classify jobs according to the nature and level of exposure to formaldehyde that they entailed into three categories: 'continuous-direct', 'intermittent'or 'background'. Smoking histories were obtained for about 90% of subjects, primarily by interviewing living co-workers. Of the 481 cases, 142 (30%) had had potential exposure to formaldehyde. The data were analysed by latency period, duration of exposure, exposure level and frequency, cumulative exposure index, age at and year of death and age at and year of first exposure. In none of the analyses was the relative risk for lung cancer significantly greater than 1.0 ($p > 0.05$). When a cancer induction period of 20 years was allowed for, 39 subjects with lung cancer and 39 controls had potentially been exposed to formaldehyde; the odds ratios were 1.20 [95% CI, 0.6–2.8] and 0.79 [95% CI, 0.4–1.6] for subgroups with < 5 years and ≥ 5 years of exposure, respectively.

In a population-based case–control study, Coggon *et al.* (1984) used death certificates to obtain information on the occupations of all men under the age of 40 years in England and Wales who had died from bronchial carcinoma during 1975–79. These were compared with controls who had died from any other cause, and who were matched for sex, year of death, local authority district of residence and date of birth (within 2 years). Of 598 cases

Table 19. Case–control studies of cancers of the lung and larynx

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Andersen *et al.* (1982), Denmark, 1943–77	Lung	84 doctors (79 men, five women) registered in Denmark who died of lung cancer	252 randomly selected from official list of Danish doctors, matched on sex and age	Information on postgraduate specialization and professional career employment	Ever employed in pathology, forensic medicine or anatomy	1.0 (0.4–2.4)		Both cases and controls were medical doctors.
Fayerweather *et al.* (1983), USA, 1957–79	Lung and larynx	Active or pensioned employees (all men) who died of cancer (181 lung, eight larynx)	189 employees matched on sex, age, pay class and date at first employment, selected from annual payroll roster among employees active during the case's last year of employment	Job–exposure matrix to classify exposure according to frequency and intensity (continuous/ direct, intermittent, background) based on personnel and medical records and interviews with colleagues	Lung < 5 years ≥ 5 years	 1.20 [0.6–2.8] 0.79 [0.4–1.6]	Tobacco smoking	Analysis included a latency period of 20 years between exposure and disease.
Coggon *et al.* (1984), United Kingdom, 1975–79	Lung (bronchial carcinoma)	598 men ≤ 40 years old who died of bronchial carcinoma in England and Wales	1180 men who had died from any other cause, matched by year of death, district of residence and date of birth (± 2 years)	Job–exposure matrix based on classification coding in three categories (none, low, high) of exposure	All exposed occupations Occupations with high exposure	1.5 (1.2–1.8) 0.9 (0.6–1.4)		$p < 0.001$

Table 19 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Gérin *et al.* (1989), Canada, 1979–85	Lung (oat-cell carcinoma; squamous-cell carcinoma; adenocarcinoma; others including unspecified)	857 men aged 35–70 years resident in the area of Montréal	1523 men with cancer at other sites (cancer controls) and 533 men selected from electoral list (population controls), stratified by age	Semi-structured questionnaire on lifetime work history; exposure profile developed based on probability, frequency, concentration and duration of exposure and period of first exposure	Cancer controls Ever Short Long-low Long-medium Long-high Population controls Ever Short Long-low Long-medium Long-high	 0.8 (0.6–1.0) 0.8 (0.6–1.2) 0.5 (0.3–0.8) 1.0 (0.7–1.4) 1.5 (0.8–2.8) 0.8 (0.6–1.1) 1.0 (0.6–1.8) 0.5 (0.3–0.8) 0.9 (0.5–1.6) 1.0 (0.4–2.4)	Age, ethnic group, socio-economic status, cigarette smoking, dirtiness of job and various other potential confounders	Increased relative risk for adenocarcinoma of the lung with long exposure to high concentration
Wortley *et al.* (1992), United Kingdom, 1983–87	Larynx (ICD-0 161.0–161.9)	235 [sex distribution not given] identified through local cancer surveillance system	547 identified by random-digit dialling selected to be similar in age and same sex	In-person interview; job–exposure matrix based on both likelihood and degree of exposure	Peak Low Medium High Duration < 1 year 1–9 years ≥ 10 years Exposure scores < 5 5–19 ≥ 20	 1.0 (0.6–1.7) 1.0 (0.4–2.1) 2.0 (0.2–19.5) 1.0 0.8 (0.4–1.3) 1.3 (0.6–3.1) 1.0 1.0 (0.5–2.0) 1.3 (0.5–3.3)	Age, tobacco smoking, alcohol drinking and education	
Brownson *et al.* (1993), USA, 1986–91	Lung	429 white women aged 30–84 years, former or never smokers	1021 women selected from state driver's licence files (< 65 years old) or health care roaster (≥ 65 years old), group- matched for age	Telephone and in-person interview	Ever exposed	0.9 (0.2–3.3)	Age and history of previous lung disease	All exposed cases and controls were lifelong non-smokers.

Table 19 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Gustavsson *et al.* (1998), Sweden, 1988–91	Larynx (ICD-9 161)	157 male incident cases aged 40–79 years	641 selected by stratified random sampling; frequency-matched to cases by age (10–15-year groups) and region	Work history reviewed by occupational hygienist; occupations coded by intensity and probability of exposure	Ever exposed	1.45 (0.83–2.51)	Region of incidence, age, alcohol intake and tobacco smoking status	
Laforest *et al.* (2000), France, 1989–91	Larynx (ICD code not given)	296 men with confirmed histology of cancer of the epilarynx, glottis, supraglottis, subglottis and larynx unspecified	296 men with other (selected) primary tumours selected from the same or nearby hospitals, recruited in 1987–91, matched by age	Structured in-person interviews; occupational exposures were assessed with a job–exposure matrix developed earlier	Ever exposed Exposure probability < 10% 10–50% > 50% *Excluding subjects with exposure probability < 10%* Ever exposed Duration of exposure < 7 years 7–20 years > 20 years Cumulative exposure Low Medium High	1.14 (0.76–1.70) 1.16 (0.73–1.86) 1.12 (0.55–2.30) 1.04 (0.44–2.47) 1.17 (0.63–2.17) 1.68 (0.60–4.72) 0.86 (0.33–2.24) 1.14 (0.47–2.74) 0.68 (0.12–3.90) 1.86 (0.76–4.55) 0.91 (0.42–1.99)	Age, tobacco smoking, alcohol drinking and exposure to coal dust	

Table 19 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Berrino *et al.* (2003), France, Italy, Spain, Switzerland, 1979–82	Larynx (glottis, supraglottis)	213 male incident cases aged ≤ 55 years	819 men from general local population of each centre, stratified by age	Structured in-person interviews; occupational exposures assessed by an expert panel using a previously established job–exposure matrix	Probability of exposure Possible Probable or definite	 1.4 (0.8–2.7) 1.0 (0.4–2.3)	Age, centre, tobacco use, alcohol drinking, diet, socioeconomic status, asbestos, PAHs, chromium, arsenic, wood dust, solvents, other dusts and gases	[The credibility of the negative finding is limited because formaldehyde was the agent for which the validity of the job–exposure matrix was lowest.]
Elci *et al.* (2003), Turkey, 1979–84	Larynx (ICD-0 161.0–2, –9)	940 male incident cases at Oncology Treatment Center	1519 male patients with malignant or benign pathology	Standardized questionnaire administered at hospital on occupational history; job–exposure matrix	Ever exposed Intensity Low Medium High Probability Low Medium High	1.0 (0.8–1.3) 1.1 (0.8–1.5) 0.5 (0.2–1.3) 0.7 (0.1–7.1) 1.0 (0.7–1.4) 1.1 (0.6–2.2) 1.0 (0.1–11.2)	Age, tobacco use and alcohol drinking	Analysis by subtype of cancer (glottis, supraglottis, other) did not show any elevation of risk. No trend with intensity or probability of exposure

CI, confidence interval; ICD, international code of diseases; PAHs, polycyclic aromatic hydrocarbons

who were identified, 582 were matched with two controls and the remainder with one control. Occupations were coded according to the Office of Population Census and Surveys 1970 classification, and a job–exposure matrix was constructed by an occupational hygienist, in which the occupations were grouped according to three levels (high, low and none) of exposure to nine known or putative carcinogens, including formaldehyde. The group of occupations that were classed as entailing exposure to formaldehyde was associated with an elevated odds ratio for bronchial carcinoma of 1.5 (95% CI, 1.2–1.8); for those occupations in which exposure was presumed to be high, the odds ratio was 0.9 (95% CI, 0.6–1.4). [The Working Group noted that information on occupation from death certificates is limited; they also noted the young age of the subjects and the consequent short exposure and latency.]

In a population-based case–control study in the area of Montréal, Canada, 857 men who were diagnosed with histologically confirmed primary lung cancer during 1979–85 were identified (Gérin *et al*., 1989). Two groups of control subjects were established: one was composed of 1523 men who were diagnosed during the same years as cases with cancers of other organs (oesophagus, stomach, colorectum, liver, pancreas, prostate, bladder, kidney, melanoma and lymphoid tissue) and the other was composed of 533 men who were selected from electoral lists of the Montréal area. Interviews or completed questionnaires that yielded lifelong job history and information on potential non-occupational confounders were obtained from the cancer patients or their next of kin and from the population controls, with response rates of 82% and 72%, respectively. Each job was classified by a group of chemists and hygienists according to the probability, intensity and frequency of exposure to some 300 agents, including formaldehyde. Nearly one-quarter of all men had potentially been exposed to formaldehyde in at least one of the jobs they had held during their working life; however, only 3.7% were considered to be definitely exposed and only 0.2% were considered to have had high exposure, defined as more than 1.0 ppm [1.23 mg/m^3] formaldehyde in the ambient air. Odds ratios, adjusted for age, ethnic group, socioeconomic status, cigarette smoking, the 'dirtiness' of the jobs held and various other potentially confounding workplace exposures, were 0.8 (95% CI, 0.6–1.2) for < 10 years of exposure to formaldehyde, 0.5 (95% CI, 0.3–0.8) for ≥ 10 years of presumed exposure to < 0.1 ppm [0.12 mg/m^3], 1.0 (95% CI, 0.7–1.4) for ≥ 10 years of presumed exposure to 0.1–1.0 ppm [0.12–1.23 mg/m^3] and 1.5 (95% CI, 0.8–2.8) for ≥ 10 years of presumed exposure to > 1.0 ppm formaldehyde compared with controls with other cancers. In comparison with the population controls, the equivalent odds ratios were 1.0 (95% CI, 0.6–1.8), 0.5 (95% CI, 0.3–0.8), 0.9 (95% CI, 0.5–1.6) and 1.0 (95% CI, 0.4–2.4), respectively. Marginally increased risks were seen for subjects with the adenocarcinoma subtype of lung cancer who had had long exposure to a high concentration of formaldehyde, with odds ratios of 2.3 (95% CI, 0.9–6.0) and 2.2 (95% CI, 0.7–7.6) in comparison with the cancer and population control groups, respectively; however, the estimates were based on only seven exposed cases.

Wortley *et al.* (1992) studied 291 male and female residents aged 20–74 years of a 13-county area of western Washington, USA, in whom laryngeal cancer was diagnosed in

1983–87 and notified to a population-based cancer registry in the area; 81% were successfully interviewed. Control subjects were identified by random-digit dialling and were selected when similar in age and of the same sex as cases; 80% of eligible subjects were interviewed, which left 547 for analysis. Lifetime histories of occupational, tobacco smoking and alcohol drinking were obtained by personal interview, and each job held for at least 6 months was coded according to the US census codes for industries and occupations. A job–exposure matrix was used to classify each job according to the probability and degree of exposure to formaldehyde and five other agents. Summary measures were derived for each subject's lifetime peak exposure, duration of exposure and a score based on both duration and level of exposure. The risk for laryngeal cancer, adjusted for age, smoking and drinking habits and length of education, was not associated with exposure to formaldehyde to a significant degree. The odds ratios were 1.0 (95% CI, 0.6–1.7) for patients with any 'low' exposure, 1.0 (95% CI, 0.4–2.1) for any 'medium' exposure and 2.0 (two exposed cases; 95% CI, 0.2–20) for any 'high' exposure. Odds ratios of 0.8 (95% CI, 0.4–1.3) and 1.3 (95% CI, 0.6–3.1) were seen for exposure for < 10 years and ≥ 10 years and of 1.0 (95% CI, 0.5–2.0) and 1.3 (95% CI, 0.5–3.3) for medium and high formaldehyde score, respectively. [The report suggests that the cases in fact came from only three of the 13 counties, whereas the controls came from the larger area. If this is the case, there may have been important potential for bias.]

A case–control study in Missouri, USA, focused on white women aged 30–84 years, who were lifelong nonsmokers or who had stopped smoking for at least 15 years (Brownson *et al*., 1993). Incident cases of lung cancer during 1986 to mid-1991 were identified through the local cancer registry; information for inclusion in the study was successfully obtained for 429 (69%) of the 650 eligible subjects. This was achieved through two series of interviews completed either by the subject (42%) or her next of kin, during which questions were asked on demographic characteristics, non-occupational risk factors and 28 occupational risk factors, including formaldehyde. For cases under the age of 65 years, controls were obtained from state drivers' licence files, while controls for older cases were selected from Medicare files, group-matched to the cases for age, with a ratio of approximately 2.2:1. Of 1527 potentially eligible controls, 1021 (73%) completed two interviews similar to those for the cases. Analysis was performed using multiple logistic regression. Three cases and 10 controls, all of whom were lifelong nonsmokers, reported occupational exposure to formaldehyde which, with adjustment for age and history of previous lung disease, gave an odds ratio of 0.9 (95% CI, 0.2–3.3).

A case–control study in Sweden of squamous-cell carcinoma of the upper airways and upper digestive tract (Gustavsson *et al*., 1998) (described in detail in Section 2.2.3) compared 157 men who had laryngeal cancer with 641 referents. After adjustment for region of incidence, age, average alcohol intake over the past 5 years and smoking status, the estimated incidence rate ratio for cancer of the larynx in men exposed to formaldehyde was 1.45 (95% CI, 0.83–2.51) based on 23 exposed cases. No dose–response trend was apparent for either cumulative exposure or duration of exposure.

A case–control study at 15 hospitals in France (Laforest *et al*., 2000) (described in detail in Section 2.2.3) included 296 patients with laryngeal cancer. For this disease, comparison with the 296 controls gave an odds ratio (adjusted for age, alcohol consumption, smoking and exposure to coal dust) of 1.14 (95% CI, 0.76–1.70) for exposure to formaldehyde overall. No clear pattern of risk estimates was observed in relation to probability, duration or cumulative levels of exposure.

A case–control study by Berrino *et al*. (2003) at six centres in France, Italy, Spain and Switzerland (described in detail in Section 2.2.3) included 213 cases of laryngeal cancer who were under 55 years of age. No association was found with probable or definite exposure to formaldehyde at levels above the background for the general population (odds ratio, 1.0; 95% CI, 0.4–2.3).

A case–control study of laryngeal cancer in Turkey (Elci *et al*., 2003) focused on patients who were admitted to the oncology centre of a hospital in Istanbul during 1979–84. Information on occupational history and consumption of alcohol and tobacco was elicited at the time of admission by a trained interviewer using a standardized questionnaire, and a job–exposure matrix was applied to the occupational history to assign probability and intensity of exposure to each of five substances including formaldehyde. After exclusion of women and patients with incomplete information on risk factors or tumour site, 940 of 958 cases were available for analysis (mean age, 52.9 years). These men were compared with 1308 controls who had various cancers that are not thought to have the same causes as carcinoma of the larynx and 211 who had benign pathologies. Analysis was performed using unconditional logistic regression with adjustment for age, use of tobacco (ever versus never) and consumption of alcohol (ever versus never). The odds ratio for any exposure to formaldehyde was 1.0 (95% CI, 0.8–1.3) based on 89 exposed cases. No significant elevation of risk was found for subsets of cases classified by anatomical location of the tumour (supraglottis, glottis, others), and there were no significant trends in risk by intensity or probability of exposure. [It is unclear how completely the occupational information in this study reflected lifetime histories of work.]

2.2.5 *Lymphohaematopoietic malignancies*

The study design of and results from the case–control studies of the association of lymphohaematopoietic malignancies and exposure to formaldehyde are summarized in Table 20.

In the study of Gérin *et al*. (1989) (described in detail in Section 2.2.4) in Montréal, Canada, levels of occupational exposure to formaldehyde of 53 cases of Hodgkin lymphoma and 206 cases of non-Hodgkin lymphoma were compared with those of 2599 cases of other cancers and 533 population controls. Using population controls and adjusting for age, ethnic group, self-reported income, tobacco smoking and dirtiness of jobs held, plus occupational and non-occupational factors that were identified as potential confounders, odds ratios for non-Hodgkin lymphoma were 0.7 (13 exposed cases; 95% CI, 0.3–1.6) for < 10 years of exposure compared with non-exposed and 1.1 (15 exposed cases; 95% CI,

Table 20. Case–control studies of lymphohaematopoietic malignancies

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Gérin *et al.* (1989), Canada, 1979–85	Hodgkin lymphoma Non-Hodgkin lymphoma	53 male incident cases 206 male incident cases	533 population-based	Lifetime job histories obtained by interview and translated into level of exposure to formaldehyde	Ever < 10 years duration ≥ 10 years duration Low[a] Medium[a] High[a]	0.5 (0.2–1.4) 0.7 (0.3–1.6) 1.1 (0.5–2.2) 1.0 (0.5–2.1) 0.5 (0.1–1.7)	Age, ethnic group, self-reported income, tobacco smoking, dirtiness of jobs held and potentially confounding occupational and non-occupational factors	Similar results were obtained when 2599 cases of other cancers were used as control group.
Linos *et al.* (1990), USA (years of study not given)	Leukaemia Non-Hodgkin lymphoma	578 male incident cases 622 male incident cases	1245 population-based	Lifetime occupational history obtained	Ever employed in funeral home or crematorium	2.1 [0.4–10.0] based on four exposed cases 3.2 [0.8–13.4] based on six exposed cases	Adjusted for age and state of residence	Significantly elevated relative risks of 6.7 and 6.7 for acute myeloid leukaemia and follicular non-Hodgkin lymphoma, but based on small numbers
Partanen *et al.* (1993), Finland, 1957–1982	Leukaemia Hodgkin disease Non-Hodgkin lymphoma	12 male cases diagnosed among a cohort of 7307 production workers in wood industry Four male cases Eight male cases	79 randomly selected from cohort and matched by year of birth and vital status in 1983 21 52	Work history from company records complemented for cases only by interviews with plant personnel and questionnaires completed by subjects or next of kin; plant- and period-specific job–exposure matrix	< 3 ppm–months ≥ 3 ppm–months < 3 ppm–months ≥ 3 ppm–months < 3 ppm–months ≥ 3 ppm–months	1.00 1.40 (0.25–7.91) (two exposed cases) 1.00 NA (one exposed case) 1.00 4.24 (0.68–26.6) (four exposed cases)	Matching factors accounted for by conditional logistic regression	Data collection was more exhaustive for cases than for controls, which could have led to bias. Relative risk for all three outcomes combined did not substantially change when adjusted for wood dust or for solvents.

Table 20 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
West *et al.* (1995), United Kingdom (years of study not given)	Myelo-dysplastic syndrome	400 (216 men, 184 women) newly diagnosed, resident in study area and aged > 15 years	400 cancer-free patients from out-patient clinics and inpatient wards; matched 1:1 by age (± 3 years), sex, area of residence and hospital and year of diagnosis (± 2 years)	Personal interview on work history and for duration and intensity of exposure to formaldehyde; all questionnaires reviewed by team of experts	> 10 h lifetime exposure of any intensity > 50 h lifetime exposure of medium or high intensity > 2500 h lifetime exposure of medium or high intensity	1.17 [0.51–2.68] 2.33 [0.55–11.35] 2.00 [0.32–15.67]	No adjustment for smoking or other factors	
Tatham *et al.* (1997), USA, 1984–88	Non-Hodgkin lymphoma and sub-groups	1048 men (185 small-cell diffuse lymphoma, 268 follicular lym-phoma and 526 large-cell diffuse lymphoma) from population-based cancer registries, born 1929–53	1659 selected by random-digit dialling, matched by area of registry and 5-year categories of date of birth	Telephone interview including questions on specific materials which participants may have worked with	Ever exposed All combined Small-cell diffuse Follicular Large-cell diffuse	 1.20 (0.86–1.50) 1.40 (0.87–2.40) 0.71 (0.41–1.20) 1.10 (0.79–1.70)	Matching factors, age at diagnosis, year entered the study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviours, use of seizure medication, service in or off the coast of Viet Nam and cigarette smoking	

Table 20 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Blair *et al*. (2001), USA, 1980–83	Leukaemia and myelo-dysplasia	513 white men, 30 years or older, identified from the Cancer Registry of Iowa and among all men from a surveillance network of hospitals in Minnesota; 214 chronic lymphoid, 132 acute myeloid, 46 chronic myeloid, 13 acute lymphoid, 58 myelodysplasia and 50 others	1087 selected by random-digit dialling from Health Care Financing Administration lists and from state death certificate files, frequency-matched by 5-year age group, vital status at time of interview and state of residence	Personal interviews including lifetime occupational history; formaldehyde assessed in a blinded fashion in terms of probability and intensity, each on a 4-point scale based on job title and industry	Acute myeloid Low-medium High Chronic myeloid Low-medium High Chronic lymphoid Low-medium High Myelodysplasia Low-medium High All combined Low-medium High	 0.9 (0.5–1.6) – (no case) 1.3 (0.6–3.1) 2.9 (0.3–24.5) 1.2 (0.7–1.8) 0.6 (0.1–5.3) 0.8 (0.3–1.9) – (no cases) 1.0 (0.7–1.4) 0.7 (0.2–2.6)	Matching factors, post-secondary education, hair dye use, tobacco smoking, first degree relative with hematolympho-poietic tumour and agricultural use of pesticides	None of the acute lymphocytic lymphoma cases was exposed.

AIDS, acquired immunodeficiency syndrome; CI, confidence interval; ICD, international code of diseases; NA, not applicable
[a] Average exposure index

0.5–2.2), 1.0 (14 exposed cases; 95% CI, 0.5–2.1) and 0.5 (five exposed cases; 95% CI, 0.1–1.7) for > 10 years of exposure to low, medium and high cumulative levels, respectively. Because there were only eight exposed cases of Hodgkin lymphoma, the odds ratio for ever versus never exposed was calculated to be 0.5 (95% CI, 0.2–1.4). Odds ratios did not differ substantially when cases of other cancers were used as the control group.

In an analysis of the same multi-site case–control study of Gérin *et al*. (1989), Fritschi and Siemiatycki (1996) evaluated risk from occupational exposure to 294 substances, including formaldehyde, with slightly different numbers of cases of Hodgkin lymphoma (54) and non-Hodgkin lymphoma (215) and 23 cases of myeloma. Cases were compared with a pool of 1066 controls that comprised 533 population controls who were selected from electoral lists of the Montréal area and by random-digit dialling and a random sample of 533 of 2357 patients who had other cancers (excluding lung cancer). Results for exposure to formaldehyde were not presented for Hodgkin or non-Hodgkin lymphoma due to a lack of previous evidence of an association, or for myeloma due to the same lack of previous evidence and because fewer than four cases had been exposed.

In a study of 578 male cases of leukaemia, 622 male cases of non-Hodgkin lymphoma and 1245 population-based controls in Iowa and Minnesota (USA), Linos *et al*. (1990) observed elevated risks for both leukaemia (four exposed cases; odds ratio, 2.1 [95% CI, 0.4–10]) and non-Hodgkin lymphoma (six exposed cases; odds ratio, 3.2 [95% CI, 0.8–13.4]) among men who had been employed in funeral homes and crematoria, which indicated some degree of occupational exposure to formaldehyde and other compounds. The risks were particularly high for the acute myeloid subtype of leukaemia (odds ratio, 6.7 [95% CI, 1.2–36]) and the follicular subtype of non-Hodgkin lymphoma (odds ratio, 6.7 [95% CI, 1.2–37]). However, each of these estimates was based on only three exposed cases.

In Finland, Partanen *et al*. (1993) identified eight cases of non-Hodgkin lymphoma, four cases of Hodgkin disease and 12 cases of leukaemia that were diagnosed between 1957 and 1982 and reported to the Finnish Cancer Registry among a cohort of 7307 production workers who were first employed in the wood industry between 1945 and 1963. One to eight referents were matched to each case by year of birth and vital status in 1983 from among cancer-free cohort members, which resulted in a total of 152 referents. Exposure to a number of substances, including formaldehyde, was estimated based on company records and a job–exposure matrix. For cases, but not for controls, job histories were completed by interviews of selected persons at the plants and by questionnaires sent to the cases or their next of kin in 1982–83. Using a 10-year lag interval, subjects were classified as exposed to formaldehyde when their estimated cumulative exposure reached 3 ppm–months. For leukaemia and lymphomas combined, exposure to formaldehyde was associated with an odds ratio of 2.49 (seven exposed cases; 95% CI, 0.81–7.59) based on conditional logistic regression. Adjustment of the analysis for exposure to solvents or for wood dust or exclusion of subjects who were exposed to solvents did not substantially alter the result. Odds ratios for specific cancers were 4.24 (four exposed cases; 95% CI, 0.68–26.6) for non-Hodgkin lymphoma and 1.40 (two exposed cases; 95% CI, 0.25–7.91) for leukaemia. Only one case of Hodgkin disease was exposed and the odds ratio was not calculated. [The Working Group

as well as the authors noted the small number of cases and the possibility of bias due to the higher accuracy and completeness in the collection of exposure data for cases compared with controls that most probably resulted in an upward bias of odds ratios for all exposures evaluated. However, the odds ratio for all cancers combined was not elevated for wood dust, terpenes, chlorophenols or engine exhaust.]

West *et al*. (1995) evaluated lifetime exposures through occupation, environment and hobby among 400 patients over 15 years of age who had been newly diagnosed with myelodysplastic syndrome in South Wales, Wessex and West Yorkshire, United Kingdom. Of 635 eligible cases, 28% died before the interview, 3% were too ill, 2% had moved out of the study area and 5% refused to participate. Cancer-free controls were selected from outpatient clinics and inpatient wards of medicine, ear, nose and throat surgery, orthopaedics and geriatrics and were individually matched to cases by age (± 3 years), sex, area of residence and hospital, and year of diagnosis (± 2 years). The personal interviews collected, among other information, data on work history and probed study subjects for duration and intensity (low, medium, high) of exposure to more than 70 hazards, including formaldehyde. Lifetime duration of exposure was estimated after consultation with industrial chemists and occupational hygienists. A minimal practical background level of exposure was set at 10 h in a lifetime, under which people were considered to be unexposed. Odds ratios were calculated as the ratio of discordant pairs and were 1.17 (15 exposed cases [95% CI, 0.51–2.68]) for ≥ 10 h lifetime exposure of any intensity versus no exposure, 2.33 ([95% CI, 0.55–11.35]) for > 50 h lifetime exposure of medium or high intensity versus no exposure and 2.00 ([95% CI, 0.32–15.67]) for > 2500 h lifetime exposure of medium or high intensity versus no exposure.

In a population-based case–control study, Tatham *et al*. (1997) evaluated the risks for subtypes of non-Hodgkin lymphoma with respect to exposure to formaldehyde among 1048 male cases that included 185 cases of small-cell diffuse lymphoma, 268 cases of follicular lymphoma and 526 cases of large-cell diffuse lymphoma who were born between 1929 and 1953, diagnosed between 1984 and 1988 and listed in the population-based cancer registries of the states or cities of Connecticut, Iowa, Kansas, Atlanta, Miami, San Francisco, Detroit or Seattle, USA. Diagnosis was confirmed by a panel of three pathologists. A total of 1659 controls were selected by random-digit dialling and were frequency-matched to cases on area of the registry and 5-year categories of date of birth. Of the 2354 and 2299 eligible cases and controls, respectively, 2073 [88%] and 1910 [83%] were alive and could be interviewed, while a further 1025 cases and 251 controls were excluded for various reasons, that included non-confirmation of diagnosis [562 cases], not being a resident in the USA before 1969, a history of acquired immunodeficiency syndrome (AIDS) or related illness, systemic lupus erythematosus, non-AIDS-related immunodeficiency, rheumatoid arthritis or a history of treatment with immunosuppressive drugs, chemotherapy or radiation. Cases and controls were interviewed by telephone on their background characteristics, lifestyle and medical, military and work history. The job history included questions on specific materials with or around which participants may have worked, including formaldehyde. Relative risks were based on conditional logistic regression, stratified for the matching factors (area of registry

and date of birth) and adjusted for age at diagnosis, year of entry into the study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviours, use of seizure medication, service in or off the coast of Viet Nam and cigarette smoking. For ever versus never having been exposed to formaldehyde, relative risks were 1.40 (21 exposed cases; 95% CI, 0.87–2.40) for small-cell diffuse lymphoma, 0.71 (17 exposed cases; 95% CI, 0.41–1.20) for follicular lymphoma, 1.10 (46 exposed cases; 95% CI, 0.79–1.70) for large-cell diffuse lymphoma and 1.20 (93 exposed cases; 95% CI, 0.86–1.50) for all cases of non-Hodgkin lymphoma combined. Of all the controls, 130 (7.8%) reported having been exposed to formaldehyde.

Blair *et al*. (2000) evaluated occupational exposure to formaldehyde in a population-based case–control study of leukaemia and myelodysplasia. Cases were identified among white men who were 30 years or older from the Cancer Registry of Iowa (1981–83) and among all men from a surveillance network of hospitals in Minnesota which covered 97% of hospital beds in this area (1980–82). Controls were identified by random-digit dialling, from Health Care Financing Administration lists or from state death certificate files, depending on their age and vital status, and were frequency-matched to cases by 5-year age group, vital status at the time of interview and state of residence. A total of 669 eligible cases was identified, and interviews were conducted with 340 cases of leukaemia and 238 surrogates for deceased subjects and those who were too ill to interview. Cases and controls who lived in four large cities were excluded because the main purpose of the study was to evaluate agricultural risks; furthermore, subjects who had farming as their sole occupation were excluded from this analysis because the incidence of leukaemia has been shown to be elevated among farmers. This left 214 cases of chronic lymphocytic leukaemia, 132 of acute myeloid leukaemia, 46 of chronic myeloid leukaemia, 13 of acute lymphocytic leukaemia, 58 of myelodysplasia and 50 others and 1087 controls. Interviews were conducted in 1981–84 and included a lifetime occupational history with job titles and industries. Exposure to selected substances, including formaldehyde, was assigned by an industrial hygienist in terms of probability and intensity in a blinded fashion, each on a four-point scale (non-exposed, low, medium and high intensity). Odds ratios were based on unconditional logistic regression adjusted for the matching factors and agricultural use of pesticides, post-secondary education, use of hair dyes, tobacco smoking and having a first-degree relative who had a haematolymphopoietic tumour. Compared with no exposure to formaldehyde, odds ratios were 0.9 (14 exposed cases; 95% CI, 0.5–1.6) for low/medium intensity of exposure for acute myeloid leukaemia (no cases with high exposure); 1.3 (seven exposed cases; 95% CI, 0.6–3.1) for low/medium exposure and 2.9 (one exposed case; 95% CI, 0.3–24.5) for high exposure for chronic myeloid leukaemia; 1.2 (29 exposed cases; 95% CI, 0.7–1.8) for low/medium exposure and 0.6 (one exposed case; 95% CI, 0.1–5.3) for high exposure for chronic lymphocytic leukaemia; 0.8 (six exposed cases; 95% CI, 0.3–1.9) for low/medium exposure for myelodysplasia (no cases with high exposure); and 1.0 (61 exposed cases; 95% CI, 0.7–1.4) for low/medium exposure and 0.7 (three exposed cases; 95% CI, 0.2–2.6) for high exposure for all leukaemias and myelodysplasia combined. Of the 1087 controls, 128 [11.8%] were estimated to have low/

medium and nine [0.8%] to have high exposure to formaldehyde. None of the cases of acute lymphocytic leukaemia was exposed.

Nisse *et al*. (2001) evaluated the risk for myelodysplastic syndrome among 204 incident cases who were diagnosed during 1991–96 at the University Hospital of Lille (northern France) and 204 controls who were randomly selected from the electoral register and individually matched to cases by size of town of residence, sex and age (± 3 years). Cases who had secondary myelodysplastic syndrome after treatment for cancer and those who were unable to answer the questionnaire were excluded. The questionnaire was the same as that used in the study by West *et al*. (1995) and exposure evaluation was based on the method of Siemiatycki *et al.* (1981). Odds ratios for exposure to formaldehyde were not reported because the 95% CI for the univariate odds ratio for ever versus never having been exposed included 1, or because there were fewer than four exposed subjects.

2.2.6 *Cancers at other sites*

The study design of and results from the case–control studies of exposure to formaldehyde and cancer at sites other than those presented in the above sections are summarized in Table 21, in chronological order. The description of the studies below, in contrast, groups the reports by study population.

Within the Montréal multisite cancer study, the database that was analysed for lung cancer (see Section 2.2.4), Hodgkin disease, non-Hodgkin lymphoma and myeloma (see Section 2.2.5) was also used to study various other cancer sites in relation to exposure to formaldehyde. The results were published in separate reports and are presented below.

In addition to the sites cited above, Gérin *et al*. (1989) (see Section 2.2.4) analysed data for cancer of the oesophagus, stomach, colorectum, liver, pancreas, prostate, urinary bladder and kidney and for melanoma of the skin. Odds ratios were not elevated for any of these cancers.

Siemiatycki *et al.* (1994) conducted an analysis of urinary bladder cancer using a set of 484 pathologically confirmed cases of bladder cancer, 1879 controls who had cancers at other sites, excluding lung and kidney cancers, and 533 population controls. No evidence of an association was found between exposure to formaldehyde and the risk for bladder cancer: odds ratios, adjusted for non-occupational and occupational confounders, were 1.2 (67 exposed cases; 95% CI, 0.9–1.6) for non-substantial exposure and 0.9 (17 exposed cases; 95% CI, 0.5–1.7) for substantial exposure.

Dumas *et al.* (2000) analysed the association between occupational exposure to a large number of substances, occupations and industries and rectal cancer. A total of 257 men, who were aged 35–70 years and diagnosed with a rectal cancer between 1979 and 1985, were compared with 1295 controls who had cancers at sites other than the rectum, lung, colon, rectosigmoid junction, small intestine and peritoneum; adjustments were made for potential non-occupational (age, education, cigarette smoking, beer consumption, body mass index and respondent status) but not for occupational variables. Exposure to formaldehyde was associated with rectal cancer: the odds ratios were 1.2 (36 exposed

Table 21. Case–control studies of cancers at other sites

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Gérin *et al.* (1989), Canada, 1979–85	Oesophagus Stomach Colorectum Liver Pancreas Prostate Bladder Kidney Skin melanoma	Men aged 35–70 years resident in Montréal 107 250 787 50 117 452 486 181 121	Pool of population selected from electoral list, and cancer controls; depending of the cancer site under study, the number of controls varied from 1733 to 2741.	Semi-structural probing interview, assessment of exposures by chemists and industrial hygienists	Short Long-low Long-medium Long-high	No association for any of these sites (most odds ratios very close to 1.0)	Selection of data-based confounders (variables according to each specific cancer), plus age, ethnic group, socio-economic status, cigarette smoking and dirtiness of job	Short and long refer to the duration, and low, medium and high to the intensity of exposure.
Merletti *et al.* (1991), Italy, 1982–84	Oral cavity or oropharynx	86 male incident cases	Random sample of 385 men, stratified by age, from the files of residents	Full occupational history linked to a job–exposure matrix	Any exposure Probable or definite	1.6 (0.9–2.8) 1.8 (0.6–5.5)	Age, education, area of birth, tobacco smoking and alcohol drinking	Only six exposed cases in the probable or definite exposure group
Goldoft *et al.* (1993), USA, 1979–89	Melanoma of the nasal cavity or nasopharynx	Nine cases [sex distribution not reported]	Random-digit dialling, frequency-matched on sex and age at diagnosis (controls from Vaughan *et al.*, 1986a,b)	Interview	Living in a residence with foam insulation Occupational exposure Employed in industries with potential exposure[a]	3.57 (0.09–19.8) Obs./exp. 0/0.27 Obs./exp. 0/0.8		
Siemiatycki *et al.* (1994), Canada, 1979–86	Bladder	484 men aged 35–70 years resident in Montréal	533 population and 1879 cancer controls	See Gérin *et al.* (1989)	Non-substantial Substantial	1.2 (0.9–1.6) 0.9 (0.5–1.7)	Age, ethnicity, socioeconomic status, tobacco smoking, coffee consumption, status of respondent and other occupational exposures	Results based on pooled controls

Table 21 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cantor *et al.* (1995), USA, 1984–89	Breast (female)	33 509 women with breast cancer as the cause of death	117 794 women who died from non-cancer causes; frequency-matched for age and race	Usual occupation on death certificate linked to a job–exposure matrix, with levels of probability and of intensity of exposure	Exposure levels *Blacks* Low Medium High *Whites* Low Medium High	 *Blacks* 1.14 $p < 0.05$ 0.93 1.20 $p < 0.05$ *Whites* 1.38 $p < 0.05$ 1.30 $p < 0.05$ 1.36 $p < 0.05$	Age at death, socioeconomic status and excluding women with lowest probability of exposure	No trend was observed.
Holly *et al.* (1996), USA, 1978–87	Uveal melanoma	221 white men aged 20–74 years	447 white men selected by random-digit dialling; matched for area and age	Recall through telephone interviews	Ever	2.9 (1.2–7.0)	Age, number of naevis, eye colour and skin response to exposure to midday summer sun	
Gustavsson *et al.* (1998), Sweden, 1988–91	Oral cavity and oesophagus (ICD-9 141, 143-5, 150)	250 incident cases among men aged 40–79 years resident in two regions (oral cavity, 128; oesophagus, 122)	641 men selected by stratified random sampling; frequency-matched to cases by age (10–15-year groups) and region	Work history reviewed by occupational hygienist; occupations coded by intensity and probability of exposure	Ever Oral cavity Oesophagus	 1.28 (0.64–2.54) 1.90 (0.99–3.63)	Region, age, alcohol consumption and tobacco smoking habits	
Kernan *et al.* (1999), USA, 1984–93	Pancreas	63 097 persons with pancreatic cancer as the cause of death [sex and race distribution not reported]	252 386 persons who died from non-cancer causes; frequency-matched by state, sex, race and age (5-year groups)	Usual occupation on death certificate linked to a job–exposure matrix, with levels of probability and of intensity of exposure	Exposure level Low Medium High Exposure probability Low Medium High	 1.2 (1.1–1.3) 1.2 (1.1–1.3) 1.1 (1.0–1.3) 1.2 (1.1–1.3) 1.2 (1.1–1.3) 1.4 (1.2–1.6)	Age, marital status, residential status, sex and race	No trend was observed; analysis by race and sex also provided

Table 21 (contd)

Reference, study location, years of study	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Dumas *et al.* (2000), Canada, 1979–85	Rectum	257 men aged 35–70 years resident in Montréal	533 population and 1295 cancer controls	See Gérin *et al.* (1989)	Any Substantial	1.2 (0.8–1.9) 2.4 (1.2–4.7)	Age, education, cigarette smoking, beer drinking, body mass index and respondent status	Results based on cancer controls and not in accordance with those of Gérin *et al.* (1989)
Wilson *et al.* (2004), USA, 1984–89	Salivary gland (ICD-9, 142.0–1, –9)	[2405] persons with cancer of the salivary gland as the cause of death (whites: 1347 men, 890 women; African–Americans: 93 men, 75 women)	[9420] persons who died from non-cancer causes, excluding infectious diseases; frequency-matched for age, race, sex and region	Usual occupation on death certificate linked to a job–exposure matrix, with levels of probability and of intensity of exposure	Mid–high probability and intensity	*White men and women* 1.6 (1.3–2.0) *Black women* 1.9 (0.8–5.1)	Age, marital status and socioeconomic status	High level of diagnosis misclassification suspected

CI, confidence interval; ICD, international code of diseases

[a] Wood-work, furniture manufacture, pulp and paper mill, textile, foundry and smelter

cases; 95% CI, 0.8–1.9) for any exposure and 2.4 (13 exposed cases; 95% CI, 1.2–4.7) for substantial exposure, with an increase in risk by concentration and duration of exposure. [This result contrasts with the findings of Gérin *et al*. (1989), in which none of the odds ratios for colorectal cancer was greater than 1.0 in any of the exposure subgroups, including the highest. These odds ratios were for all colorectal cancers, but the authors stated that "the results for subsites of the colorectum — colon, rectosigmoid and rectum — were essentially similar to those of the entire category".]

A series of systematic case–control analyses of various cancers in relation to exposure to different occupational agents, including formaldehyde, were conducted using death certificates collected from 1984 to 1989 in 24 states of the USA (Cantor *et al.*, 1995; Kernan *et al.*, 1999; Wilson *et al.*, 2004). Death certificates were coded for usual occupation and industry according to the classification designed for the 1980 US census. Individual exposures were derived by linking the occupation–industry codes with a job–exposure matrix that assessed the probability and level of exposure to 31 occupational agents.

Cantor *et al.* (1995) conducted a case–control study of occupational exposure and female breast cancer mortality in the USA. After excluding homemakers, 33 509 cases and 117 794 controls remained. Estimates were adjusted for age at death and socioeconomic status and excluded women who had a low probability of exposure. Exposure to formaldehyde was associated with the risk for breast cancer among white and black women: for whites, odds ratios were 1.14 ($p < 0.05$), 0.93 and 1.2 ($p < 0.05$) for women who had low, medium and high intensity of exposure, respectively; among black women, significantly elevated ($p < 0.05$) odds ratios of 1.38, 1.30 and 1.36 were found for those who had low, medium and high intensity of exposure, respectively [confidence intervals not shown].

Kernan *et al.* (1999) conducted a case–control study of pancreatic cancer. Cases were 63 097 persons who had died from pancreatic cancer in 1984–93. Controls were 252 386 persons who had died from causes other than cancer during the same period. Occupational exposure to formaldehyde was associated with a moderately increased risk for pancreatic cancer for both men and women and for both racial groups (blacks and whites), with odds ratios of 1.2 (95% CI, 1.1–1.3), 1.2 (95% CI, 1.1–1.3), 1.1 (95% CI, 1.0–1.3) for subjects with low, medium and high intensity of exposure, respectively, and 1.2 (95% CI, 1.1–1.3), 1.2 (95% CI, 1.1–1.3) and 1.4 (95% CI, 1.2–1.6) for subjects with low, medium and high probabilities of exposure, respectively. There was no apparent exposure–response pattern with intensity, but the exposure–response relationships by probability of exposure were consistent across each level of exposure intensity.

Using the same database as Cantor *et al.* (1995), Wilson *et al.* (2004) conducted a study of salivary gland cancer. The cases were [2405] persons who had died from salivary gland cancer between 1984 and 1989. Four controls per case, frequency-matched for sex, age, race and region, were selected from among persons who had died during the same period from other causes, excluding infectious diseases (because of a suspected viral etiology of salivary gland cancer); a total of 9420 controls were included. Occupation as coded on the death certificate was available for 95.3% of white and 87.3% of black men and for 45% of white and 30.9% of black women. Among white men and women, an odds ratio, adjusted

for age, marital status and socioeconomic status, of 1.6 (95% CI, 1.3–2.0) was observed with 'mid–high' probability and 'mid–high' intensity of exposure to formaldehyde [categories not further defined]. The trend was significant ($p < 0.001$), but there was no dose–response pattern of monotonically increasing risk with increasing intensity and probability of exposure. No association between exposure to formaldehyde and salivary gland cancer was observed among African-American men and women combined. Among African-American women, the adjusted odds ratio for 'mid–high' intensity of exposure was 1.9 (95% CI, 0.8–5.1). No results were given separately for African-American men.

[The Working Group considered that this series of systematic analyses was limited by potential misclassification of some specific cancers when ascertained through death certificates, and by the use of occupation codes from death certificates to assess lifelong occupational exposure to formaldehyde.]

Merletti *et al*. (1991) reported a case–control study of 86 male residents of Turin, Italy, who had a diagnosis of cancer of the oral cavity or oropharynx that was notified to the population-based cancer registry of the city between 1 July 1982 and 31 December 1984, and a random sample of 385 men, stratified by age, who were chosen from files of residents of Turin. The cancers among the cases were: oropharynx (12), tongue (15), floor of the mouth (24), soft palate complex (14), other sites (11) and unspecified sites of the oral cavity (10). Detailed occupational history since 1945 and lifelong histories of tobacco smoking and alcohol drinking were obtained by personal interview. Each job that had been held for at least 6 months was coded according to the International Standard Classification of Occupations and the International Standard Industrial Classification, and a job–exposure matrix for 13 agents (including formaldehyde) which are known or suspected carcinogens of the respiratory tract and three non-specific exposures (dust, gas and solvents) was applied to the occupation–industry code combination of study subjects; the matrix was developed at the IARC for use in a similar study of laryngeal cancer. Study subjects were grouped into three categories of presumed frequency and intensity of exposure to formaldehyde (no, any, probable or definite exposure), with the 'no exposure' group (exposure not higher than that of the general population) as the reference level. Odds ratios were calculated using unconditional logistic regression adjusting for age, tobacco smoking, alcohol drinking, education and place of birth. An association was suggested between cancer of the oral cavity or oropharynx and exposure to formaldehyde, with odds ratios of 1.6 (95% CI, 0.9–2.8) for 'any exposure' and 1.8 (95% CI, 0.6–5.5) for 'probable or definite' exposure; however, only 25 and six cases were exposed, respectively. No relationship was seen with duration of exposure to formaldehyde, with odds ratios of 1.7 for 1–15 years of exposure and 1.5 for ≥ 16 years within the 'any exposure' category, and of 2.1 and 1.4, respectively, within the 'probable or definite' exposure category. Separate results for an association with exposure to formaldehyde were not reported for the 12 men who had oropharyngeal cancer. [The Working Group noted that confounding by tobacco and alcohol could not be excluded from the interpretation of the observed association between exposure to formaldehyde and oral cancer.]

As part of the population-based case–control study of sinonasal cancer by Vaughan *et al.* (1986a,b) (see Section 2.2.1), Goldoft *et al.* (1993) interviewed nine of 14 patients who had been diagnosed with melanoma of the nose or nasopharynx between 1979 and 1989. The frequency of their exposure to formaldehyde was compared with that of the control subjects included in the study of Vaughan *et al*. (1986a,b). One subject had lived in a residence that was insulated with formaldehyde-based foam [0.3 expected]. None of the melanoma patients reported specific occupational exposure to formaldehyde (0.3 expected), and none reported having been employed in industries that would probably entail exposure to formaldehyde (0.8 expected). [The Working Group noted that it was unclear how the expected numbers were calculated.]

Holly *et al.* (1996) conducted a case–control study in the western USA to determine the relation of occupations and chemical exposures to the risk for uveal melanoma. Two hundred and twenty-one white men, aged 20–74 years and referred for treatment to a specialized unit in San Francisco between 1978 and 1987, were included and successfully interviewed. A group of 447 controls were selected by random-digit dialling (white men from the same geographical area and within the same 5-year age group), and 77% were successfully interviewed by telephone. Exposure to chemicals, including formaldehyde, was determined by asking the subjects whether they thought they were ever regularly exposed (at least 3 h per week for at least 6 months) in their jobs, hobbies, leisure or home maintenance. When ever to never having been exposed to formaldehyde was compared, an elevated odds ratio of 2.9 (13 exposed cases; 95% CI, 1.2–7.0), adjusted for potential non-occupational confounders, was found. [The Working Group and the authors noted the potential for recall bias when chemical exposures are ascertained from the subject's memory.]

A case–control study by Gustavsson *et al*. (1998) (see Section 2.2.3) included 128 cases of oral cancer and 122 cases of oesophageal cancer (in addition to cancers of the pharynx and larynx). There was no significant association between exposure to formaldehyde and the risk for oral cancer (14 exposed cases; odds ratio, 1.28; 95% CI, 0.64–2.54), but the risk for cancer of the oesophagus was elevated and bordered on statistical significance (19 exposed cases; odds ratio, 1.90; 95% CI, 0.99–3.63).

2.3 Pooled analysis and meta-analyses

2.3.1 *Pooled analysis*

Luce *et al*. (2002) performed a pooled analysis of data from 12 case–control studies on sinonasal cancer [cancer of the nasal cavity and paranasal sinuses, ICD-9 code 160] that were conducted in China (Zheng *et al.*, 1992), France (Luce *et al.*, 1992, 1993; Leclerc *et al.*, 1994), Germany (Bolm-Audorff *et al.*, 1990), Italy (Merler *et al.*, 1986; Comba *et al.*, 1992a,b; Magnani *et al.*, 1993), the Netherlands (Hayes *et al.*, 1986a,b), Sweden (Hardell *et al.*, 1982) and the USA (Brinton *et al.*, 1984, 1985; Vaughan *et al.*, 1986a; Vaughan, 1989; Vaughan & Davis, 1991). An earlier pooled analysis ('t Mannetje *et al*., 1999) used data

from eight of these 12 studies. As the earlier study is subsumed by the more extensive analysis of Luce *et al*. (2002), results from 't Mannetje *et al*. (1999) are not presented.

The analysis by Luce *et al.* (2002) included data from four (Brinton *et al*., 1984; Vaughan *et al.*, 1986a; Hayes *et al*., 1986a; Luce *et al*., 1993) of the six case–control studies that primarily focused on exposure to formaldehyde that are described in Section 2.2.1, but not those by Olsen *et al*. (1989) or Roush *et al*. (1987). In addition, data were obtained from a further seven studies that were originally designed to address exposures to substances other than formaldehyde (particularly wood dust) and one unpublished study. A total of 195 cases of adenocarcinoma (169 men, 26 women) and 432 cases of squamous-cell carcinoma (330 men, 102 women) were compared with 3136 controls (2349 men, 787 women). The study by Luce *et al.* (1993) in France contributed approximately half of the cases of adenocarcinoma. Cases were diagnosed between 1968 and 1990 and were ascertained from different sources; study subjects were interviewed between 1979 and 1990 using different methods. Studies also varied with respect to the mode of selection of controls and the vital status of subjects at recruitment. Lifetime occupational histories collected in the individual studies were recoded with the occupation and industry codes from International Standard Classifications. These codes and industrial hygiene data were the basis for the development of a job–exposure matrix that provided estimates of the probability (unexposed, 1–10%, 10–50%, 50–90%, > 90%) and intensity (< 0.25 ppm, 0.25–1 ppm, > 1 ppm) of exposure to formaldehyde. Numerical values were assigned to each exposure category, and the job-specific products of the assigned value and duration of employment were summed over each individual's total work history (using 0-, 10- and 20-year lag intervals) to estimate cumulative exposure. For the analysis, the cumulative exposure index was categorized into one of four classes (unexposed and tertiles among controls) that were denoted as no, low, medium and high exposure. Odds ratios were derived by unconditional logistic regression and were stratified by sex and histology with adjustment for age (three categories) and study. In analyses of adenocarcinoma in men, adjustment was also made for wood and leather dust. Tobacco smoking was evaluated as a potential confounder, but was not included in the final models because effect estimates did not change substantially after adjustment. Among subjects exposed to low, medium or high levels of formaldehyde compared with unexposed subjects, estimated odds ratios were 1.2 (43 exposed cases; 95% CI, 0.8–1.8), 1.1 (40 exposed cases; 95% CI, 0.8–1.6) and 1.2 (30 exposed cases; 95% CI, 0.8–1.8) for squamous-cell carcinoma among men; 0.7 (six exposed cases; 95% CI, 0.3–1.9), 2.4 (31 exposed cases; 95% CI, 1.3–4.5) and 3.0 (91 exposed cases; 95% CI, 1.5–5.7) for adenocarcinoma among men; 0.6 (six exposed cases; 95% CI, 0.2–1.4), 1.3 (seven exposed cases; 95% CI, 0.6–3.2) and 1.5 (six exposed cases; 95% CI, 0.6–3.8) for squamous-cell carcinoma among women; and 0.9 (two exposed cases; 95% CI, 0.2–4.1), 0.0 (no cases) and 6.2 (five exposed cases; 95% CI, 2.0–19.7) for adenocarcinoma among women, respectively. Slight increases in these odds ratios were observed with 10- and 20-year lag intervals. Among men, studies were heterogeneous with respect to the effects of exposure to formaldehyde on adenocarcinoma, with a significantly better fit of a model that included interaction terms between exposure effects and study compared with a model with

no such interaction terms ($p < 0.01$). [The Working Group noted that this heterogeneity may have led to inappropriately narrow confidence intervals since the analytical model did not account for random effects.] Among men with little or no exposure to wood dust, the odds ratios for adenocarcinoma with high level exposure to formaldehyde was 2.2 (95% CI, 0.8–6.3). [The Working Group considered that, for adenocarcinoma, residual confounding by exposure to wood dust was possible despite the attempts to control for it. This is because of the high degree of correlation between exposure to wood dust and exposure to formaldehyde, and the very strong association between adenocarcinoma and exposure to wood dust. Only 11 male cases of adenocarcinoma who had low, medium or high exposure to formaldehyde were categorized as never having been exposed to wood dust.]

2.3.2 *Meta-analyses*

(*a*) *Respiratory cancers* (Table 22)

In a meta-analysis on the relationship between exposure to formaldehyde and cancer, Blair *et al*. (1990b) added up the observed and expected numbers of various cancers across 32 cohort and case–control studies. They found no substantially elevated mortality from cancer of the lung or of the nasal nasal cavity for persons who were ever exposed or for those who had a higher level or duration of exposure. For cancer of the nasopharynx, mortality in persons who had a higher level or duration of exposure was elevated 2.1-fold [95% CI, 1.1–3.5] with 13 observed deaths. Among professionals, mortality from leukaemia (SMR, 1.6 [95% CI, 1.3–1.9]) and that from brain cancer (SMR, 1.5 [95% CI, 1.1–1.9]) were elevated. No significant associations were observed for other cancers.

In addition to the studies evaluated by Blair *et al*. (1990b), a meta-analysis of respiratory cancers by Partanen (1993) included two additional studies (Brinton *et al.*, 1984; Merletti *et al.*, 1991) and two updates (Gallagher *et al.*, 1989; Partanen *et al.*, 1990). The analysis used lagged and confounder-adjusted inputs, whenever available, and derived summary relative risks using a log-Gaussian, fixed effects model. For nasopharyngeal cancer, risk ratios were 1.59 (23 deaths; 95% CI, 0.95–2.65) and 2.74 (11 deaths; 95% CI, 1.36–5.55) for low/medium and substantial level or duration of exposure, respectively. Partanen (1993) found a relative risk for cancer of the nasal cavities and paranasal sinuses of 1.68 (95% CI, 1.00–2.82) for the highest category of exposure, while the corresponding risk calculated by Blair *et al*. (1990b) was 1.1 [95% CI, 0.7–1.5]. [This discrepancy may be explained by differences in the selection of studies for inclusion in the two meta-analyses or by differences in the way in which exposure categories were defined]. For the combined category of cancers of the oropharynx, lip, tongue, salivary glands and mouth, the aggregated data did not suggest associations with exposure to formaldehyde. Overall, Blair *et al*. (1990b) and Partanen (1993) were in good agreement with regard to the risks for lung cancer, nasopharyngeal carcinoma and miscellaneous cancers of the upper respiratory tract.

Collins *et al*. (1997) calculated meta-relative risks for cancers of the lung, nose or nasopharynx based on results from 11 cohort studies, three proportionate mortality studies

Table 22. Summary of results from three meta-analyses on respiratory cancers and exposure to formaldehyde

Level or duration of exposure to formaldehyde	Site							
	Lung		Nose and nasal sinuses		Nasopharynx		Other respiratory	
	O/E	mRR (95% CI)	O/E	mRR (95% CI)	O/E	mRR (95% CI)	O/E	mRR (95% CI)
Any								
Blair *et al.* (1990b)[a]	[1692/1681]	[1.0 (0.95–1.06)]	[61/58]	[1.0 (0.8–1.3)]	[35/27]	[1.3 (0.9–1.8)]	NR	NR
Partanen (1993)[b,c]	833/752	1.11 (1.03–1.19)	93/78	1.11 (0.81–1.53)	36/21	2.00 (1.36–2.90)	69/57	1.18 (0.87–1.59)
Collins *et al.* (1997)[d]	2080/2506	1.0 (0.9–1.0)	936/808	1.0 (1.0–1.1)	455/412	1.3 (1.2–1.5)	NR	NR
Low/medium								
Blair *et al.* (1990b)[a]	514/422	1.2 [1.1–1.3]	38/46	0.8 [0.6–1.1]	30/27	1.1 [0.7–1.6]	NR	NR
Partanen (1993)[b,c]	518/425	1.2 (1.1–1.3)	33/30	1.10 (0.67–1.79)	23/16	1.59 (0.95–2.65)	52/48	1.05 (0.74–1.51)
Substantial								
Blair *et al.* (1990b)[a]	250/240	1.0 [0.9–1.2]	30/28	1.1 [0.7–1.5]	13/6	2.1 [1.1–3.5]	NR	NR
Partanen (1993)[b,c]	233/216	1.1 (0.95–1.2)	36/21	1.68 (1.00–2.82)	11/4	2.74 (1.36–5.55)	23/20	1.15 (0.64–2.09)

CI, confidence interval; mRR, meta-relative risk; NR, not reported; O/E, observed/expected

[a] Blair *et al*. (1990b) included the following studies in their analysis: Harrington & Shannon (1975), Petersen & Milham (1980), Jensen & Andersen (1982), Fayerweather *et al*. (1983), Friedman & Ury (1983), Marsh (1983), Milham (1983), Walrath & Fraumeni (1983), Wong (1983), Acheson *et al*. (1984a,b), Coggon *et al*. (1984), Harrington & Oakes (1984), Levine *et al*. (1984), Liebling *et al*. (1984), Malker & Weiner (1984), Olsen *et al*. (1984), Walrath & Fraumeni (1984), Partanen *et al*. (1985), Stayner *et al*. (1985), Walrath *et al*. (1985), Bertazzi *et al*. (1986), Blair *et al*. (1986), Bond *et al*. (1986), Gallagher *et al*. (1986), Hayes *et al*. (1986a,b), Logue *et al*. (1986), Stroup *et al*. (1986), Vaughan *et al*. (1986a,b), Blair *et al*. (1987), Roush *et al*. (1987), Stayner *et al*. (1988), Bertazzi *et al*. (1989), Gérin *et al*. (1989), Blair *et al*. (1990a) and Hayes *et al*. (1990).

[b] The analysis for lung cancer was performed for industrial workers only, as at least some of the data for professionals were confounded by social class.

[c] Partanen (1993) included in his analysis the above studies and: Brinton *et al.* (1984), Merletti *et al.* (1991); in addition, Partanen *et al.* (1985) was updated with Partanen *et al.* (1990), and Gallagher *et al.* (1986) was updated with Gallagher *et al.* (1989).

[d] Collins *et al*. (1997) included in their analysis the above studies (except for Petersen & Milham (1980), Friedman & Ury (1983), Marsh (1983), Milham (1983), Wong (1983), Acheson *et al*. (1984a,b), Harrington & Oakes (1984), Liebling *et al*. (1984), Malker & Weiner (1984), Stayner *et al*. (1985), Walrath *et al*. (1985), Gallagher *et al*. (1986), Logue *et al*. (1986), Blair *et al*. (1987, 1990a) and Merletti *et al*. (1991)) and added the following studies: Hernberg *et al*. (1983a,b), Olsen & Asnaes (1986), Hall *et al*. (1991), Matanoski (1991), Chiazze *et al*. (1993), Gardner *et al*. (1993), Luce *et al*. (1993), West *et al*. (1993), Marsh *et al*. (1994) and Andjelkovich *et al*. (1995).

and 15 case–control studies that were published between 1975 and 1995. The analysis did not include all of the studies from the meta-analyses by Blair *et al.* (1990b) and Partanen (1993), but added several studies, most of which were published after 1992. Using a fixed effects model, an overall meta-relative risk for lung cancer of 1.0 (95% CI, 0.9–1.0) was calculated based on 24 studies with 2080 observed cases, but there was substantial heterogeneity across studies ($p < 0.00001$) which was mainly due to the difference between industrial cohort studies (meta-relative risk, 1.1; 95% CI, 1.0–1.2) and case–control studies (meta-relative risk, 0.8; 95% CI, 0.7–0.9). For nasal cancer, the overall meta-relative risk was 1.0 (95% CI, 1.0–1.1) based on 20 studies with 936 observed cases. Separate analyses by study type gave a meta-relative risk of 0.3 (95% CI, 0.1–0.9) for cohort studies and 1.8 (95% CI, 1.4–2.3) for case–control studies. Meta-relative risks for nasopharyngeal cancer were 1.3 (95% CI, 1.2–1.5) overall based on 12 studies with 455 cases, and 1.6 (95% CI, 0.8–3.0) for cohort studies with reported expected deaths. To address a potential publication bias, all cohort studies were combined and missing expected numbers were estimated based on an approximation of the ratio of deaths from nasopharyngeal and lung cancer from the corresponding ratio observed in another study; this gave a meta-relative risk of 1.0 (95% CI, 0.5–1.8).

(*b*) *Pancreatic cancer* (Table 23)

Ojajärvi *et al*. (2000) evaluated occupational exposures in relation to pancreatic cancer in a meta-analysis based on 92 studies that represented 161 different exposed populations. Eligible studies had to fulfil certain criteria and had to be agent-specific with direct risk estimates for one or several of 23 agents or for job titles with verified exposures to the agents. Proportionate mortality and incidence studies were excluded. For exposure to formaldehyde, five eligible populations were identified with a meta-relative risk of 0.8 (95% CI, 0.5–1.0), and point estimates of the meta-relative risks for different subsets of the meta-analysis by gender, type of diagnosis and study design ranged from 0.5 to 1.0. There was no evidence of heterogeneity of point estimates between populations. [The studies or populations included in the evaluation of formaldehyde were not clearly identified. The NCI cohort study by Blair *et al*. (1986) (see Section 2.1.1(*a*)) was apparently not included.]

Collins *et al*. (2001a) calculated a meta-relative risk for pancreatic cancer based on results from 14 studies, including eight cohort studies, four proportionate cancer mortality or incidence studies and two case–control studies that were published between 1983 and 1999. Based on a fixed effects model, an overall meta-relative risk of 1.1 (95% CI, 1.0–1.2) was calculated with no substantial heterogeneity across studies ($p = 0.12$). Meta-relative risks by type of job were 0.9 (95% CI, 0.8–1.1) for industrial workers (five studies that included 137 pancreatic cancers), 1.3 (95% CI, 1.0–1.6) for embalmers (four studies that included 88 pancreatic cancers) and 1.3 (95% CI, 1.0–1.7) for pathologists and anatomists (three studies that included 60 pancreatic cancers). There was no indication of publication bias. It was mentioned that the two studies that evaluated risk for pancreatic cancer at various exposure levels (Blair *et al.*, 1986; Kernan *et al.*, 1999) did not find monotonically increasing risks with increasing exposure levels. [Four (three cohort

Table 23. Summary of results from meta-analyses of pancreatic cancer and exposure to formaldehyde

	Ojajärvi *et al*. (2000)[a]		Collins *et al.* (2001a)[b]		
	Populations	mRR (95% CI)	Studies	No. of cases	mRR (95% CI)
All studies	5	0.8 (0.5–1.0)	14	364	1.1 (1.0–1.2)
Sex					
Men	3	0.8 (0.5–1.3)			
Unspecified or both	2	0.6 (0.3–1.1)			
Histological diagnosis					
Yes	2	0.5 (0.3–0.9)			
No	3	0.9 (0.7–1.3)			
Study type					
Case–control and cohort with internal reference	2	0.5 (0.3–1.6)			
SMR/SIR	3	0.9 (0.7–1.3)			
Cohort			8	132	1.0 (0.8–1.2)
Case–control			2	79	1.0 (0.5–2.0)
PMR/PIR			4	153	1.2 (1.0–1.4)
Type of job					
Industrial			5	137	0.9 (0.8–1.1)
Embalmer			4	88	1.3 (1.0–1.6)
Pathologist and anatomist			3	60	1.3 (1.0–1.7)

CI, confidence interval; mRR, meta-relative risk; PMR/PIR, proportionate mortality ratio/proportionate incidence ratio; SMR/SIR, standardized mortality ratio/standardized incidence ratio

[a] Ojajärvi *et al.* (2000) studied occupational exposures and pancreatic cancer in 92 studies and 161 different exposed populations. The studies used for their evaluation of formaldehyde are not listed specifically. However, the study by Blair *et al.* (1986) was apparently not included.

[b] Collins *et al.* (2001a) included the following studies in their analyses: Walrath & Fraumeni (1983), Levine *et al.* (1984), Walrath & Fraumeni (1984), Blair *et al.* (1986), Stroup *et al.* (1986), Stayner *et al.* (1988), Gérin *et al.* (1989), Hayes *et al.* (1990), Matanoski (1991), Hall *et al.* (1991), Gardner *et al.* (1993), Andjelkovich *et al.* (1995), Hansen & Olsen (1995) and Kernan *et al.* (1999).

studies and one proportionate incidence study) of the 14 studies included were also referenced in the meta-analysis by Ojajärvi *et al*. (2000).]

(*c*) *Leukaemia*

Collins and Lineker (2004) calculated meta-relative risks for leukaemia based on the results from 12 cohort studies, four proportionate mortality or incidence studies and two case–control studies that were published between 1975 and 2004. Using a fixed effects model, an overall meta-relative risk for leukaemia of 1.1 (95% CI, 1.0–1.2) was calculated

based on 287 observed cases with borderline heterogeneity across studies ($p = 0.07$). Separate analyses by study type showed heterogeneity among proportionate mortality or incidence studies (meta-relative risk, 1.2; 95% CI, 1.0–1.5; p-heterogeneity = 0.02), but not among cohort studies (meta-relative risk, 1.0; 95% CI, 0.9–1.2) or among the two case–control studies (meta-relative risk, 2.4; 95% CI, 0.9–6.5). Increased risk was observed in studies of embalmers (meta-relative risk, 1.6; 95% CI, 1.2–2.0) and pathologists and anatomists (meta-relative risk, 1.4; 95% CI, 1.0–1.9), but not among industrial workers (meta-relative risk, 0.9; 95% CI, 0.8–1.0). There was no indication of substantial publication bias. [This meta-analysis did not include the studies by Logue *et al*. (1986), Partanen *et al*. (1993), Stellman *et al*. (1998) or Blair *et al*. (2001). Results from Harrington and Shannon (1975) and Harrington and Oakes (1984) were both included despite overlapping study populations. The Working Group noted that the findings of the meta-analysis would be sensitive to the choice of effect measures based on external rather than internal comparisons from some studies. Also, the analysis did not take into account risk estimates for higher-exposure subgroups or information on exposure–response relationships in the industrial cohort studies.]