2. Studies of Cancer in Humans

2.1 Case reports

Halperin *et al.* (1983) and Brandwein *et al.* (1987) reported cases of squamous-cell carcinoma of the sinonasal cavities associated with exposure to formaldehyde at work or at home. Holmstrom and Lund (1991) drew attention to the possibility of a causal relationship with malignant melanoma of the nasal cavity on the basis of three cases seen after occupational exposure to formaldehyde.

2.2 Descriptive studies

Gallagher *et al.* (1989) calculated proportionate mortality ratios (PMRs) by occupation for 320 423 men who died in British Columbia, Canada, during 1950–84. One of the 79 funeral directors included in the study had died from sinonasal cancer (PMR, 16; 95% confidence interval [CI], 0.4–87).

A similar analysis was conducted by Petersen and Milham (1980) on about 200 000 white male residents of California, USA, for the period 1959–61. Funeral directors and embalmers accounted for 130 deaths, none of which were from cancer of the buccal cavity or pharynx (one expected) or from sinonasal cancer (< 0.1 expected).

Malker *et al.* (1990) used data from the Swedish Cancer–Environment Registry, which combines data from the 1960 census with those from the National Cancer Registry through 1979, to calculate standardized incidence ratios (SIRs) for nasopharyngeal cancer (471 cases) in various occupational and industrial groups in 1961–79. Significant excesses were seen for glassmakers (SIR, 6.2; 3 cases), bookbinders (6.1; 3 cases), shoemakers (3.8; 5 cases) and workers in shoe repair (4.0; 5 cases) and fibre-board manufacture (3.9; 4 cases). No significantly high risks for nasopharyngeal cancer were seen in other occupations in which exposure to formaldehyde probably occurs [expected numbers not given].

2.3 Cohort studies

The relationship between exposure to formaldehyde and cancer has been investigated in over 25 cohort studies of professional (pathologists, anatomists and embalmers) and industrial groups (formaldehyde producers, formaldehyde resin makers, plywood and particle-board manufacturers, garment workers and workers in the abrasives industry). Relative risks have been estimated as standardized mortality ratios (SMRs), PMRs, proportionate cancer mortality ratios (PCMRs) and SIRs. In some studies, exposure was not assessed but was assumed on the basis of the subject's occupation or industry; in others, it was based on duration of exposure and quantitative estimates of historical exposure levels. Mortality in several of the cohorts was followed beyond the period covered by the original report; only the latest results are reviewed below, unless there were important differences in the analyses performed or changes in the

cohort definition. Reviews are available which summarize the epidemiological data (Blair *et al.*, 1990a; Partanen, 1993; McLaughlin, 1995); in the first two, the technique of meta-analysis was used.

For each point estimate expressed as an SMR, PMR, PCMR or SIR, a 95% CI is given, even if the original authors did not report one. The 95% CI bears a relationship to the usual judgement of statistical significance, in that a CI that does not include the value of 1.0 occurs when the point estimate is significant at the traditional 5% level. The 95% CI provides more information, however, in that it shows the magnitude of the estimated random variation around the point estimate.

2.3.1 Professional groups

Pathologists, anatomists, embalmers and funeral directors were studied because they use formaldehyde as a tissue preservative. Investigations of these occupations have several methodological problems. Use of national statistics to generate expected numbers may bias estimates of relative risks toward the null for some cancers and away from the null for others because these groups have a higher socioeconomic level than the general population; only a few investigations included a special referent population designed to diminish potential socio-economic confounding. None of these studies had the data necessary to adjust for tobacco use. Since anatomists and pathologists in the United States 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 smoking may be strong enough to preclude any possibility of detecting 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 summarized 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 with and without the cancer of interest, diminishes the chances of uncovering an underlying association, as it biases estimates of the relative risk toward the null.

Harrington and Shannon (1975) evaluated the mortality of pathologists and medical laboratory technicians in the United Kingdom. Members of the Royal College of Pathologists and the Pathological Society who were alive in 1955 were enrolled and followed through 1973. Of the 2079 pathologists included, only 13 could not be traced successfully; 156 deaths were identified. The Council for Professions Supplementary to Medicine was used to identify 12 944 technicians; 154 subsequently died and 199 could not be traced. 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-, five-year calendar period- and five-year age group-specific rates for England and Wales or Scotland, as appropriate. The SMRs for all causes of deaths were 0.6 for pathologists and 0.7 for medical technicians; the numbers of deaths from all cancers and from ischaemic heart disease were also fewer than expected. The SMR for lymphatic and haematopoietic cancer was elevated

among pathologists ([2.0; 95% CI, 0.9–3.9]; 8 observed), but not among technicians ([0.6; 0.1–1.6]; 3 observed). The SMRs for cancers at other sites were 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 1980. The population now included 2307 men and 413 women. Vital status was confirmed for 99.9% of the men and 99.5% of the women. SMRs were calculated using expected rates based on age-, sex- and calendar time-specific data from England and Wales. The SMRs for all causes and for all cancers among men were both 0.6; among women, the SMR for all causes was 1.0 and that for all cancers, 1.4. Mortality from brain cancer was elevated among men (SMR, 3.3 [95% CI, 0.9–8.5]; 4 deaths). No nasal cancer and no cancer of the nasal sinuses was seen.

This cohort was further evaluated by Hall *et al.* (1991), who extended follow-up of mortality from 1980 through 1986 and added new members of the Pathological Society, resulting in 4512 individuals available for study (3478 men; 803 women; and 231 unaccounted subjects [who may have been women from Scotland, but it was not clear in the article]). Sex-specific SMRs were based on expected rates for England and Wales or Scotland, as appropriate, and were adjusted for age and calendar time. The SMRs for all causes of death were all considerably below 1.0: men from England and Wales, 0.4 (95% CI, 0.4–0.5); women from England and Wales, 0.7 (0.4–1.0); men from Scotland, 0.5 (0.3–0.7). The SMRs for cancers at all sites were 0.4 (0.3–0.6) and 0.6 (0.3–1.1) among men from England and Wales and Scotland, respectively, and 1.0 (0.5–1.9) among women from England and Wales. No significant excess was seen for cancer at any site. Nonsignificant excesses occurred for brain cancer (SMR, 2.4; 0.9–5.2) and lymphatic and haematopoietic cancer (1.4; 0.7–2.7) among men from England and Wales, breast cancer (1.6; 0.4–4.1) among women from England and Wales and prostatic cancer (3.3; 0.4–12) among men from Scotland.

Walrath and Fraumeni (1983) used licensure records from the New York State (United States) Department of Health, Bureau of Funeral Directing and Embalming to identify 1678 embalmers who had died between 1925 and 1980. Death certificates were obtained for 1263 (75%) decedents (1132 white men, 79 nonwhite men, 42 men of unknown race and 10 women), and PMRs and PCMRs were calculated for white men and nonwhite 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 nonwhite men, but the paper indicated that there was significant excess mortality from arteriosclerotic heart disease (PMR, 1.5 [95% CI, 1.1–2.2]; 33 observed) and from cancers of the larynx (2 observed) and lymphatic and haematopoietic system (3 observed). Among white men, the PMRs were 1.1 [1.0–1.3] for all cancer combined, 1.1 [1.0–1.3] for arteriosclerotic heart disease, 0.7 [0.3–1.2] for emphysema, and 1.3 [0.9–1.9] for cirrhosis of the liver. The PCMRs for other cancers were 1.0 [0.4–2.0] for buccal cavity and pharynx, 1.3 [0.9–1.9] for colon, 1.1 [0.9–1.4] for lung, 0.8 [0.4–1.4] for prostate, 1.4 [0.6–2.7] for brain, 1.2 [0.8–1.8] for lymphatic and haematopoietic system (PMR), 0.8 [0.3–1.9] for lymphoma and 1.2 [0.6–2.1] for leukaemia. No deaths occurred from cancer of the nasal sinuses or nasopharynx. There was little difference in PMR by time since first licensure. Although the subjects had been licensed as either embalmers or embalmers/funeral

directors, these two groups were analysed separately because the authors assumed that embalmers would have had more exposure to formaldehyde than embalmers/funeral directors. The PMR for brain cancer was increased among people licensed only as embalmers (2.3 [0.8–5.0]; 6 observed) but not among those also licensed as a funeral director (0.9 [0.2–2.7]; 3 observed). A difference was also observed for mortality from cancer of the buccal cavity and pharynx; the PMR for embalmers was 2.0 ([0.8–4.1] 7 observed), and that for embalmers/funeral directors was 0.3 ([0.0–1.5] 1 observed).

Walrath and Fraumeni (1984) used the records of the California (United States) Bureau of Funeral Directing and Embalming to examine mortality among embalmers first licensed in California between 1916 and 1978. They identified 1109 embalmers who died between 1925 and 1980, comprising 1007 white men, 39 nonwhite men, 58 white women and five nonwhite women. Only mortality of white men was analysed. The expected numbers of deaths were calculated on the basis of age-, race-, sex- and calendar year-specific proportions from the general population. The PMRs for major categories of death were 1.2 [95% CI, 1.0–1.4] for all cancers combined (205 observed), 1.2 [1.1–1.3] for ischaemic heart disease (355 observed), 0.4 [0.1–1.0] for emphysema (4 observed) and 1.8 [1.3–2.4] for suicide (44 observed). The PCMRs for specific cancers were 1.0 [0.4–2.0] for buccal cavity and pharynx (8 observed), 1.4 [0.9–2.0] for colon (30 observed), 0.9 [0.6–1.2] for lung (41 observed), 1.3 [0.8–2.0] for prostate (23 observed), 1.7 [0.8–3.2] for brain (9 observed), 1.2 (PMR) [0.7–1.9] for lymphatic and haematopoietic system (19 observed), [1.0 (PMR); 0.2–2.8] for lymphoma (3 observed) and 1.4 [0.7–2.4] for leukaemia (12 observed). There was no death from cancer of the nasal passages (0.6 expected). The PMRs by length of licensure (< 20 years and ≥ 20 years) were 2.0 and 1.9 for brain cancer and 1.2 and 2.2 for leukaemia.

Mortality among 1477 male embalmers licensed by the Ontario (Canada) Board of Funeral Services between 1928 and 1957 was evaluated by Levine *et al.* (1984a) by following-up the cohort through 1977: 359 deaths were identified; 54 (4%) could not be traced. The expected numbers 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, leaving 1413 men known to be alive in 1950. The SMRs for all causes and for all cancers were 1.0 [95% CI, 0.9–1.1] and 0.9 [0.7–1.1], respectively. Excesses were seen for chronic rheumatic heart disease (2.0 [0.9–3.9]; 8 observed) and cirrhosis of the liver (2.4 [1.4–3.7]; 18 observed). For specific cancers, the numbers of deaths and those expected were as follows: buccal cavity and pharynx (1/2.1), nose, middle ear, sinuses (0/0.2), lung (19/20.2), prostate (3/3.4), brain (3/2.6), lymphatic and haematopoietic system (SMR, 1.2; 8/6.5) and leukaemia (4/2.5).

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 time period, they were not included. Follow-up of the cohort for vital status through 1979 resulted in 738 deaths; 39 individuals could not be traced. The expected numbers of deaths were calculated from age-, race-, sex- and calendar time-specific rates for the general population of the United States 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. Between 1925 and 1979, 738 anatomists died and only 2% were of unknown vital status at the close of the follow-up. In comparison with the general population, the cohort showed a very large 'healthy worker effect', with SMRs of 0.7 for all causes (738 observed), 0.6 (95% CI, 0.5–0.8) for cancer at all sites (118 observed) and 0.8 (0.7–0.9) for ischaemic heart disease (271 observed). The SMRs were less than 1.0 for individual cancers (e.g. lung cancer, SMR, 0.3; 0.1–0.5; 12 observed; oral and pharyngeal cancer, 0.2; 0.0–0.8; 1 observed), except for cancers of the brain (2.7; 1.3–5.0; 10 observed), lymphatic and haematopoietic system (2.0; 0.7–4.4; 6 observed) and leukaemia (1.5; 0.7–2.7; 10 observed). No death from nasal cancer occurred (0.5 expected). 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 [trend cannot be calculated]; no such pattern was seen for lung cancer. Anatomists had deficits of lung cancer (0.5; 0.2–1.1) and leukaemia (0.8; 0.2–2.9) when compared with members of the American Psychiatric Association, but they still had an excess of brain cancer (6.0; 2.3–16).

Logue *et al.* (1986) evaluated mortality among 5585 members of the College of American Pathologists listed in the Radiation Registry of Physicians; 496 deaths were identified. The cohort was established by enrolling members between 1962 and 1972 and following them up through 1977. SMRs were calculated on the basis of the mortality rates for white men in the United States in 1970, but information on age and calendar-year categories was not provided. The SMRs were 0.7 [observed number of cases calculated from rates, 4] for cancer of the buccal cavity and pharynx, 0.2 [14] for cancer of the respiratory system ($p < 0.01$), 0.8 [36] for cancer of the digestive organs, 0.5 [5] for cancers of the lymphatic and haematopoietic system and 1.1 [7] for leukaemia. The age-adjusted mortality rates for these cancers were similar to those calculated for members of the American College of Radiology who were also listed in the Registry.

Hayes *et al.* (1990), in the United States, 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 between 1975 and 1985. Decedents included in studies in New York (Walrath & Fraumeni, 1983) and California (Walrath & Fraumeni, 1984) were excluded. Death certificates were received for 5265. Exclusion of 449 decedents included in previous studies of embalmers, 376 subjects who probably did not work in the funeral industry, eight subjects of unknown race or age and 386 women left 4046 decedents available for analysis (3649 whites and 397 nonwhites). PMRs and PCMRs were calculated on the basis of expected numbers from race- and sex-specific groups of the general population, adjusted for five-year age and calendar-time categories. The PMR for all cancers was 1.1 (95% CI, 1.0–1.2; 900 observed) for whites and 1.1 (0.9–1.3; 102 observed) for nonwhites. The PMR for ischaemic heart disease was elevated in both whites (1.1; 1.1–1.2; 1418 observed) and nonwhites (1.5; 1.2–1.7; 135 observed). That for emphysema was about as expected among whites (1.0; 0.8–1.4; 48 observed), but only one death from this cause occurred among nonwhites (0.5; 0.1–2.6; 1 observed). The PMRs for specific cancers were: buccal cavity and pharynx (whites: 1.2; 0.8–1.7; 26 observed; nonwhites: 1.3; 0.3–3.2; 4 observed), nasopharynx (whites: 1.9; 0.4–5.5; 3 observed; nonwhites: 4.0; 0.1–22;

1 observed), colon (whites: 1.2; 1.0–1.4; 95 observed; nonwhites: 2.3; 1.3–3.8; 16 observed), nasal sinuses (whites and nonwhites: 0 observed, 1.7 expected), lung (whites: 1.0; 0.9–1.1; 285 observed; nonwhites: 0.8; 0.5–1.1; 23 observed), prostate (whites: 1.1; 0.8–1.3; 79 observed; nonwhites: 1.4; 0.8–2.1; 19 observed), brain (whites: 1.2; 0.8–1.8; 24 observed; nonwhites: 0 observed, 0.8 expected) and lymphatic and haematopoietic system (whites: 1.3; 1.1–1.6; 100 observed; nonwhites: 2.4; 1.4–4.0; 15 observed). The risks for cancers of the lymphatic and haematopoietic system and brain did not vary substantially by licensing category (embalmer versus funeral director), by geographic 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 (1.6; 1.0–2.3; 24 observed) and other and unspecified leukaemia (2.3; 1.4–3.5; 20 observed); nonsignificant excesses were observed for several other histological types.

In a study of users of various medicinal drugs based on computer-stored hospitalization records of the out-patient pharmacy at the Kaiser–Permanente Medical Center in San Francisco (CA, United States), 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 (5.7 [1.6–15]) for people using formaldehyde, with four cases observed. Information on smoking was not provided. [The Working Group noted the short period of follow-up.]

Cohort and proportionate mortality studies of professional groups are summarized in Table 10.

2.3.2 Industrial groups

Several studies of industrial groups included evaluations by duration of exposure or employment, but only four contained assessments by level of exposure: a study in the United Kingdom (Acheson *et al.*, 1984a; Gardner *et al.*, 1993) and three in the United States (Blair *et al.* 1986; Stewart *et al.*, 1986; Blair *et al.*, 1990b) (Andjelkovich *et al.*, 1995) (Marsh *et al.*, 1994a). Information on tobacco use was generally absent, although Blair *et al.* (1990b) and Andjelkovich *et al.* (1995) obtained some information. The reports on industrial cohorts are not entirely independent; some publications are based on extended follow-ups (reports on the British cohort by Acheson *et al.* (1984a) and Gardner *et al.* (1993) and the Italian cohort by Bertazzi *et al.* (1986, 1989)). There is also partial overlap because of inclusion of the same workers in several studies: the two reports on the garment industry by Stayner *et al.* (1985, 1988) included two common facilities; the 10-plant study by Blair *et al.* (1986, 1990b) included workers also reported in cohort studies by Marsh (1982), Wong (1983), Liebling *et al.* (1984) and Marsh *et al.* (1994a) and in a case–control study by Fayerweather *et al.* (1983). Analyses of the data from the cohort study by Blair *et al.* (1986, 1990b) have also been published by others (Robins

Table 10. Cohort and proportionate mortality studies of cancer in professionals exposed to formaldehyde

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comments
United Kingdom (Hall *et al.*, 1991) (update of Harrington *et al.* (1984) plus new members since 1973)	Pathologists, SMR (4512), 1974–87	None	All causes	0.4 (0.4–0.5)	194 deaths
			All cancers	0.5 (0.4–0.6)	55 deaths
			Colon	1.0 (0.4–2.0)	Seven deaths
			Lung	0.2 (0.1–0.4)	Nine deaths
			Brain	2.2 (0.8–4.8)	Six deaths
			Lymphatic/haematopoietic	1.4 (0.7–2.7)	10 deaths
			Leukaemia	1.5 (0.4–3.9)	Four deaths
			Breast	1.6 (0.4–4.1)	Four deaths among women
			Prostate	3.3 (0.4–12)	Two deaths among men in Scotland
New York, USA (Walrath & Fraumeni, 1983)	Embalmers, PMR, PCMR (1132 men), 1925–80	None	All cancers	1.1 [1.0–1.3]	243 deaths, PMR
			Buccal/pharynx	1.0 [0.4–2.0]	Eight deaths, PCMR
				2.0 [0.8–4.1]	Embalmers only, seven deaths, PMR
				0.3 [0.0–1.5]	Funeral directors, one death, PMR
			Colon	1.3 [0.9–1.9]	29 deaths, PCMR
			Lung	1.1 [0.9–1.4]	70 deaths, PCMR
			Brain	1.4 [0.6–2.7]	Nine deaths, PCMR
				2.3 [0.8–5.0]	Embalmers only, six deaths, PMR
				0.9 [0.2–2.7]	Funeral directors, three deaths, PMR
			Lymphatic/haematopoietic	1.2 [0.8–1.8]	25 deaths, PMR
			Lymphoma	0.8 [0.3–1.9]	Five deaths, PCMR
			Leukaemia	1.2 [0.6–2.1]	12 deaths, PCMR
California, USA (Walrath & Fraumeni, 1984)	Embalmers, PMR, PCMR (1007 white men), 1925–80	Duration	All cancer	1.2 [1.0–1.4]	205 deaths, PMR
			Buccal/pharynx	1.3 [0.6–2.6]	Eight deaths, PMR, inverse trend with duration
			Colon	1.4 [0.9–2.0]	30 deaths, PCMR, no trend
			Lung	0.9 [0.6–1.2]	41 deaths, PCMR, no trend
			Nasal	–	0 deaths
			Prostate	1.3 [0.8–2.0]	23 deaths, PCMR, no trend
			Brain	1.9 ($p < 0.05$)	Nine deaths, PMR, no trend
			Lymphatic/haematopoietic	1.2 [0.7–1.9]	19 deaths, PMR
			Lymphoma	[1.0] [0.2–2.8]	Three deaths, PMR
			Leukaemia	1.4 [0.7–2.4]	12 deaths, PCMR, trend with duration

Table 10 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comments
Canada (Levine *et al.*, 1984a)	Embalmers, SMR (1477 men), 1950–77	None	All causes	1.0 [0.9–1.1]	319 deaths
			All cancers	0.9 [0.7–1.1]	58 deaths
			Nasal	–	0 deaths (0.2 expected)
			Buccal/pharynx	[0.5] (NA)	One death
			Lung	0.9 [0.6–1.5]	19 deaths
			Brain	[1.2] [0.2–3.4]	Three deaths
			Prostate	[0.9] [0.2–2.6]	Three deaths
			Lymphatic/haematopoietic	1.2 [0.5–2.4]	Eight deaths
			Leukaemia	[1.6] [0.4–4.1]	Four deaths
USA (Stroup *et al.*, 1986)	Anatomists, SMR (2239 men), 1925–79	Duration	All causes	0.7 (0.6–0.7)	738 deaths
			All cancers	0.6 (0.5–0.8)	118 deaths
			Buccal/pharynx	0.2 (0.0–0.8)	One death
			Colon	1.1 (0.7–1.7)	20 deaths
			Nasal	– (0.0–7.2)	0 deaths, 0.5 expected
			Lung	0.3 (0.1–0.5)	12 deaths, no trend with duration
			Prostate	1.0 (0.6–1.6)	19 deaths
			Brain	2.7 (1.3–5.0)	10 deaths, trend with duration
			Lymphatic/haematopoietic	1.2 (0.7–2.0)	18 deaths
			Lymphoma	0.7 (0.1–2.5)	Two deaths
			Leukaemia	1.5 (0.7–2.7)	10 deaths
			Other lymphatic tissue	2.0 (0.7–4.4)	Six deaths
USA (Logue *et al.*, 1986)	Pathologists, SMR (5585 men), 1962–77	None	Buccal/pharynx	0.7 (NA)	
			Digestive organs	0.8 (NA)	
			Respiratory system	0.2 ($p < 0.01$)	
			Lymphatic/haematopoietic	0.5 (NA)	
			Leukaemia	1.1 (NA)	

Table 10 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comments
USA (Hayes *et al.*, 1990)	Embalmers, PMR (3649 white men, 397 nonwhite men), 1975–85	None	All cancers	1.1 (1.0–1.2)	900 deaths among white men
				1.1 (0.9–1.3)	102 deaths among nonwhite men
			Buccal/pharynx	1.2 (0.8–1.7)	26 deaths among white men
				1.3 (0.3–3.2)	Four deaths among nonwhite men
			Nasopharynx	1.9 (0.4–5.5)	Three deaths among white men
				4.0 (0.1–22)	One death among nonwhite men
			Colon	1.2 (1.0–1.4)	95 deaths among white men
				2.3 (1.3–3.8)	16 deaths among nonwhite men
			Nasal	–	0 deaths among white and nonwhite men
			Lung	1.0 (0.9–1.1)	285 deaths among white men
				0.8 (0.5–1.1)	23 deaths among nonwhite men
			Prostate	1.1 (0.8–1.3)	79 deaths among white men
				1.4 (0.8–2.1)	19 deaths among nonwhite men
			Brain	1.2 (0.8–1.8)	24 deaths among white men
				–	0 deaths among nonwhite men
			Lymphatic/haematopoietic	1.3 (1.1–1.6)	100 deaths among white men
				2.4 (1.4–4.0)	15 deaths among nonwhite men
			Lymphoma	1.1 (0.5–1.9)	11 deaths among white men
				1.9 (0.1–11)	One death among nonwhite men
			Lymphatic leukaemia	0.6 (0.2–1.3)	Five deaths among white men
				3.0 (0.4–11)	Two deaths among nonwhite men
			Myeloid leukaemia	1.6 (1.0–2.4)	23 deaths among white men
				1.1 (0.1–5.9)	One death among nonwhite men
California, USA (Friedman & Ury, 1983)	Patients, SIR (143 574 pharmacy users), 1969–78	Use as a drug	All cancers	0.8 [0.3–2.0]	Five cases
			Lung	5.6 [1.6–15]	Four cases

CI, confidence interval; SMR, standardized mortality ratio; PMR, proportionate mortality ratio; PCMR, proportionate cancer mortality ratio; NA, not available; SIR, standardized incidence ratio

et al., 1988; Sterling & Weinkam, 1988, 1989a,b; Marsh *et al.*, 1992a,b, 1994a; Sterling & Weinkam, 1994).

Studies that provided detailed information indicate that workers had a range of levels of exposure to formaldehyde. Blair *et al.* (1986) found that 4% of their cohort was exposed to ≥ 2 ppm (≥ 2.5 mg/m^3); Acheson *et al.* (1984a) found that 35% were exposed to > 2 ppm; Andjelkovich *et al.* (1995) found 25% exposed to > 1.5 ppm (> 1.8 mg/m^3) and Marsh *et al.* (1994a) found 25% exposed to > 0.7 ppm (> 0.9 mg/m^3).

Cohort mortality studies in which cancers of the upper and lower respiratory tract are addressed may be biased by differences in the prevalence of tobacco smoking between the cohort and the referent population. Axelson and Steenland (1988), Blair *et al.* (1988), Siemiatycki *et al.* (1988) and others have shown that this potential bias is not a major problem, because the distribution of smoking habits between most occupational cohorts and referent populations differs little, if at all. Furthermore, when respiratory tract cancer rates are evaluated across a gradient of occupational exposures within the same cohort, the prevalence of smoking is generally so similar among the groups that tobacco smoking does not confound the relationship between occupation and cancer. In the present context, this theoretical lack of confounding was confirmed by Blair *et al.* (1990b) and Andjelkovich *et al.* (1995), who obtained data on the smoking habits of individual workers and found no effect on the risk estimates.

Three groups of workers were studied, which were totally or partially subsumed in the study of Blair *et al.* (1986, 1990b), described below. Marsh (1982) evaluated proportionate mortality patterns among workers engaged in the production of phenolic resins, urea–formaldehyde resins, melamine–formaldehyde resins, hexamethylenetetramine and resorcinol in the United States. He identified 603 deaths that occurred among men in 1950–76 and included 580 (132 exposed to formaldehyde for one month or more and 448 others) in the analysis. Wong (1983) studied workers employed at a formaldehyde production plant between the early 1940s and 1977. After exclusion of about 200 women, 12 blacks and two orientals, 2026 white men were included in the analysis. Tracing through 1977 was successful for all but 51 workers (2.5%), and 146 deaths were identified (death certificates were obtained for 136). Approximately 800 workers who were exposed to formaldehyde were included in the investigation of Blair *et al.* (1986, 1990b). Liebling *et al.* (1984) evaluated the proportionate mortality of 24 workers in the formaldehyde resin plant studied by Marsh (1982), who were also included by Blair *et al.* (1986, 1990b).

Blair *et al.* (1986) conducted a cohort mortality study of workers employed at 10 plants in the United States where formaldehyde was produced and used before 1966 and followed the workers up through 1979; some were included in the three studies mentioned above. The 10 plants were selected from a survey of about 200 companies because they had the most workers, the longest use of formaldehyde and the records necessary for a study. The cohort was assembled from company personnel records and verified for completeness from Social Security Quarterly Earnings reports. Relative risks were estimated from SMRs and directly standardized rate ratios. The expected numbers were calculated from rates for the general population and for the populations of the 10 counties in which the plants were located and were adjusted for race, sex, age and calendar time. Directly standardized rate ratios were adjusted to the distribution of

age and calendar-time person-years of the entire cohort for internal comparisons. Quantitative estimates of exposure were made on the basis of monitoring data available from the companies, from monitoring conducted by the study investigators and from information on tasks, plant operations, effects of controls and production levels (Stewart *et al.* (1986). On the basis of the job held with the highest exposure, 11% of the workers were in the background/unexposed category, 12% were exposed to < 0.1 ppm (< 0.12 mg/m^3), 34% to 0.1–0.5 ppm (0.12–0.6 mg/m^3), 40% to 0.5–2.0 ppm (0.6–2.5 mg/m^3) and 4% to ≥ 2.0 ppm (≥ 2.5 mg/m^3). The vital status of the 26 561 people in the cohort (20 714 white men, 1839 black men, 3104 white women, 26 black women and 878 workers of unknown race or sex) was determined successfully as of 1980 for 96% of the men and 83% of the women, yielding 4396 deaths. Death certificates were obtained for 4059 of the decedents (92%). The SMRs for all causes for workers exposed to formaldehyde were 1.0 (95% CI, 0.9–1.0) for white men, 0.9 (0.8–1.0) for white women and 0.8 (0.7–0.9) for black men. The SMRs for all cancers combined were 1.0 (0.9–1.1) for white men, 0.8 (0.6–1.0) for white women and 0.7 (0.5–1.0) for black men. Neither emphysema (SMR, 0.9; 0.7–1.3) nor cirrhosis of the liver (0.9; 0.7–1.1) occurred in excess among white men. No significant excess of mortality from any cancer was seen among exposed white men, white women or black men. Among exposed white men (the only group for which there was sufficient information), there were fewer deaths from leukaemia (0.8 [0.5–1.2]; 19 deaths) and brain cancer (0.8 [0.5–1.3]; 17 deaths) than expected, while the number of deaths from prostate cancer was about that expected (1.2 [0.8–1.6]; 33 deaths). Two nasal cancers occurred among white men, with 2.2 expected; none was observed among white women or black men. Although based on small numbers, the risk for cancer of the nasopharynx was increased ([3.2; 1.3–6.6] 7 deaths). One cancer of the nasopharynx occurred in a person who was not exposed to formaldehyde and one in a person not exposed to particulates, i.e. work environments in the formaldehyde-resin industry where the particles include urea–, phenol– and melamine–formaldehyde resins. The risk for death from nasopharyngeal cancer (5 deaths) among white men exposed to particulates rose with cumulative exposure to formaldehyde (0 deaths among unexposed; 1.9 (1 death) among those exposed for < 0.5 ppm-years; 4.0 (2 deaths) exposed for 0.5–5.5 ppm-years; and 7.5 (2 deaths) exposed for ≥ 5.5 ppm-years) (Blair *et al.*, 1987). In the same group, the SMRs for cancer of the oropharynx by cumulative exposure were 0 (no deaths) for the unexposed, 4.6 (3 deaths) for those exposed for < 0.5 ppm-years, 0 for exposure for 0.5–< 5.5 ppm-years and ≥ 5.5 ppm-years. Collins *et al.* (1988) pointed out that the excess occurred primarily at one plant and that subjects included in the analysis of Blair *et al.* (1987) were not required to have had simultaneous exposure to formaldehyde and particulates. They extended the follow-up of workers at the plant where four of the seven nasopharyngeal cancer deaths occurred and found no additional death for 13 656 person-years of follow-up. Tamburro and Waddell (1987) objected to the interpretation of the pattern of nasopharyngeal cancers as a trend in the absence of a significant exposure–response gradient. Lucas (1994) compared death certificate diagnoses of four nasopharyngeal cancers with information from a cancer registry. Because one of the four cancers was incorrectly labelled as nasopharyngeal cancer on the death certificate, Lucas (1994) suggested that corrected diagnoses should be used. Marsh *et al.* (1994b) and Blair and Stewart (1994) discussed the appropriateness of this recommendation. [The Working Group noted that

correction of the diagnoses in the cohort and not in the comparison population would bias estimates of relative risks towards the null. This bias would occur because there are deaths in the comparison population that are also incorrectly diagnosed as nasopharyngeal cancer. In fact, large surveys indicate that about 25% of death certificates coded as nasopharyngeal cancer are incorrect.] The SMRs for lung cancer among exposed and unexposed workers were 1.1 (95% CI, 1.0–1.3) and 0.9 (0.7–1.2) among white men, 1.3 (0.6–2.5) and 1.7 (0.7–3.5) among white women and 0.7 (0.4–1.3) and 0.6 (0.1–1.7) among black men. Internal comparisons resulted in directly adjusted rate ratios (compared with the unexposed category) for white men of 1.7 (35 deaths) for exposure to < 0.1 ppm (< 0.12 mg/m^3), 1.6 (70 deaths) for 0.1–0.4 ppm (0.12–0.5 mg/m^3), 1.8 (125 deaths) for 0.5–1.9 ppm (0.6–2.3 mg/m^3) and 0.8 (6 deaths) for ≥ 2.0 ppm (≥ 2.5 mg/m^3). There was a significant excess of deaths from lung cancer (1.2 [1.0–1.4] 219 observed) among white male wage workers (mainly non-managerial). Restricting analyses to wage (non-managerial) workers is valuable because it focuses on those employees likely to have had more intense exposures. Combining wage and salaried (managerial) workers in the same exposure–response analysis may introduce socioeconomic confounding, because salaried workers who have lower exposures to formaldehyde also have lower lung cancer rates. The risk was slightly higher when the analysis was restricted to events occurring 20 or more years after first exposure (1.3 [1.1–1.6] 151 observed). The SMRs for workers with a 20-year latency did not rise with cumulative exposure categories: 1.0 [0.3–2.3] (5 deaths) among unexposed; 1.4 [1.0–1.8] (49 deaths) for < 0.5 ppm-years, 1.4 [1.0–1.8] (53 deaths) for 0.5–5.5 ppm-years and 1.3 [0.9–1.7] (44 deaths) for ≥ 5.5 ppm-years.

In further analyses of the deaths from lung cancer in this cohort, Blair *et al.* (1990b) found no exposure–response gradient between the SMRs or directly-adjusted rate ratios and a variety of exposure indicators, including duration, intensity, cumulative exposure, peak, average and cumulative exposure restricted to lagged exposures (5, 10, 20 and 30 years). No exposure–response pattern was observed by duration of employment in various cumulative exposure categories or by cumulative exposure with duration of exposure categories. No increased risk for lung cancer was seen for workers exposed to formaldehyde alone (SMR, 1.0 [0.8–1.2] 88 observed). When exposures other than formaldehyde were considered, the risk for lung cancer was elevated (1.4 [1.2–1.7] 124 deaths) for workers in contact with asbestos, anti-oxidants, carbon black, dyes, melamine, phenol, urea and wood dust. Significant exposure–response trends were observed between mortality from lung cancer and duration of exposure to melamine and urea. Information on smoking was sought from medical records for 190 subjects with cancer and 950 controls. Although information was found for only about one-third of the subjects, the prevalence of smoking in this small sample did not appear to be associated with exposure to formaldehyde (80% who had ever smoked among the unexposed; 67% among those with a cumulative exposure of < 0.5 ppm-years, 84% with cumulative exposure of 0.5–< 5.5 ppm-years and 70% with cumulative exposure of ≥ 5.5 ppm-years).

Short-term workers sometimes have different mortality patterns from longer-term workers. Stewart *et al.* (1990) compared mortality among short-term (employed in the plants studied for one year or less) and long-term workers (employed for more than one year) in the cohort developed by Blair *et al.* (1986). Short-term workers had higher total mortality (SMR, 1.3;

95% CI, 1.2–1.3) than long-term workers (1.0; 0.9–1.0), and this overall excess was due to elevated rates of deaths from arteriosclerotic heart disease (1.1; 1.0–1.3), emphysema (1.7; 1.0–2.8) and cancers at all sites (1.3; 1.1–1.4). Excess rates were seen for cancers at several sites, including the stomach (1.4; 0.7–2.4), lung (1.4; 1.1–1.7) and brain (1.4; 0.7–2.5). The long-term workers had no cancer excesses. Data on nasal and nasopharyngeal cancers were not presented.

Others have re-analysed the study of Blair *et al.* (1986, 1990b). Robins *et al.* (1988), using a G-null test to adjust for the 'healthy worker survivor effect', found no indication of an association between exposure to formaldehyde and lung cancer but found a positive association with non-malignant respiratory disease. They adjusted the analysis for bias that may be created when ill workers leave the workforce: healthy workers continue to have the opportunity for exposure, while ill workers do not. This problem is most likely to occur in connection with debilitating diseases that do not lead to immediate death, such as emphysema.

Marsh *et al.* (1992a) used Poisson regression to analyse the data from the study of Blair *et al.* (1986, 1990b). They found excess mortality from lung cancer, which did not increase with level of cumulative exposure: relative risk, 1.0 for < 0.1 ppm-years, 1.4 (95% CI, 0.9–2.0) for 0.1–0.5 ppm-years, 1.2 (0.7–1.9) for 0.5–2.0 ppm-years and 1.3 (0.8–2.3) for ≥ 2.0 ppm-years, and no trend with duration of exposure. In a second report of their analyses, Marsh *et al.* (1992b) found no significant associations between lung cancer and cumulative, average or duration of exposure to formaldehyde. Significant positive associations with lung cancer were found with exposure to formaldehyde in the presence of other agents (antioxidants, hexamethylenetetramine, melamine and urea), but not in the absence of these cofactors. Finally, Marsh *et al.* (1994a) re-assessed the exposures in a five-year update of one of the plants in the study of Blair *et al.* (1986) and found a significant excess of lung cancer among short-term workers (SMR, 1.3 [95% CI, 1.1–1.8]; 63 deaths) but not among long-term workers (1.2 [0.9–1.6]; 50 deaths). Poisson regression analysis also showed larger relative risks in association with exposure to formaldehyde among short-term workers than long-term workers. No additional case of nasopharyngeal cancer was observed. Two nasopharyngeal cancers occurred among short-term workers.

Sterling and Weinkam (1988, 1989a,b, 1994) performed three re-analyses of the data and reported an exposure–response relationship between mortality from lung cancer and exposure to formaldehyde. The first two re-analyses contained errors (Blair & Stewart, 1989; Sterling & Weinkam, 1994).

Acheson *et al.* (1984a) studied 7680 British workers in six factories producing formaldehyde or formaldehyde-based resins, after excluding 7898 men who had begun work in 1965 or later, 1326 women and 689 workers for whom essential information was lacking. The date of first use of formaldehyde in the six factories ranged from the 1920s to the 1950s. Each worker was traced through 31 December 1981 from national mortality resources, and more than 98% of the cohort was successfully traced, yielding 1619 deaths. SMRs were used to estimate relative risks, and the expected numbers were based on death rates in England and Wales, adjusted for age and calendar time. Mortality rates in the areas where the factories were located were also used to generate expected numbers. Exposures were estimated on the basis of available data from monitoring (none before 1970) and information from management and labour. Exposure

was quantified in consultation with the staff of the six plants and placed in one of four categories: high (> 2.0 ppm; > 2.5 mg/m^3), moderate (0.6–2.0 ppm; 0.7–2.5 mg/m^3), low (0.1–0.5 ppm; 0.12–0.6 mg/m^3) and background/nil (< 0.1 ppm; < 0.12 mg/m^3). According to the job held with the highest exposure, 25% of the cohort were classified as having had background/nil exposure, 24% as low exposure, 9% as moderate exposure, 35% as high exposure and 6% unknown. Although the authors attempted to obtain information on tobacco use from company medical records, they were unsuccessful (Acheson *et al.*, 1984b). They point out that the workers may have had contact with other chemicals, including asbestos. Additional analyses using different approaches for dealing with exposure and death (cumulative and mortality over entire follow-up period, cumulative and mortality after leaving the factory, and cumulative at various calendar periods and subsequent mortality) (Acheson *et al.*, 1984c) yielded no further patterns.

The cohort of Acheson *et al.* (1984a) was further followed-up from 1981 through 1989 by Gardner *et al.* (1993). This follow-up includes 7660 people employed before 1965 rather than the 7680 in the original publication, because additional eligibility checks resulted in exclusion of 20 workers. The cohort also included 6357 workers who were first employed from 1965 onwards and who were thus excluded from the original report. The distribution of workers by highest formaldehyde exposure category was nil (25%), low (24%), moderate (9%), high (35%) and unknown (6%) among workers first employed before 1965 and 30%, 31%, 10%, 21% and 8%, respectively, for those first employed in 1965 or later. A further 1582 deaths were identified in the extended follow-up, for a total of 3201. SMRs are presented for workers first employed before 1965 and those first employed later. The SMRs for all causes were 1.0 (95% CI, 1.0–1.1) for workers first employed before 1965 and 1.0 (0.9–1.0) for those employed later, and the respective SMRs for all cancers were 1.1 (1.1–1.2; 802 deaths) and 1.0 (0.8–1.2; 128 deaths). One death from nasal cancer occurred (1.4 expected) in the group first employed before 1965 and none (0.3 expected) in those employed later. No deaths occurred from nasopharyngeal cancer, whereas 1.3 were expected, and no non-fatal cases were reported to the National Cancer Registry [expected number not reported]. Significant excess mortality was noted for cancers of the stomach (1.4; 1.2–1.7) and rectum (1.4; 1.0–1.9) among workers employed before 1965, although both decreased with adjustment for local rates. Non-significant SMRs greater than 2.0 were noted for cancer of the gall-bladder (2.9; 2 observed), breast (6.0; 1 observed) and other genital tumours (4.5; 1 observed) in workers employed in 1965 onwards and for bone cancer (2.4; 5 observed) in workers employed before 1965. For sites of special interest by period of first employment, the SMRs were 1.2 (1.1–1.4) and 1.1 (0.9–1.5) for lung cancer, 1.5 (0.6–3.0) and 0 deaths (1.1 expected) for pharyngeal cancer, 0.9 (0.5–1.5) and 0.9 (0.3–2.1) for brain cancer, 0.9 (0.5–1.6) and 1.9 (0.8–3.9) for non-Hodgkin's lymphoma and 0.9 (0.5–1.5) and 0.9 (0.3–2.3) for leukaemia. For background, low, moderate and high exposure categories, the relative risks for lung cancer were 1.0 (95% CI, 0.8–1.3), 1.1 (0.9–1.4), 0.9 (0.6–1.3) and 1.2 (1.1–1.4) for those first employed before 1965 and 1.4 (0.8–2.1), 1.0 (0.5–1.6), 1.0 (0.4–2.2) and 1.4 (0.8–2.3) for those first employed after 1964. There were no trends in lung cancer mortality that could be associated with level or duration of exposure.

Mortality among workers at a formaldehyde resin plant in Italy was studied by Bertazzi *et al.* (1986, 1989), who included 1330 male workers who were ever employed for at least 30 days between the start-up of the plant in 1959 and 1980. Vital status was determined as of December 1986, and 179 deaths were identified. Work histories of past employees were reconstructed from interviews with retired workers, current workers and foremen; and actual or reconstructed work histories were available for all but 16% 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 levels in measurements taken between 1974 and 1979 were 0.2–3.8 mg/m^3. SMRs were used to estimate relative risks. The expected numbers were based on national and local mortality rates, adjusted for age and calendar time. The SMRs based on local rates were 0.9 ([95% CI, 0.7–1.0] 179 deaths) for all causes, 0.9 ([0.7–1.1] 62 deaths) for all cancers, 2.4 ([0.8–5.8] 5 deaths) for liver tumours, 1.0 ([0.6–1.5] 24 deaths) for lung cancer and 1.4 ([0.6–2.9] 7 deaths) for cancers of the lymphatic and haematopoietic system. The rates for lung cancer were not associated with duration of exposure, latency or age at first exposure. The SMRs for lung cancer were 0.7 ([0.3–1.5] 6 deaths) for workers exposed to formaldehyde, 0.8 ([0.4–1.5] 9 deaths) for those exposed to other chemicals and 2.1 ([1.0–4.0] 9 deaths) for those whose exposure to formaldehyde could not be determined. The risk for liver cancer was greater among workers with a latency of 20 or more years (SMR, 4.0) and among those who were first exposed at 45 years of age or older (3.8). The excess of liver cancer was seen in all three exposure categories: formaldehyde (2.4; 2 deaths), other chemicals (2.3; 2 deaths) and exposure unknown (2.9; 2 deaths). In the first report (Bertazzi *et al.*, 1986), no nasal cancer was seen (0.03 expected).

Mortality among workers in the abrasives industry in Sweden was evaluated by Edling *et al.* (1987a) in plants where grinding wheels were manufactured from abrasives held together by formaldehyde resins. The levels of formaldehyde were reported to be 0.1–1.0 mg/m^3. A cohort of 911 workers (211 women and 700 men; 521 were blue-collar workers) employed between 1955 and 1983 was traced for mortality through 1983 and cancer incidence through 1981, yielding 79 deaths and 24 incident cancers. Deaths and events occurring at the age of 75 or more were excluded because of concerns about diagnostic validity. Loss to follow-up was 2%. The expected numbers were based on rates for the general population, stratified for age, calendar year and sex. No significant excesses were seen. The relative risks for mortality were 1.0 (95% CI, 0.8–1.2; 79 deaths) for all causes, 0.9 (0.5–1.5; 17 deaths) for all cancers and 1.3 (0.3–3.2; 4 deaths) for respiratory diseases. The relative risks for cancer incidence were 0.6 (0.1–2.1; 2 cases) for lung cancer, 0.9 (0.2–2.2; 4 cases) for prostatic cancer and 2.0 (0.2–7.2; 2 cases) for non-Hodgkin's lymphoma.

Stayner *et al.* (1988) conducted a cohort study of mortality among workers who had been employed for at least three months in three garment manufacturing plants in the United States between 1955 and 1977. The cohort consisted of 11 030 workers and comprised 1602 white men, 406 nonwhite men, 6741 white women and 2281 nonwhite women. Vital status was determined through 1982, and 609 deaths were uncovered. Vital status was determined for 96%

of the cohort. The expected numbers for determining SMRs were derived from the age-, calendar time-, race- and sex-specific rates of the general population. Formaldehyde levels were monitored in each of the plants, but the data were not used in the epidemiological analyses. The geometric mean levels in various departments ranged from 0.14 to 0.17 ppm [0.17–0.21 mg/m^3]. The SMRs for most major causes of death were low, including those for all causes (0.7; 95% CI [0.7–0.8]), all cancers (0.8 [0.7–1.0]), diseases of the circulatory system (0.7 [0.6–0.8]) and diseases of the respiratory system (0.7 [0.5–1.1]). Significant excesses occurred for cancers of the buccal cavity (3.4 [0.9-8.5]) and connective tissue (3.6 [1.0-9.3]). The SMRs for other cancers were 1.1 [0.8–1.6] for lung, 0.6 [0.2–1.6] for lymphosarcoma and 1.1 [0.5–2.2] for leukaemia. The four deaths from cancer of the buccal cavity occurred among white women. Some cancers were evaluated by duration of exposure (< 4 years, 4–9 years and ≥ 10 years), resulting in SMRs of 0, 2.8 (1 death) and 7.6 [1.6–22] (3 deaths) for cancer of the buccal cavity [linear trend, $p < 0.01$]; and 1.5 [0.9–2.4] (18 deaths), 1.1 [0.5–2.0] (11 deaths) and 0.8 [0.4–1.5] (10 deaths) for cancer of the lung [linear trend, $p < 0.05$]. In a previous report, Stayner *et al.* (1985) gave the findings of a proportionate mortality study of workers in three garment plants (two of which were included in the later cohort study). Significantly increased PMRs were observed for malignant neoplasms of the buccal cavity, biliary tract and liver and 'other lymphatic and haematopoietic sites'.

Andjelkovich *et al.* (1995) reported on the mortality of a subset of a previously studied cohort of workers with potential exposure to formaldehyde in an automotive iron foundry in the United States. A cohort of 3929 men (2635 white, 1294 nonwhite) was followed from 1 January 1960 to 31 December 1989 (83 064 person-years of follow-up). For comparison, an unexposed group was also analysed, which consisted of 2032 men (1629 white, 403 nonwhite) who had worked during the same period but had not been exposed to formaldehyde (40 719 person-years of follow-up). The expected numbers of deaths were derived from rates for the general population. Men who worked predominantly in core-making and related operations were exposed to formaldehyde from 1960 through 1987, while all workers in the foundry were exposed to silica. Detailed work histories and an evaluation of occupational exposures by an industrial hygienist permitted categorization of the levels of exposure to formaldehyde (none, low, medium, high) and silica (low, medium, high) for every occupational title. Values for these exposure levels were assigned on the basis of sparse sampling data (low, 0.05; medium, 0.55; high, 1.5 ppm (formaldehyde) or mg/m^3 (silica)). Quartiles were based on each person's cumulative exposure. Basic information was obtained on the smoking habits of the exposed (ever, 1934; never, 637; unknown, 1358) and unexposed (ever, 811; never, 309; unknown, 912) men. In the exposed cohort, 608 men died during the observation period, 3263 lived, and vital status was unknown for 58. In the unexposed cohort, 422 died, 1583 lived and 27 were of unknown vital status. For the men exposed to formaldehyde, the SMRs were 0.93 (95% CI, 0.86–1.0) for all causes, 0.99 (0.82–1.2) for all cancers, 1.3 (0.48–2.9) for cancer of the buccal cavity and pharynx (no deaths from cancer of the nasopharynx [0.5 expected]), 1.2 (0.89–1.6) for lung cancer, 0.62 (0.07–2.2) for brain cancer, 0.43 (0.05–1.6) for leukaemia and 1.3 (0.47–2.8) for emphysema. No death occurred from cancer of the nasal cavity. A similar mortality pattern was seen for unexposed men, with SMRs of 0.91 (0.82–1.0) for all causes, 0.97 (0.79–

1.2) for all cancers, 1.7 (0.54–4.0) for cancer of the buccal cavity and pharynx (one death from cancer of the nasopharynx), 1.2 (0.84–1.6) for lung cancer, 0.41 (0.01–2.3) for brain cancer, 0.86 (0.17–2.5) for leukaemia and 2.3 (1.2–4.1) for emphysema. Race-specific analyses revealed no major differences from the analyses of all races, except that an excess of cancers of the buccal cavity and pharynx was seen only among nonwhites. Several comparisons, including rate ratios for exposed and unexposed men, SMRs with expected numbers based on rates in a working population and Poisson regression with adjustment for smoking, revealed no association between lung cancer and exposure to formaldehyde.

The cohort and proportionate mortality studies of cancer among industrial workers exposed to formaldehyde are summarized in Table 11. Table 12 gives an overview of the occurrence of nasal and nasopharyngeal cancer in the cohort studies of both professionals and industrial workers.

2.4 Case–control studies

The Working Group systematically reviewed case–control studies of cancers of the oral cavity, pharynx and respiratory tract. Although case–control studies of cancer at other sites sporadically contained information on exposure to formaldehyde, these studies were not reviewed systematically .

2.4.1 Cancers of the nasal cavity, paranasal sinuses, nasopharynx, oropharynx and pharynx (unclassified)

With the purpose of investigating the carcinogenic effects of exposures to wood dust, Hernberg *et al.* (1983) 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. There were 167 country-, age- and sex-matched controls in whom cancers of the colon and rectum had been diagnosed. 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 smoking habits of the study subjects was obtained by telephone interview on a standardized form. A review of occupations in which exposure to formaldehyde can occur [exposure frequencies not stated] gave no indication of any association with sinonasal cancer. 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. The authors considered the category 'painting, lacquering and glueing' as a possible exception, as minimal exposure to formaldehyde may occur; 18 cases and six controls had had this exposure [odds ratio, 3.2; 95% CI, 1.3–8.1]. When people with exposure to wood dust were excluded, however, the difference was in the opposite direction (three cases, six controls [odds ratio, 0.5; 0.1–1.9]. [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).]

Table 11. Cohort and proportionate mortality studies of cancer and exposure to formaldehyde among industrial workers

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
United States (Blair *et al.*, 1986, 1987)	Formaldehyde producers, resin makers, other users, SMR (26 561; 20 714 white men, 1839 black men, 3104 white women, 904 others), 1934–80	Quantitative estimate, duration	All causes	1.0 (0.9–1.0)	2836 deaths, exposed white men
				0.9 (0.8–1.0)	200 deaths, exposed white women
				0.8 (0.7–0.9)	232 deaths, exposed black men
			All cancers	1.0 (0.9–1.1)	570 deaths, exposed white men
				0.8 (0.6–1.0)	50 deaths, exposed white women
				0.7 (0.5–1.0)	31 deaths, exposed black men
			Buccal/pharynx	1.0 (0.6–1.5)	18 deaths, exposed white men
				[0] (NA)	No deaths, exposed white women
				[1.5]	Three deaths, exposed black men
					With particulate exposure, white men:
			Nasopharynx	0 (0 death)	No formaldehyde
				1.9 (1 death)	< 0.5 ppm-years formaldehyde
				4.0 (2 deaths)	0.5–< 5.5 ppm-years formaldehyde
				7.5 (2 deaths)	≥ 5.5 ppm-years formaldehyde
			Colon	0.9 (0.6–1.2)	42 deaths, exposed white men
				1.1 (0.4–2.2)	Seven deaths, exposed white women
				1.9 (0.6–4.3)	Five deaths, exposed black men
			Nasal	[0.9]	Two deaths, exposed white men
				[0]	No deaths, exposed white women/black men
			Lung	1.1 (1.0–1.3)	201 deaths, exposed white men; no trend with level or duration
				1.3 (0.6–2.5)	Eight deaths, exposed white women
				0.7 (0.4–1.3)	11 deaths, exposed black men
			Breast	0.8 (0.4–1.4)	12 deaths, exposed white women
			Prostate	1.2 (0.8–1.6)	33 deaths, exposed white men
				[0.7]	Two deaths, exposed black men

Table 11 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
Blair *et al.* (contd)			Brain	0.8 (0.5–1.3)	17 deaths, exposed white men
				–	No deaths, 2 expected, exposed white women
			Lymphoma	[1.0] (NA)	One death, exposed black man
				0.5 (0.2–1.1)	Seven deaths, exposed white men
				–	No deaths, exposed white women/black men
			Leukaemia	0.8 (0.5–1.2)	19 deaths, exposed white men
				–	No deaths, exposed white men
				[1.0] (NA)	One death, exposed black man
United Kingdom (Gardner *et al.*, 1993; update of Acheson *et al.*, 1984a)	Chemical industry, SMR (7660 men employed < 1965, 6357 men employed ≥ 1965), 1941–89	Quantitative estimation, duration	Employed < 1965		
			All causes	1.0 (1.0–1.1)	2744 deaths
			All cancers	1.1 (1.1–1.2)	802 deaths
			Mouth	1.4 (0.3–4.0)	Three deaths
			Pharynx	1.5 (0.6–3.0)	Seven deaths
			Nasal	0.7	One death, 1.4 expected
			Lung	1.2 (1.1–1.4)	348 deaths, no trend with level or duration
			Prostate	0.7 (0.4–1.0)	26 deaths
			Brain	0.9 (0.5–1.5)	16 deaths
			Lymphoma	0.9 (0.5–1.6)	12 deaths
			Leukaemia	0.9 (0.5–1.5)	15 deaths
			Employed ≥ 1965		
			All causes	1.0 (0.9–1.0)	
			All cancers	1.0 (0.8–1.2)	457 deaths
			Mouth	1.9 (0.1–11)	128 deaths
			Pharynx	–	One death
			Nasal	0	0 deaths, 1.1 expected
			Lung	1.1 (0.9–1.5)	No death, 0.3 expected
					54 deaths, no trend with level or duration, slight trend with years of follow-up

Table 11 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
United Kingdom (Gardner *et al.*, 1993; update of Acheson *et al.*, 1984a) (contd)			Prostate	1.2 (0.5–2.7)	Six deaths
			Brain	0.9 (0.3–2.1)	Five deaths
			Lymphoma	1.9 (0.8–3.9)	Seven deaths
			Leukaemia	0.9 (0.3–2.3)	Four deaths
Italy (Bertazzi *et al.*, 1986, 1989)	Formaldehyde resin makers, SMR (1330 men), 1959–86	Duration of employment	All causes	0.9 [0.7–1.0]	179 deaths, local rates
			All cancers	0.9 [0.7–1.1]	62 deaths, local rates
			Alimentary tract	1.0 [0.6–1.5]	21 deaths, local rates
			Lung	1.0 [0.6–1.5]	24 deaths, local rates; no positive trend with duration
			Liver	2.4 [0.8–5.8]	Five deaths, local rates
			Lymphatic/ haematopoietic	1.4 [0.6–2.9]	Seven deaths, local rates
Sweden (Edling *et al.*, 1987a)	Abrasives industry, SMR, SIR (521 men), 1955–83	None	All causes	1.0 (0.8–1.2)	79 deaths
			All cancers	0.9 (0.5–1.5)	17 deaths
			All cancers	0.8 (0.5–1.3	24 incident cases
			Nasopharynx	– (NA)	One incident case
			Colon	1.0 (0.1–2.9)	Two incident cases
			Lung	0.6 (0.1–2.1)	Two incident cases
			Prostate	0.9 (0.2–2.2)	Four incident cases
			Lymphoma	2.0 (0.2–7.2)	Two incident cases
			Myeloma	4.0 (0.5–14)	Two incident cases

Table 11 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
United States (Stayner *et al.*, 1988)	Garment industry, SMR (11 030: 1602 white men, 406 nonwhite men, 6741 white women, 2281 nonwhite women), > 3 months, 1955–82	Duration	All causes	0.7 [0.7–0.8]	609 deaths
			All cancers	0.8 [0.7–1.0]	186 deaths
			Buccal cavity	3.4 [0.9–8.5]	Four deaths, all in white women, trend with duration
			Pharynx	1.1 [0.1–4.0]	Two deaths
			Intestine	0.7 [0.4–1.1]	15 deaths
			Lung	1.1 [0.8–1.6)	39 deaths, inverse trend with duration
			Breast	0.7 [0.5–1.0]	33 deaths
			Brain	0.7 [0.2–1.7]	Five deaths
			Connective tissue	3.6 [1.0–9.3]	Four deaths
			Lymphatic/ haematopoietic	0.9 [0.5–1.4]	18 deaths
			Lymphoma	0.6 [0.2–1.6]	Four deaths
			Leukaemia	1.1 [0.5–2.2]	Nine deaths
United States (Andjelkovich *et al.*, 1995)	Cohort in foundry, RR (2635 exposed white men, 1294 exposed nonwhite men; 1629 unexposed white men, 403 unexposed nonwhite men), 1960–89	Duration, quantitative estimate	Buccal cavity, pharynx	0.59 (0.14–2.9)	Any exposure
				1.2 (0.2–6.5)	3rd–4th quartile of exposure
			Lung	0.71 (0.43–1.2)	Any exposure
				0.59 (0.28–1.2)	3rd–4th quartile of exposure

CI, confidence interval; SMR, standardized mortality ratio; NA, not available; SIR, standardized incidence ratio; RR, relative risk

Table 12. Results for nasal and nasopharyngeal cancers in cohort studies of professionals and industrial workers exposed to formaldehyde

Reference	Study size	Nasal			Nasopharyngeal		
		RR	Obs	Exp	RR	Obs	Exp
Professional workers							
Harrington & Oakes (1984)	2 720	-	0	NR	-	0	NR
Hall *et al.* (1991)	4 512	NR			NR		
Walrath & Fraumeni (1983)	1 263	-	0	NR	-	0	NR
Walrath & Fraumeni (1984)	1 007	-	0	0.6	NR	NR	NR
Levine *et al.* (1984a)	1 477	-	0	0.2	NR	NR	NR
Stroup *et al.* (1986)	2 317	-	0	0.5	NR	NR	NR
Hayes *et al.* (1990)	4 046	-	0	1.7	2.2	4	1.9
Friedman & Ury (1983)	143 574	NR			NR		
Industrial workers							
Blair *et al.* (1986)	20 714	0.9	2	2.2	3[a]	6	2.0
Gardner *et al.* (1993)	14 017	[0.6]	1	1.7	-	0	1.3
Bertazzi *et al.* (1986)	1 330	-	0	0.03	NR		
Stayner *et al.* (1988)	11 030	NR			NR		
Edling *et al.* (1987a)	911	NR			NR		
Andjelkovich *et al.* (1995)	3 929	-	0	NR	-	0	[0.5]

NR, not reported

[a] Trend with level among those also exposed to particulates

In a case–control study conducted in four hospitals in North Carolina and Virginia, United States, in 1970–80, 193 men and women with 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 from records of the state vital statistics offices. Patients with oesophageal and sinonasal cancers and various nasal disorders were excluded from the control group. Telephone interviews were completed with 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 subjects' responses to a checklist of potentially high-risk industries and exposures, including formaldehyde. Exposure to formaldehyde was reported for two nasal cancer patients (one man and one woman), yielding an odds ratio of 0.35 (95% CI, 0.1–1.8). [The Working Group noted that the power of the study may have been decreased by

the high proportion of interviews that were with next-of-kin and that exposure to formaldehyde was reported by subjects or their next-of-kin.]

In a population-based study in Denmark (Olsen *et al.*, 1984), 839 men and women in whom cancer of the sinonasal cavities (525) and nasopharynx (314) was diagnosed during the period 1970–82 and reported to the national Cancer Registry were matched to 2465 controls for sex, and age and year of diagnosis, who were selected among all patients in whom cancer of the colon, rectum, prostate and breast was 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. With regard to individual compounds, the industrial hygienists determined whether a subject had not been exposed, had definitely been exposed or had probably been exposed, or whether no information could be obtained. Of the controls, 4.2% of males and 0.1% of females had had occupations with presumed exposure to formaldehyde. The results were presented only for the carcinoma subgroup of sinonasal cancer (93% of cases). 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 for both men and women (95% CI, 1.8–4.3 and 0.5–14, respectively) and 3.1 (1.8–5.3) for men in whom the diagnosis was made more than 10 years after first exposure. Adjustment for exposure to wood dust reduced both risk estimates for men to 1.6, which were 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; 0.8–1.7). There was no increase in the risk for carcinoma of the nasopharynx among men with definite exposure to formaldehyde (0.7; 0.3–1.7). [The Working Group noted that the employment histories of study subjects were restricted to 1964 or later and that the study is limited by the fact that the formaldehyde-using industries in Denmark seem to be dominated by exposure to wood dust, which makes it difficult to assess the separate effect of exposure to formaldehyde on the risk for sinonasal cancer.]

A re-analysis was performed (Olsen & Asnaes, 1986) in which data on men with squamous-cell carcinoma (215) and adenocarcinoma (39) 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 subjects who had ever been exposed to formaldehyde; of these, four had not been exposed to wood dust (2.0; 0.7–5.9). Introduction of a 10-year latent period into the analysis yielded odds ratios of 2.4 (0.8–7.4) and 1.4 (0.3–6.4), respectively. The analysis confirmed that the risk associated with exposure to wood dust is high for adenocarcinoma (odds ratios, 16 for any exposure and 30 for exposure 10 or more years before diagnosis) and small or non-existent for squamous-cell carcinoma (odds ratio, 1.3 irrespective of period). 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 (0.7–7.2), and that among men who had been exposed 10 or more years before diagnosis was 1.8 (0.5–6.0); however, only one man with an adenocarcinoma had been exposed to formaldehyde alone. Analysis of the risk for histologically specified carcinomas of the nasopharynx showed no

association with exposure to either formaldehyde or wood dust. [The Working Group noted possibly incomplete adjustment for confounding from exposure to wood dust in the assessment of the risk for adenocarcinoma associated with exposure to formaldehyde, but also noted that the assessment of risk for squamous-cell carcinoma was less likely to have been affected because squamous-cell carcinoma is 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.* (1986) identified 116 men, aged 35–79, in whom a histologically confirmed epithelial cancer of the nasal cavity and paranasal sinuses had been diagnosed in 1978–81. The cases were frequency matched on age with 259 population controls chosen randomly from among living male residents 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' smoking habits, were obtained by personal interview of study subjects or their next-of-kin, with response rates of 78% for case patients and 75% for controls. Independently of one another, two industrial hygienists (A and B) evaluated possible exposure to formaldehyde on a 10-point scale, and subsequently used three categories. 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 44% by assessment B; little or no exposure to wood dust was considered to have occurred in 15 and 30%, respectively. A large excess risk for adenocarcinoma (odds ratio, 26 [95% CI, 7.0-99]) was associated with high levels of exposure to wood dust; thus, there were too few cases (six) with no or limited exposure to wood dust to allow a meaningful assessment of risks associated with exposure to formaldehyde alone. Separate analyses among the 45 men with squamous-type sinonasal cancer who had had little or no exposure to wood dust showed an increase in risk with increasing level of exposure to formaldehyde, with odds ratios for moderate and high exposures of 2.7 [95% CI, 0.8–8.8] and 3.1 [0.7–13] in assessment A and 1.4 [0.4–4.4] and 2.4 [1.0–6.0] in assessment B, respectively. The overall relative risks for squamous-cell carcinoma associated with any exposure to formaldehyde were 3.0 [1.2–7.8] in assessment A and 1.9 [0.9–4.1] in assessment B. [The Working Group noted that a greater proportion of case patients than controls were dead (36% versus 14%) and variable numbers of next-of-kin were interviewed; besides, 10% of controls, but none of the case patients, were interviewed by telephone. The Group noted, however, that although assessments A and B were different both gave positive results.]

In the population of a 13-county area in western Washington State, United States, Vaughan *et al.* (1986a) studied 415 patients, aged 20–74 years, in whom cancer of the sinonasal cavities and pharynx (53 patients with sinonasal cancer, 27 with nasopharyngeal cancer and 205 with oro- or hypopharyngeal cancer) had been newly diagnosed, and 690 control subjects who were identified by random-digit dialing and were of similar age and the same sex as the cases. Medical, smoking, alcohol use, residential and occupational histories were collected in a telephone interview with study subjects or their next-of-kin. The response rates were 69% for cases and 80% for controls; interviews were conducted with next-of-kin for about half of the cases and none of the controls. Occupational exposure to formaldehyde was assessed by means

of a job–exposure linkage system, in which each job within each industry was related to the likelihood and intensity of exposure and was categorized as background, low, medium or high exposure. In addition, exposure scores were calculated for maximal and usual exposures weighted by the time spent in the relevant job. The odds ratios for sinonasal cancer, adjusted for sex, age, cigarette smoking and alcohol consumption, were 0.8 (95% CI, 0.4–1.7; nine cases) for low exposure, 0.3 (0.0–1.3; three cases) for medium or high exposure and 0.3 (0.0–2.3) for a high exposure score. The corresponding odds ratios for nasopharyngeal cancer were 1.2 (0.5–3.3), 1.4 (0.4–4.7) and 2.1 (0.6–7.8), and those for oropharyngeal cancer were 0.8 (0.5–1.4), 0.6 (0.1–2.7) [high exposure only] and 1.5 (0.7–3.0). When a latent period of 15 years or more was introduced into the analysis, the odds ratio associated with the highest exposure to formaldehyde was unchanged (2.1; 0.4–10) for nasopharyngeal cancer and was slightly reduced (1.3; 0.6–3.1) for oropharyngeal cancer; no exposed cases of sinonasal cancer remained in this latency category. [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 tumours and residential exposure to formaldehyde. Living in a mobile home and the presence of urea–formaldehyde foam insulation and 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, yielding odds ratios of 1.8 (0.9–3.8) for periods of < 10 years and 1.5 (0.7–3.2) for ≥ 10 years. An association was found between living in a mobile home and risk for nasopharyngeal cancer, with odds ratios of 2.1 (0.7–6.6; four exposed cases) for < 10 years and 5.5 (1.6–19; four exposed cases) for ≥ 10 years. No association was found with the risk for oropharyngeal cancer (0.9; 0.5–1.8 and 0.8; 0.2–2.7, respectively). No association was seen between the risk for oro- or hypopharyngeal cancer and reported exposure to particle-board or plywood. The risks associated with exposure to formaldehyde foam insulation could not be estimated, owing to low exposure frequencies. [The Working Group considered that living in a mobile home was a poor proxy for exposure to formaldehyde because of large variations in the use of formaldehyde-containing foams and the sharply declining release of formaldehyde to indoor air with time.]

Roush *et al.* (1987) reported on a population-based case–control study of 371 men registered at the Connecticut (United States) Tumor Registry with a diagnosis of sinonasal cancer (198) or nasopharyngeal cancer (173) and who had died (of any cause) in Connecticut in 1935–75, and 605 male controls who died in 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. Each occupation held by case patients and controls was assessed by an industrial hygienist with regard to the likelihood and level of work-place exposure to formaldehyde, and study subjects were subsequently categorized into one unexposed and four exposed groups according to four degrees of probable exposure to formaldehyde. The odds ratio, adjusted for age at death, year of death and availability of information on occupation for case patients with

sinonasal cancer who had probably been exposed to the same level of formaldehyde for most of their working life was 0.8 (95% CI, 0.5–1.3); for those who fulfilled the more restricted exposure criteria of being probably exposed to the same level for most of their working life and probably exposed to high levels for some years, the odds ratio was 1.0 (0.5–2.2); that for men who had probably been exposed to the same level for most of their working life and probably exposed to high levels at some point 20 or more years before death, it was 1.5 (0.6–3.9). The corresponding odds ratios for men with nasopharyngeal cancer were 1.0 (0.6–1.7), 1.4 (0.6–3.1) and 2.3 (0.9–6.0). There was no excess risk for sinonasal cancer among formaldehyde-exposed men who had also been exposed wood dust (0.9; 0.4–1.9).

Luce *et al.* (1993) conducted a case–control study of 303 men and women with primary malignancies of the nasal cavities and paranasal sinuses diagnosed in one of 27 hospitals in France between January 1986 and February 1988, and 443 control subjects 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) or from a list of names of healthy individuals provided by the cases (103). Occupational exposures to formaldehyde and 14 other substances or groups of substances were assessed by an industrial hygienist on the basis of information 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 smoking habits. The response rates were 68% of cases and 92% of controls. Histological confirmation was available in the medical records of all but one of the remaining 207 case patients. Study subjects were classified according to the likelihood of exposure to each of the suspected determinants of sinonasal cancer and 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 levels and calendar periods of exposure and combinations thereof. The risks associated with exposure to formaldehyde were reported for men only. Possible exposure to formaldehyde was considered to have occurred in 12% of the 59 men with squamous-cell carcinoma of the sinonasal cavities and 11% of the 320 control subjects (odds ratio, 1.0; 95% CI, 0.4–2.4). The corresponding proportions with probable or definite exposure to formaldehyde were 27% and 25%, respectively [1.1; 0.6–2.1]. No relationship was observed between any of the measures of exposure to formaldehyde and risk for squamous-cell carcinoma. Nearly all of the adenocarcinomas occurred in men with medium to high exposure to wood dust (77/82). For those exposed to both wood dust and formaldehyde, the odds ratio was 692 (92–5210), and for those exposed to wood dust but not formaldehyde the odds ratio was 130 (14–1191); however, the latter estimate was based on only six exposed cases. For four men who were exposed to formaldehyde but who had had no or little exposure to wood dust, the odds ratio for adenocarcinoma was 8.1 (0.9–73). [The Working Group noted that residual confounding by exposure to wood dust may have occurred.]

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) are intermediate between those in China and those in western

countries. The case patients (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, and 101 community controls (77% response rate), who were matched on sex, age and neighbourhood. A personal interview included questions on smoking habits, adult diet, demographic 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 duration of employment in such occupations. The risk for nasopharyngeal carcinoma was associated with likely exposure to formaldehyde; the odds ratios, adjusted for the effects of dusts and exhaust fumes and other suspected risk factors, were 1.2 (0.4–3.6; 12 exposed cases) for subjects first exposed < 25 years before diagnosis and 4.0 (1.3–12; 14 exposed cases) for those 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 16 (2.7–91) was found relative to people exposed to neither factor [numbers exposed not given]. A reverse trend was seen, however, with increasing duration of exposure to formaldehyde, with odds ratios of 2.7 (1.1–6.6) for < 15 years and 1.2 (0.5–3.2) for ≥ 15 years of exposure. [The Working Group noted that the authors did not control for the presence of Epstein–Barr viral antibodies, which showed a strong association with nasopharyngeal cancer (odds ratio, 21) in the study of Hildesheim *et al.* (1992).]

2.4.2 Cancers of the lung and larynx

Andersen *et al.* (1982) conducted a case–control study of 79 male and five female Danish doctors with a notification of lung cancer in the files of the nationwide Danish Cancer Registry during the period 1943–77. Three times as many control subjects, 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 with 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, giving 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 United States where formaldehyde was manufactured or used. All 481 active or pensioned men who were known to have died of cancer in 1957–79 were individually matched on age, pay class, sex and date of first employment to 481 men selected at random from annual payroll rosters at the plants. The cases included 181 lung cancers, 12 brain cancers and 7 cancers of the buccal cavity and pharynx. The work histories of both case and control subjects were supplied by the plants, and the categories of exposure to formaldehyde were defined, on the basis of frequency and intensity of exposure, as 'continuous direct', 'intermittent' and '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. For no cancer site examined was the odds ratio significantly greater than 1.0 in relation to any of the defined categories of exposure to formaldehyde. After allowance for a cancer induction period of 20 years, 39 patients with lung cancer and 39 controls had potentially been exposed to formaldehyde [odds ratio, 1.0; 95% CI, 0.6–1.7; unadjusted for smoking habits]; the odds ratios were 1.2 [0.6–2.8] and 0.8 [0.4–1.6] for subgroups with < 5 years and ≥ 5 years of exposure, respectively. Only one of the seven patients who died of cancer of the buccal cavity or pharynx was thought to have been exposed to formaldehyde; this was equivalent to the frequency observed among the matched controls. No death from nasal cancer was identified.

In a population-based case–control study, Coggon *et al.* (1984) used death certificates to obtain information about the occupations of all men under the age of 40 years in England and Wales who had died of bronchial carcinoma during 1975–79; 598 cases were identified, 582 of which were matched for sex, year of death, local authority district of residence and year of birth with two controls and the rest with one control who had died from any other cause. 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. All occupations that entail exposure to formaldehyde were associated with an elevated, crude odds ratio for bronchial carcinoma of 1.5 (95% CI, 1.2–1.8); however, for occupations in which exposure was presumed to be high, the odds ratio was 0.9 (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.]

Partanen *et al.* (1985) conducted a case–control study in a cohort of 3805 male production workers who had been employed for at least a 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 subjects were notified to the Finnish Cancer Registry with 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 combined with the work histories of the subjects to yield several indicators of exposure; supplementary information on smoking was collected for 68% of cases and 76% of controls by means of a questionnaire posted to study subjects or their relatives. A slight, nonsignificant increase in risk for all cancers combined was seen among workers with any exposure to at least 0.1 ppm (0.12 mg/m^3) formaldehyde, as contrasted to workers with no exposure to formaldehyde, to give an odds ratio of 1.4 [95% CI, 0.6–3.5]; an odds ratio of 1.3 [0.5–3.5] was seen 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 and cumulative exposure, repeated peak exposures and 'formaldehyde in wood dust'). Adjustment for cigarette smoking did not change the overall picture.

In an expansion of the study to include a total of 35 Finnish factories and 7307 woodworkers employed in 1944–65, Partanen *et al.* (1990) identified 136 cases of newly diagnosed 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 cancer registry, 1957–82. The additional factories were mainly involved in construction carpentry and furniture manufacture. Three controls were provided for each of the new cancer cases, 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 with any exposure to formaldehyde (odds ratio, 1.4 [95% CI, 0.6–3.1]), 18 were cancers of the lung (1.3 [0.5–3.0]) and two were cancers at other sites (2.4 [0.3–18]). Adjustment for smoking reduced the odds ratios to 1.1 for all cancers combined and to 0.7 for lung cancer separately and made the odds ratio for cancers at other sites unassessable. The unadjusted odds ratios for all cancers were 1.5 [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 [0.1–8.2] for > 1 ppm, in comparison with no exposure. Other indicators of exposure to formaldehyde showed similar inverse 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 of the subgroups with presumably the highest exposures, with odds ratios generally below 1.0. [The Working Group noted that there were too few cancers at sites other than the lung to allow meaningful analysis; consequently, this is essentially a study of lung cancer.]

Bond *et al.* (1986) conducted a case–control study in a cohort of 19 608 men employed for one year or more at a large chemical production facility in Texas, United States, between 1940 and 1980, including 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 and year of hire, were selected: one among men 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, excluding formaldehyde, were assessed in greater detail. Only nine men with 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 0.6 (95% CI, 0.3–1.3); incorporation into the analysis of a 15-year minimal latency gave an odds ratio of 0.3 (0.1–0.9).

In a population-based case–control study in the area of Montréal, Canada, 857 men with histologically confirmed primary lung cancer diagnosed during 1979–85, were identified (Gérin *et al.*, 1989). Two groups of control subjects were established, one composed of 1523 men diagnosed during the same years with cancers of other organs (oesophagus, stomach, colorectum, liver, pancreas, prostate, bladder, kidney, melanoma and lymphoid tissue), the other composed of 533 men selected from electoral lists of the Montréal area. Interviews or completed questionnaires, yielding lifelong job history and information on potential nonoccupational confounders, were obtained from the cancer patients or their next-of-kin and from the population

controls, with response rates at 82 and 72%, respectively. Each job was translated by a group of chemists and hygienists into a list of 300 potential exposures, including formaldehyde, which were categorized according to the likelihood, intensity and frequency of exposure. Nearly one-quarter of all men had 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] of formaldehyde in the ambient air. Odds ratios, adjusted for age, ethnic group, socioeconomic status, cigarette smoking, the 'dirtiness' of the jobs held and other potential workplace exposure, were 0.8 (95% CI, 0.6–1.2) for < 10 years of exposure to formaldehyde, 0.5 (0.3–0.8) for ≥ 10 years of presumed exposure to < 0.1 ppm [0.12 mg/m^3], 1.0 (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 (0.8–2.8), for ≥ 10 years of presumed exposure to ≥ 1.0 ppm formaldehyde, in relation to controls with other cancers. In comparison with the population controls, the equivalent odds ratios were 1.0 (0.6–1.8), 0.5 (0.3–0.8), 0.9 (0.5–1.6), and 1.0 (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 (0.9–6–0) and 2.2 (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 of a 13-county area of western Washington State, United States, in whom laryngeal cancer was diagnosed in 1983–87 and notified to a population-based cancer registry in the area; 81% were interviewed. Control subjects were identified by random-digit dialing and selected to be similar in age and sex to the cases; 80% of eligible subjects were interviewed, leaving 547 for analysis. Lifetime occupational, smoking and drinking histories were obtained by personal interview, and each job held for least six months was coded according to the United States census codes for industries and occupations. Codes for exposure to formaldehyde and five other agents were assigned to each classified job held by the study subjects, using a job–exposure matrix assessing both likelihood and degree of exposure and created *ad hoc*, and combined with information on duration of exposure; finally, three summary variables for presumed exposure were derived. 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 (0.4–2.1) for any 'medium' exposure and 2.0 (0.2–20; two exposed cases) for any 'high' exposure. Odds ratios of 0.8 (0.4–1.3) and 1.3 (0.6–3.1) were seen for exposure < 10 years and ≥ 10 years and of 1.0 (0.5–2.0) and 1.3 (0.5–3.3) for a medium and high formaldehyde score, respectively; the latter were calculated as the sum of years exposed weighted by the level of exposure in each of the years.

2.4.3 Cancers at other sites

In a study of 578 male leukaemia cases, 622 male non-Hodgkin's lymphoma cases and 1245 population-based controls in Iowa and Minnesota (United States), Linos *et al.* (1990) observed elevated risks for both leukaemia (odds ratio, 2.1 [95% CI, 0.4–10]) and non-Hodgkin's lymphoma (3.2 [0.8–13]) among subjects who had been employed in funeral homes

and crematoria, indicating some degree of professional exposure to formaldehyde and other compounds. The risks were particularly high for the acute myeloid subtype of leukaemia (6.7 [1.2–36]) and the follicular subtype of non-Hodgkin's lymphoma (6.7 [1.2–37]), however, these estimates were each based on only three exposed cases.

In the study of Gérin *et al.* (1989) in Montréal, Canada (see p. 274), 206 cases of non-Hodgkin's lymphoma were compared with cases of other cancer. No association was found with estimated exposure to formaldehyde.

Merletti *et al.* (1991) reported a case–control study of 103 male residents of Turin, Italy, with a diagnosis of cancer of the oral cavity or oropharynx notified to the population-based cancer registry of the city, and a random sample of 679 males, stratified by age, chosen from files of residents of Turin. Detailed occupational (since 1945) and lifelong smoking and drinking histories were obtained by personal interview, with response rates of 84% for cases and 57% for controls. Each job held for at least six 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 respiratory tract carcinogens and three non-specific exposures (including dust) were applied to the occupation–industry code combination of study subjects; the matrix was developed at the International Agency for Research on Cancer 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, with a 'no exposure' group (exposure not higher than that of the general population) as the reference level. 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 (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: non-significantly raised odds ratios were estimated of 1.7 for 1–15 years of exposure and 1.5 for ≥ 16 years within the 'any exposure' category, and 2.1 and 1.4, respectively, within the 'probable or definite' exposure category. Separate results in association with exposure to formaldehyde were not reported for the 12 men with oropharyngeal cancer.

Goldoft *et al.* (1993) interviewed nine of 14 patients with nasal or nasopharyngeal melanoma as part of a population-based case–control study of sinonasal cancer described above (Vaughan *et al.*, 1986a,b; see pp. 269–270). The frequency of exposure to formaldehyde was compared with the frequency of exposure of the control subjects included in the study of Vaughan *et al.* One subject had lived in a residence insulated with formaldehyde-based foam ([0.3 expected] not significant). None of the melanoma patients reported specific occupational exposure to formaldehyde (0.3 expected), and none reported having been employed in industries likely to result in exposure to formaldehyde (0.8 expected).

The case–control studies of cancer and exposure to formaldehyde are summarized in Table 13.

Table 13. Case–control studies of formaldehyde by cancer site

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Sinonasal cancer				
Hernberg *et al.* (1983) Denmark, Finland, Sweden	167 patients (distribution by sex not given) 167 controls	Employment in particle-board or plywood industry	–	No exposed subjects
Brinton *et al.* (1984) United States	160 patients (93 men, 67 women) 290 controls	Ever	0.4 (0.1–1.8)	Control for tobacco use did not change results
Olsen *et al.* (1984) Denmark	488 patients (distribution by sex not given) 2465 controls	Probably exposed ≥ 10 years previously (men)	3.1 (1.8–5.3)	Unadjusted
		Probably exposed ≥ 10 years previously (men)	1.6 (0.7–3.6)	Adjusted for exposure to wood dust
Olsen & Asnaes (1986) Denmark	215 men with squamous-cell carcinoma 2465 controls	Probably exposed ≥ 10 years previously	2.4 (0.8–7.4)	Adjusted for exposure to wood dust
	39 men with adenocarcinoma 2465 controls	Probably exposed ≥ 10 years previously	1.8 (0.5–6.0)	Adjusted for exposure to wood dust
Hayes *et al.* (1986) Netherlands	63 male patients 161 controls	Any, with no or little exposure to wood dust		
		Industrial hygienist A	2.5 [1.0–5.9]	
		Industrial hygienist B	1.6 [0.8–3.1]	
	28 male patients 34 controls	Any, with moderate or high exposure to wood dust		
		Industrial hygienist A	1.9 [0.6–6.5]	
		Industrial hygienist B	NR	
	45 male patients with squamous-cell carcinoma 161 controls	Any, with no or little exposure to wood dust		Controlling for cigarette use did not change the result
		Industrial hygienist A	3.0 [1.2–7.8]	
		Industrial hygienist B	1.9 [0.9–4.1]	
Vaughan *et al.* (1986a) United States	53 patients (distribution by sex not given) 552 controls	Low	0.8 (0.4–1.7)	Occupational exposure; adjusted for sex, age, cigarette smoking and alcohol consumption
		Medium or high	0.3 (0.0–1.3)	
		High exposure score (exposure level weighted by period of exposure)	0.3 (0.0–2.3)	

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Sinonasal cancer (contd)				
Vaughan *et al.* (1986b) United States	53 patients (distribution by sex not given) 552 controls	Any, from 'mobile home' Any from particle-board or plywood < 10 years ≥ 10 years	0.6 (0.2–1.7) 1.8 (0–9–3.8) 1.5 (0.7–3.2)	Residential exposure; adjusted for sex, age, cigarette smoking and alcohol consumption
Roush *et al.* (1987) United States	169 male patients 509 male controls	Probably exposed for most of working life Plus exposure ≥ 20 years before death Plus exposure to high level in some year Plus exposure to high level ≥ 20 years before death	0.8 (0.5–1.3) 1.0 (0.5–1.8) 1.0 (0.5–2.2) 1.5 (0.6–3.9)	Information on histological subtypes not available; information on occupation obtained from death certificates and city directories; adjusted for age and calender period
Luce *et al.* (1993) France	77 patients (59 men, 18 women) with squamous-cell carcinoma 407 controls	Possible (men) Probable or definite (men) < 20 years ≥ 20 years	1.0 (0.4–2.4) 1.1 (0.5–2.5) 0.8 (0.3–2.0)	Adjusted for age, exposure to wood dust, glues and adhesives
Nasopharyngeal cancer				
Olsen *et al.* (1984) Denmark	266 patients (distribution by sex not given) 2465 controls	Possible or probable exposure Men Women	 0.7 (0.3–1.7) 2.6 (0.3–22)	Unadjusted
Vaughan *et al.* (1986a) United States	27 patients (distribution by sex not given) 552 controls	Low Medium or high High exposure score (exposure level weighted by period of exposure)	1.2 (0.5–3.3) 1.4 (0.4–4.7) 2.1 (0.6–7.8)	Occupational exposure; adjusted for cigarette smoking and race

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Nasopharyngeal cancer (contd)				
Vaughan *et al.* (1986b) United States	27 patients (distribution on sex not given) 552 controls	Any, from 'mobile home' < 10 years ≥ 10 years Any, from particle-board or plywood < 10 years ≥ 10 years	 2.1 (0.7–6.6) 5.5 (1.6–19) 1.4 (0.5–3.4) 0.6 (0.2–2.3)	Residential exposure; adjusted for cigarette smoking and ethnic origin
Roush *et al.* (1987) United States	147 male patients 509 male controls	Probably exposed for most of working life Plus exposure ≥ 20 years before death Plus exposure to high level in some year Plus exposure to high level ≥ 20 years before death	1.0 (0.6–1.7) 1.3 (0.7–2.4) 1.4 (0.6–3.1) 2.3 (0.9–6.0)	Information on occupation obtained from death certificates and city directories; adjusted for age and calender period
West *et al.* (1993) Philippines	104 patients (76 male, 28 female) 193 controls	< 15 years ≥ 15 years First exposure < 25 years before diagnosis First exposure ≥ 25 years before diagnosis	2.7 (1.1–6.6) 1.2 (0.5–3.2) 1.3 (0.6–3.2) 2.9 (1.1–7.6)	Adjusted for other occupational exposure
Cancer of the oral cavity, oro- and hypopharynx				
Vaughan *et al.* (1986a)	205 patients with oro- or pharyngeal cancer (distribution by sex not given) 552 controls	Low Medium High High exposure score (exposure level weighted by period of exposure)	0.8 (0.5–1.4) 0.8 (0.4–1.7) 0.6 (0.1–2.7) 1.5 (0.7–3.0)	Occupational exposure; adjusted for sex, age, cigarette smoking and alcohol consumption
Vaughan *et al.* (1986b)	205 patients with oro- or pharyngeal cancer (distribution by sex not given) 552 controls	Any, from 'mobile home' < 10 years ≥ 10 years Any, from particle-board or plywood < 10 years ≥ 10 years	 0.9 (0.5–1.8) 0.8 (0.2–2.7) 1.1 (0.7–1.9) 0.8 (0.5–1.4)	Residential exposure; adjusted for sex, age, cigarette smoking and alcohol consumption

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Cancer of the oral cavity, oro- and hypopharynx (contd)				
Merletti *et al.* (1991) Italy	86 male patients with oral or oropharyngeal cancer 373 controls	Any Probable or definite	1.6 (0.9–2.8) 1.8 (0.6–5.5)	Adjusted for age, level of education, area of birth, tobacco smoking and alcohol drinking
Lung cancer				
Andersen *et al.* (1982) Denmark	84 cases among doctors (79 men and five women) 252 controls	Ever employed in exposed speciality	1.0 (0.4–2.4)	Both cases and controls were medical doctors
Fayerweather *et al.* (1983) United States	181 male cases 181 controls	Any, < 5 years Any, ≥ 5 years	1.2 [0.6–2.8] 0.8 [0.4–1.6]	Estimates but not CIs adjusted for smoking habits
Coggon *et al.* (1984) England and Wales	598 male patients 1180 controls	Any High	1.5 (1.2–1.8) 0.9 (0.6–1.4)	Matched analysis, but unadjusted for smoking habits; all subjects < 40 years at death
Bond *et al.* (1986) United States	308 male patients 588 controls	Any Any, ≥ 15 years before death	0.6 (0.3–1.3) 0.3 (0.1–0.9)	Unadjusted
Gérin *et al.* (1989) Canada	857 male patients 1523 male cancer controls (*a*) 533 male population controls (*b*)	Any, < 10 years ≥ 10 years Low Medium High	0.8 (0.6–1.2) (*a*) 1.0 (0.6–1.8) (*b*) 0.5 (0.3–0.8) (*a*) 0.5 (0.3–0.8) (*b*) 1.0 (0.7–1.4) (*a*) 0.9 (0.5–1.6) (*b*) 1.5 (0.8–2.8) (*a*) 1.0 (0.4–2.4) (*b*)	Adjusted for age, ethnic group, socioeconomic status, cigarette smoking, dirtiness of job and other occupational risk factors

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
***Lung cancer* (contd)**				
Gérin *et al.* (1989)	Adenocarcinoma subtype	Any, < 10 years	0.6 (0.3–1.3) (*a*)	
Canada (contd)	162 male patients		0.8 (0.3–2.0) (*b*)	
	1523 male cancer controls (*a*)	≥ 10 years		
	533 male population controls (*b*)	Low	0.5 (0.2–1.2) (*a*)	
		0.5 (0.2–1.3) (*b*)		
		Medium	0.8 (0.4–1.6) (*a*)	
		1.0 (0.4–2.5) (*b*)		
		High	2.3 (0.9–6.0) (*a*)	
		2.2 (0.7–7.6) (*b*)		
Partanen *et al.* (1990)	118 male woodworkers	Any	0.7 [0.2–2.8]	Adjusted for vital status
Finland	354 controls	Any, ≥ 10 years since first exposure	0.9 [0.2-3.8]	and smoking
Laryngeal cancer				
Wortley *et al.* (1992)	235 patients	Any		
United States	(185 men, 50 women)	Low	1.0 (0.6–1.7)	Adjusted for age,
	547 controls	Medium	1.0 (0.4–2.1)	smoking, drinking and
		High	2.0 (0.2–20)	level of education
		≥ 10 years previously	1.0 (0.3–3.0)	

CI, confidence interval

2.5 Meta-analyses

Recent reviews (Purchase & Paddle, 1989; McLaughlin, 1994) and meta-analyses (Blair *et al.*, 1990a; Partanen, 1993) summarize most of the available data. Some differences exist between the analyses of Blair *et al.* (1990a) and Partanen (1993). Partanen (1993) used lagged and confounder-adjusted inputs, whenever available, and developed summary relative risks using a log-Gaussian, fixed-effects model. Blair *et al.* (1990a) simply summed observed and expected numbers. Partanen (1993) also included three studies not incorporated by Blair *et al.* (1990a) and used only the values for men; there were also differences in exposure contrasts. The two meta-analyses were in overall agreement with regard to the risks for lung cancer, nasopharyngeal carcinoma and miscellaneous cancers of the upper respiratory tract but differed with regard to the risk for cancer of the nasal cavities and paranasal sinuses: Blair *et al.* (1990a) found a relative risk of 1.1 (95% CI, 0.7–1.5) for the more highly exposed category, while Partanen (1993) found a risk of 1.7 (1.0–2.8). For the mixed category of cancers of the oropharynx, lip, tongue, salivary glands and mouth, the aggregated data did not suggest associations with exposure to formaldehyde.

The results of the two meta-analyses are summarized in Table 14.