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Epidemiologic evidence on the relationship between formaldehyde exposure and cancer

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BLAIR A, SARACCI R, STEWART PA, HAYES RB, SHY C. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. *Scand J Work Environ Health* 1990;16:381–93. Over 30 epidemiologic studies have evaluated cancer risks associated with formaldehyde exposure. Excesses were reported for several sites, leukemia and cancers of the nasal cavities, nasopharynx, lung, and brain generating the greatest interest. The excesses of leukemia and brain and colon cancer found among professionals may not be related to formaldehyde exposure, since similar excesses were not observed among industrial workers. Inconsistencies among and within studies impede assigning formaldehyde a convincing causal role for the excesses of lung cancer found among industrial workers. A causal role for formaldehyde is the most probable for cancers of the nasopharynx and, to a less extent, the nasal cavities. Evidence of exposure-response relationships, the fact that direct contact with formaldehyde may occur at these upper respiratory sites, and the consistency of these findings with experimental studies make this assumption highly probable.

Key terms: lung, meta-analysis, nasal, nasopharynx, review.

Animal bioassays (1, 2) indicate that formaldehyde causes nasal tumors in rats. The widespread use of formaldehyde in industry and in commercial products has heightened public health concerns regarding this chemical. In the United States, the National Occupational Hazards Survey (3) of the National Institute for Occupational Safety and Health indicates that 1.6 million workers may be exposed to formaldehyde during the manufacture of formaldehyde resins, textiles, garments, particle board and plywood, insulating materials, dinnerware, and paper and in health-related professions. In addition, off-gassing of formaldehyde from certain consumer products may lead to exposure of large numbers of the general public.

The results of animal experiments led to epidemiologic studies on a variety of formaldehyde-exposed populations. Previous reviews of these studies have primarily focused on assessing the weight of evidence concerning formaldehyde as a human carcinogen without a detailed presentation of the study results. In one such review the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence for the carcinogenicity of formaldehyde in

animals, but limited evidence for humans (4). Another group concluded that the evidence for the carcinogenicity of formaldehyde in humans was less persuasive than did IARC (5).

In our review of the epidemiologic literature we have summarized results on a site-by-site basis and have focused on potential exposures to formaldehyde and other exposures that the study populations may have experienced to evaluate the strength of the evidence regarding formaldehyde and human cancer.

Study designs

Over 30 reports from epidemiologic studies on formaldehyde have been published (table 1). These reports have focused on professional groups such as funeral directors and embalmers, anatomists, pathologists, and workers in formaldehyde facilities producing formaldehyde, resins, plastic molding, decorative laminates, plywood, particle board, and apparel. These studies, as well as relevant broad surveys of cancer risk by occupation in the United States, Canada, and Sweden, are included in this review. The studies have been conducted in eight countries (United States, Canada, Great Britain, Denmark, The Netherlands, Finland, Sweden, and Italy) and have employed standardized mortality ratio (SMR), proportionate mortality ratio (PMR), standardized incidence ratio (SIR), and case-referent designs. The total number of cancer cases with potential exposure to formaldehyde in these studies is now large enough to provide considerable statistical power for evaluating the carcinogenicity of formaldehyde in humans for all but rare sites.

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Table 1. Description of the epidemiologic studies on formaldehyde. (PMR = proportionate mortality ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio)

Author	Study design	Population studied	Time period	Exposure evaluation	Diseases reported	Number of subjects	Control of smoking	Comparison population
<i>Professional and nonoccupational exposures</i>								
Petersen & Milham (6)	PMR	Funeral directors	1959–1961	None	All		No	California
Jensen & Andersen (7)	Case-referent	Physicians	1943–1976	Specialty	Lung cancer	84 cases, 252 referents	No	Other cancers
Friedman & Ury (8)	SIR	Pharmacy users	1969–1978	None	Lung All cancer	557	No	All pharmacy users
Milham (9)	PMR	Funeral directors	1959–1979	None	All	333	No	Washington
Walrath & Fraumeni (48)	PMR	Funeral directors, embalmers	1925–1980	Type of license	All	1132	No	United States
Harrington & Shannon (65)	SMR	Pathologists	1955–1973	None	13 selected causes	2079	No	United Kingdom
Harrington & Oakes (64)	SMR	Pathologists	1974–1980	None	13 selected causes	2307	No	United Kingdom
Levine et al (47)	SMR	Undertakers	1928–1977	Latency	All	1477	No	Ontario
Walrath & Fraumeni (10)	PMR	Embalmers	1925–1980	Duration	All	1007	No	United States
Gallagher et al (11)	PMR	Funeral directors	1950–1978	None	All		No	British Columbia
Logue et al (12)	SMR	Pathologists	1962–1977	None	Selected	5585	No	
Stroup et al (49)	SMR	Anatomists	1888–1979	Specialty, duration	All	2317	No	United States
Walrath et al (67)	SMR	Funeral directors, embalmers	1954–1970	None	All	408	No	Other veterans
Hayes et al (63)	PMR	Funeral directors	1975–1985	None	All	4046	No	United States
<i>Industrial workers</i>								
Fayerweather et al (40)	Case-referent	Chemical workers	1957–1979	Level, duration	All cancer	481 cases, 481 referents	Yes	Other workers
Marsh (35)	PMR	Chemical workers	1950–1976	Duration	32 causes	603	No	United States
Wong (36)	SMR	Chemical workers	1940–1977	Duration	23 causes	2026	No	United States
Liebling et al (37)	PMR	Chemical workers	1976–1980	None	9 causes	24	No	United States
Stayner et al (33)	PMR	Garment workers	1959–1980	Duration, latency	All	256	No	United States
Acheson et al (23, 68)	SMR	Chemical workers	1937–1981	Level, duration	13 causes	7680	No	United Kingdom, local
Coggon et al (41)	Case-referent	British deaths	1975–1979	Level	Lung, bladder	889 cases, 1758 referents	No	Other deaths
Olsen et al (44)	Case-referent	Danish Cancer Registry	1970–1982	Duration	Nasal, nasopharynx	839 cases, 2465 referents	No	Other cancers
Malker & Weiner (13)	SIR	Swedish Cancer-Environment Registry	1961–1979	None	6 cancers	67378	No	Sweden
Partanen et al (31)	Nested case-referent	Finnish wood-workers	1957–1980	Level, duration	Respiratory cancer	60 cases, 171 referents	Yes	Other workers
Bertazzi et al (30, 50)	SMR	Resin workers	1959–1986	Duration	14 causes	1332	No	Italy
Blair et al (24–28)	SMR	10 plants	1934–1980	Level, duration	All	26561	No	United States, unexposed
Bond et al (43)	Nested case-referent	Chemical workers	1940–1980	Latency	Lung	308 cases, 588 referents	Yes	Other workers
Hayes et al (42)	Case-referent	The Netherlands' hospitals	1978–1981	Level	Nasal cancer	91 cases, 195 referents	Yes	Population referents
Vaughan et al (45, 62)	Case-referent	Washington Tumor Registry	1979–1983	Level, duration	Nasal, pharynx	285 cases, 552 referents	Yes	Population referents
Roush et al (59)	Case-referent	Connecticut Tumor Registry	1935–1975	Probability of exposure	Nasal, nasopharynx	371 cases, 605 referents	No	Other deaths
Stayner et al (34)	SMR	Garment workers	1959–1982	Duration	All	11030	No	United States
Gerin et al (39)	Case-referent	Montreal	1979–1985	Level, duration	19 cancers	4259	Yes	Population and other cancer

Exposure information

Formaldehyde is ubiquitous in the environment. For the assessment of cancer risks associated with formaldehyde exposure, it is of paramount importance that the level of exposure of study subjects be determined.

In epidemiologic studies of formaldehyde exposure and cancer risk various approaches to exposure assessment have been taken, largely dictated by the constraints of the study design. Mortality surveys, such as of professional groups, have relied upon qualitative assessment

of exposure based upon job title or similar designations. Mortality studies of individual industrial facilities have generally provided more-detailed exposure estimates based on industrial exposure measurements and ancillary information. Case-referent studies composed of persons from a variety of occupations have generally relied on indirect exposure assessment based on knowledge of work practices and exposures in formaldehyde-related jobs.

Study groups

Professionals

Embalmers may come in contact with a variety of chemicals, including formaldehyde, phenol, dyes and stains, glutaraldehyde, glycol, glycerol, xylene, alcohols, and particulates, and also with biologic material and gamma radiation (14). Levels of <2 ppm for solvents (ie, isopropyl alcohol, 1,1,1-trichloroethane, isopentane, and trichloroethylene) and of 1.8 mg/m^3 for total dust, and 1.3 mg/m^3 for respirable dust measured from hardening compounds have also been reported (15). Published reports on exposure in this profession primarily discuss exposure to formaldehyde. Mean time-weighted average (TWA) values ranging from 0.30 to 1.30 ppm have been reported for formaldehyde during the embalming procedure (15–17), but a recent evaluation by three of the authors (PAS, RBH, AB) found somewhat higher TWA values (0.8 to 2.9 ppm), with instantaneous peaks of formaldehyde or other aldehydes of up to 20 ppm. On the assumption that an embalming takes about 3 h and that only one embalming occurs per day, the 8-h TWA

values in all of these cases would be about 60 % lower. Thus TWA values during embalming operations appear to be similar to those found in industry, but such high peak concentrations have not been reported in industrial facilities.

Chemicals used in anatomy laboratories may be similar to those used in funeral homes, but anatomists appear to have a greater range of exposure to formaldehyde, the TWA values ranging from 0.02 to 5.87 (18–21). Although peak levels in anatomy laboratories have not been reported, they may be similar to those generated during embalming. In studies of cancer risk among professional workers (ie, anatomists, pathologists, and funeral professionals), assessment of exposure to formaldehyde was largely qualitative, being inferred from job titles identified from state licensing records and from membership lists of professional societies with no specific estimates of exposure for study subjects.

Industrial workers

In contrast to the studies of cancer risk among professional groups, epidemiologic studies of industrial workers (table 2) have generally included quantitative estimates of the level of exposure to formaldehyde. Estimated levels in these investigations were similar and resembled measurements reported in other settings (22). The six manufacturing facilities in the study by Acheson et al (23) produced formaldehyde, formaldehyde resins, formaldehyde adhesives, paraform, and alcohols. Exposure to formaldehyde was estimated for each job and assigned to exposure categories of <0.1 , 0.1 – 5 , 0.6 – 2.0 , and >2.0 ppm. Monitoring

Table 2. Exposure levels and potential chemical confounders in studies of industrial workers.

Author	Type of operation	Formaldehyde exposures (ppm)	Percentage of cohort with high exposure	Other chemicals	Comments
Stayner et al (33)	2 garment manufacturing plants	Current = 0.1 – 1.0	..	None	Exposures believed higher in past
Acheson et al (23)	5 formaldehyde, resin, adhesive, paraform, and alcohols plants	<0.1 – >2.0	35 % >2.0 ppm	Asbestos	Dust in all plants
Blair et al (24–27)	10 formaldehyde, resin, molding, photographic film, plywood plants	<0.1 – >2.0 , peaks >4.0	3 % >2.0 ppm	Alcohol, ureas, antioxidants, plasticizers, dyes, asbestos, wood dust, phenol, stearates, amides, and others	Dust in many plants
Stayner et al (34)	3 garment manufacturing plants	Current geometric mean = 0.14 – 0.17 , no peaks measured	..	None	Higher in past
Partanen et al (31) and Kauppinen & Niemelä (32)	19 particleboard, plywood, glue, sawmill plants	..	9 % >1.5 (average exposure)	Wood dust, glues, pesticides, phenol, terpenes, solvents, exhaust gases, molds	
Bertazzi et al (30)	1 resin plant	1974–1979 mean levels = 0.2 – 3.8	..	Urea, melamine, styrene, epoxy resins, solvents, epichlorohydrin	Past levels higher

data available since 1970 and interviews with management and long-term employees about process changes and controls were used to estimate the exposure levels. Twenty-five percent of the subjects were unexposed. Among those holding jobs where exposure occurred, 35 % had their highest exposed job in the low-exposure category, 14 % had their highest exposed job in the moderate category, and 51 % had their highest exposed job in the high category (>2.0 ppm). The authors specifically mentioned the presence of only one other substance, asbestos, but we assume that many of the chemicals identified in the formaldehyde and resin plants studied by Blair et al (24–27), such as wood dust, phenol, melamine, and urea, may have also been present in the formaldehyde and resin plants in this study.

Blair et al (24–29) studied 10 plants producing a variety of products, including formaldehyde, formaldehyde resins and molding compounds, decorative laminates, photographic film, and plywood. The estimates of formaldehyde levels for each unique combination of job, department, plant, and calendar-year combination were based on the results of monitoring conducted by the investigators (about 2000 full-shift personal samples) (27), company monitoring results (over 4500 results dating back to the 1960s for some plants), plant visits, job descriptions, and interviews with management and long-term employees regarding changes in the process, controls, work practices, and sensory perceptions (26). With the use of these estimates jobs were assigned to categories of trace, ≤ 0.1 , $0.1 < 0.5$, $0.5 < 1.9$, and ≥ 2.0 ppm. In addition, for each job, estimates were made for the level and frequency of peak exposures, the potential for exposure to formaldehyde in liquid or particulate form, the possibility of other chemical exposures, and the industrial hygienists' confidence in the estimates. Eight percent of the cohort never held exposed jobs. Among the exposed workers, 44 % of the cohort had cumulative exposures which were between 0.01 and 0.5 ppm-years, 34 % had exposures of 0.51–5.5 ppm-years, and 14 % had cumulative exposures which exceeded 5.5 ppm-years. Alcohols, melamine, urea, antioxidants, ammonia, plasticizers, dyes and pigments, asbestos, phenol, carbon black, wood dust, stearates, amides, and acetone were other chemicals to which large numbers of workers were exposed.

Bertazzi et al (30) studied a urea and melamine resin plant. The jobs identified were classified as exposed to formaldehyde, exposed to other chemicals, or not exposed. Between 1974 and 1979, the mean levels of formaldehyde (based on 187 measurements) were between 0.2 and 3.8 ppm, with individual results as high as 9.8 ppm. Other operations in the plant included a styrene resin and an epoxy resin (with possible epichlorohydrin exposure) operation in which exposures may have occurred to xylene, toluene, and methyl isobutyl ketone. No specific identification of other chemicals in the resin operation was made, but we as-

sume them to be similar to those in the resin plants studied in the United States (25) and Great Britain (23).

Partanen et al (31) identified 19 sawmills and manufacturers of plywood and formaldehyde glue for a nested case-referent study of respiratory cancer. Exposure assessments by job were based on interviews of cases and referents (or their next-of-kin), available monitoring data, plant visits, and interviews with supervisors and long-term workers to obtain data on ventilation controls, work practices, and other relevant factors. Monitoring was conducted in four companies with few air sampling measurements. Jobs were assigned to one of four exposure categories (<0.1 , $0.1 < 1.0$, $1.0 < 2.0$, and ≥ 2.0 ppm). The investigations identified 74 % of the cases and referents as exposed to formaldehyde of <0.1 ppm, 17 % as exposed to 0.3 ppm, 7 % as exposed to 1.5 ppm, and 2 % as exposed to 3.0 ppm. Peaks of >2 ppm were also noted. Other exposures noted included wood dust, chlorophenols, pesticides, terpenes, phenol, casein-albumin glues, melamine glues, solvents, exhaust gases, molds, bacteria, and possibly bis(chloromethyl)ether (32).

Stayner et al identified study subjects from the company insurance fund records of three garment manufacturing firms for a PMR study (33) and from company records for an SMR study (34) (two of these plants were also in the PMR study). In the PMR study, recent measurements in two of the plants indicated that air levels ranged from 0.1 to 1.0 ppm. Levels were presumably higher in the past. No other chemical exposures were believed to be present. In the SMR study (34) the current geometric mean level of formaldehyde was low, ranging from 0.14 to 0.17 ppm (in 557 samples). Although historical exposure levels to formaldehyde were not available, they were assumed to be substantially higher. The authors stated it was unlikely that substantial peaks or intermittent exposures occurred or that there were other potential chemical confounders.

In other industry-based studies, exposure evaluations have been less detailed. Approaches have included analyses by length of employment (35, 36), ever or never exposed (35, 37), and physical state of the formaldehyde (liquid or powder) (35).

Case-referent studies

In the case-referent study by Gerin et al (38, 39) information obtained in an interview of the subjects consisted of a detailed occupational history including raw materials and final products, type of workroom, activities of other nearby workers, and presence of gaseous fumes or dusts. A team of hygienists and chemists translated this information into potential exposures (38). For formaldehyde, the authors indicated that the categories of low, medium, and high corresponded roughly to <0.1 , $0.1 < 1.0$, and >1.0 ppm. Among the 4249 subjects interviewed, 760 (18 %) were

judged to have low exposures, 203 moderate exposures (5 %), and 8 (0.2 %) high exposures.

Fayerweather et al (40) supplemented the work history information from the personnel records of seven DuPont plants with information in the medical records and from interviews with co-workers. Available monitoring results were used in the estimation of levels for "continuous" exposure. When monitoring data were nonexistent, interviews of long-term employees were made with regard to sensory perceptions and process descriptions and control changes. The following three levels of "continuous" exposure were identified: <0.1, 0.1–2.0, and ≥ 2.0 ppm. Intermittently exposed jobs were classified as low (peaks <2 ppm) or high (>2 ppm) exposure. Other chemicals which were used included asbestos, benzene, carbon tetrachloride, zinc chromate, and acrylonitrile.

In most of the other case-referent studies industrial hygienists classified the jobs held by subjects into semi-quantitative categories (41, 42) or nominal categories (43–45). Estimates of possible level of exposure were not made. In many cases the subjects were exposed to other chemicals, including known or potential carcinogens (41–45). One study had two industrial hygienists independently evaluate exposure, and risks of nasal cancer were calculated on the basis of each assessment (42).

In summary, several facets regarding the exposure assessments used in these studies are worth noting. The studies of professionals and the case-referent investigations suffer from typical limitations in that exposure is based entirely on job title without detailed information on the facility. Absence of information on levels of exposure in these investigations prevented evaluation of dose-response relationships. Moreover, in most of the studies of professions, other exposures were ignored. Among case-referent studies, those by Gerin et al (39) and Fayerweather et al (40) are stronger because they assembled more information regarding exposures and developed estimates of exposure levels. The exposure assessments in the cohort studies of industrial workers are generally better because actual site visits to the plants under study were made by industrial hygienists. In addition monitoring data were often available. With these data, quantitative estimates were developed and used in exposure-response analyses. Only two of the industrial studies included information on exposure other than formaldehyde (24, 31).

Summary of epidemiologic results

Tables 3 and 4 display results from the epidemiologic studies. To provide a comprehensive review, cancers that were excessive in two or more studies or showed some exposure-response pattern are included in the tabulations (11 sites). The observed and expected numbers presented are generally for exposed persons only. For some studies, the expected numbers were not

provided but could be calculated from the data in the paper. The expected numbers from case-referent studies were obtained by dividing the number of exposed cases by the odds ratio.

The observed and expected numbers were summed for studies of professional and industrial groups separately to create combined relative risk (CRR) estimates. This summation approach weights the risk estimates by study size. We also present the proportion of the studies having relative risks greater than 1.0, an approach which weights the contribution from each study equally. The statistical significance of the CRR estimates was assessed according to Bailar & Ederer (46).

The studies of industrial workers from the United States were not entirely independent, but total overlapping of the study populations did not occur because criteria for entry into the cohorts varied from study to study. In addition, the detail to which exposure to formaldehyde was estimated also varied among the overlapping studies. Studies by Marsh (35) and Liebling et al (37) were on a plant that was also included in the study by Blair et al (25). The plants studied by Wong (36) and Fayerweather et al (40) also included some workers that were studied by Blair et al (25). Two plants were included in both studies by Stayner (33, 34). In the summation of the observed and expected numbers, however, results from the earlier study by Stayner (33) and the studies by Marsh (35), Fayerweather et al (40), Wong (36), and Liebling et al (37) were not included because they were generally covered in the later study by Stayner et al (34) or in the study by Blair et al (25). Thus there is no double counting of cancer deaths in the summary statistics provided in this report.

Among professionals (tables 3 and 4), significant excesses occurred for leukemia (CRR 1.6) (11 of the 13 investigations showing excesses ranging from 1.1 to 3.1), brain cancer (CRR 1.5) (six of nine studies showing excesses ranging from 1.2 to 3.3), and colon cancer (CRR 1.3) (excesses in seven of nine studies ranging from 1.1 to 2.3). Fewer deaths from lung cancer occurred among the professionals than expected (CRR 0.9), nine of 15 studies showing a deficit. Overall, mortality from lung cancer among embalmers and funeral directors was about as expected (CRR 1.0), in contrast to the striking deficit among anatomists and pathologists (CRR 0.3). Only one death from nasal cancer occurred among the professionals, less than one death being expected. Observed and expected numbers were presented for nasopharyngeal cancer in only one report, and excesses were observed among black and white men (CRR 2.2). There was an overall deficit for Hodgkin's disease (CRR 0.5) (based on six deaths). Mortality from prostate cancer and for cancer of the buccal cavity and pharynx was about as expected (CRR 1.0).

In contrast to professionals, industrial workers did not show elevated mortality from leukemia (CRR 1.1)

Table 3. Mortality from cancers of the buccal cavity and pharynx, nasopharynx, lung, nose, prostate, and bladder among persons exposed to formaldehyde.^a (O = observed number of cases, E = expected number of cases, RR = relative risk)

Author	Buccal cavity and pharynx			Nasopharynx			Lung			Nose			Prostate			Bladder		
	O	E	RR	O	E	RR	O	E	RR	O	E	RR	O	E	RR	O	E	RR
<i>Professional and nonoccupational exposures</i>																		
Petersen & Milham (6)	—	1	0.0	—	0.0	—	3	3	0.9	—	—	—	2	2	0.9	1	1	1.0
Jensen & Anderson (7)	—	—	—	—	—	—	8	8.0	1.0 ^b	—	—	—	—	—	—	—	—	—
Friedman & Ury (8)	—	—	—	—	—	—	4	0.7	5.6*	—	—	—	—	—	—	—	—	—
Milham (9)	3	2	1.5	—	—	—	11	15	0.7	—	—	—	5	7	0.7	6	3	2.4*
Walrath & Fraumeni (48)	8	7.1	1.1	—	—	—	72	66.8	1.1	—	—	—	15	16.4	0.9	7	7.3	1.0
Harrington & Shanon (65)	—	—	—	—	—	—	8	24.2	0.3	—	—	—	—	—	—	—	—	1.9
Harrington & Oakes (64)	—	—	—	—	—	—	9	22.0	0.4*	—	0.1	0.0	—	—	—	2	1.9	1.1
Levine et al (47)	1	2.1	0.5	—	—	—	19	20.2	0.9	—	—	—	3	3.4	0.9	—	—	—
Walrath & Fraumeni (10)	8	6.1	1.3	—	—	—	41	42.9	1.0	—	0.6	0.0	23	13.1	1.8*	8	5.8	1.4
Gallagher et al (11)	—	—	—	—	—	—	6	6.9	0.9	1	<0.1	0.0	1	2.8	0.4	2	1.0	1.9
Logue et al (12)	—	—	—	—	—	—	—	—	0.2*	—	—	—	—	—	—	—	—	—
Stroup et al (49)	1	6.8	0.2*	—	—	—	12	43.1	0.3*	—	—	—	19	18.9	1.0	5	7.3	0.7
Walrath et al (67)	—	0.4	0.0	—	—	—	10	6.4	1.6	—	—	—	—	3.2	0.0	2	1.2	1.7
Hayes et al (63)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
White men	26	21.8	1.2	3	1.6	1.9	285	294.0	1.0	—	1.5	0.0	79	74.8	1.1	23	26.3	0.9
Nonwhite men	4	3.2	1.2	1	0.2	4.0	23	30.5	0.8	—	0.2	0.0	19	14.0	1.4	—	1.6	0.0
Total for professionals	51	50.5	1.0	4	1.8	2.2	511	583.8	0.9*	1	2.4	0.4	166	165.6	1.0	56	58.3	1.0
Anatomists and pathologists (49, 64, 65)	—	—	—	—	—	—	29	89.3	0.3*	—	—	—	—	—	—	—	—	—
Funeral directors and embalmers (9—11, 47, 48, 63, 67)	—	—	—	—	—	—	490	520.4	1.0	—	—	—	—	—	—	—	—	—
<i>Industrial workers</i>																		
Fayerweather et al (40)	1	1	1.0 ^d	—	—	—	15	19.0	0.8 ^d	—	—	—	6	2	3.6 ^e	4	0.6	7.0 ^d
Marsh (35)	—	—	—	—	—	—	6	7.1	0.8	—	—	—	1	0.0	0.0	2	0.6	3.2
Wong (36)	—	—	—	—	—	—	11	11.7	0.9	—	—	—	4	1.3	3.0	1	0.8	1.2
Liebling et al (37)	2	0.2	8.7*	1	—	—	3	2.3	1.3 ^f	—	—	—	—	—	—	—	—	—
Stayner et al (33)	3	1.3	2.3	—	—	—	11	11.6	1.0	—	0.0	0.0	—	—	—	—	—	—
Acheson et al (23, 68)	5	4.6	1.1	—	—	0.0	205	215	1.1	—	1.1	0.0	—	—	—	18	16.9	1.1
Coggon et al (41)	—	—	—	—	—	—	296	197	1.5*	—	—	—	—	—	—	132	132	1.0
Olsen et al (44)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Men	—	—	—	—	—	0.7	—	—	—	5	2.8	1.8 ^g	—	—	—	—	—	—
Women	—	—	—	—	—	2.6	—	—	—	—	—	2.8	—	—	—	—	—	—
Malker & Weiner (13)	63	68.0	0.9	—	—	—	214	183	1.2	14	7.6	1.8	228	231	1.0	—	—	—
Pertanen et al (31) ^h	—	—	—	—	—	—	13	9.8	1.3 ⁱ	—	—	—	—	—	—	—	—	—
Bartazzini et al (50)	—	—	—	—	—	—	24	23.9	1.0	—	<0.1	0.0	—	—	—	—	—	—
Blair et al (25)	18	19	1.0	6	2	3.0*	201	182	1.1	2	2.2	0.9	33	29	1.2	14	15	1.0
Bond et al (43)	—	—	—	—	—	—	9	27.0	0.6	—	—	—	—	—	—	—	—	—
Hayes et al (42)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IH-A ^{j,k}	—	—	—	—	—	—	—	—	—	15	6.0	2.5*	—	—	—	—	—	—
IH-B ^{j,l}	—	—	—	—	—	—	—	—	—	24	15.0	1.6	—	—	—	—	—	—
Vaughan et al (45, 62)																		
Occupation ^m	—	—	—	4	2.4	1.7	—	—	—	3	10.0	0.3 ⁿ	—	—	—	—	—	—
Residential ^o	—	—	—	6	2.1	2.8*	—	—	—	5	8.3	0.6	—	—	—	—	—	—
Roush et al (59)	—	—	—	21	21.0	1.0 ^p	—	—	—	21	26.2	0.8 ^p	—	—	—	—	—	—
Stayner et al (34)	6	3.9	1.6	—	—	—	39	34.1	1.1	—	—	—	—	—	—	3	2.7	1.1
Gerin et al (39)	—	—	—	—	—	—	180	225.0	0.8	—	—	—	127	115.4	1.1	126	105.0	1.2
Total for industrial workers	92	95.5	1.0	31	25.4	1.2	1181	1096.8	1.1*	60	56.0	1.1	388	375.4	1.0	293	271.6	1.1
Number of studies with relative risks >1.00 and total number of studies																		
Professionals	5/9			2/2			3/15			1/5			3/10			5/11		
Industrial workers	2/4			3/5			6/9			4/8			2/3			3/5		

^a Data in italics are included in the summary statistics.

^b Exposed were those ever employed in pathology, forensic medicine, or anatomy.

^c All respiratory cancers.

^d Unexposed versus exposed for ≥ 5 years with a 20-year latency.

^e Intermittent exposure with > 15 years of latency.

^f Respiratory cancer and related cancers.

^g Without exposure to wood dusts.

^h Lung cancers were 54 of 60 cases.

ⁱ Adjusted for cigarette smoking.

^j With little or no exposure to wood dusts.

^k Exposures estimated by industrial hygienist A (IH-A).

^l Exposures estimated by industrial hygienist B (IH-B).

^m Occupational exposure.

ⁿ Medium and high exposure strata combined.

^o Residential exposure.

^p Probably exposed to some level for most of worklife.

* $P < 0.05$.

or brain cancer (CRR 0.9) (tables 3 and 4). A small, but significant, excess of lung cancer was seen among the industrial workers (CRR 1.1), six of nine studies showing excesses. A nonsignificant excess was observed for nasopharyngeal cancer (CRR 1.2), three of five

studies showing excesses, nasal cavity cancer (CRR 1.1), four of eight studies showing excesses, and bladder cancer (CRR 1.1), three of five studies showing excesses. Mortality was about as expected from cancers of the buccal cavity and pharynx (CRR 1.0) and pros-

Table 4. Mortality from cancers of the brain, colon and skin, leukemia, and Hodgkin's disease among persons exposed to formaldehyde.^a (O = observed number of cases, E = expected number of cases, RR = relative risk)

Author	Brain			Colon			Skin			Leukemia			Hodgkin's disease		
	O	E	RR	O	E	RR	O	E	RR	O	E	RR	O	E	RR
<i>Professional and nonoccupational exposures</i>															
Petersen & Milham (6)	—	0.0	0.0	3	2	1.6	..	..	..	2	1	2.0	—	0.0	0.0
Jensen & Andersen (7)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Friedman & Ury (8)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Milham (9)	1	2	0.6	5	5	0.9	..	..	..	8	3	3.1*	..	..	..
Walrath & Fraumeni (48)	9	5.8	1.6	29	20.3	1.4*	8	3.6	2.2*	12	8.5	1.4	2	2.3	0.9
Harrington & Shannon (65)	..	..	..	..	..	..	..	..	..	1	1.3	0.8	1	0.6	1.6
Harrington & Oakes (64)	4	1.2	3.3*	..	..	..	..	..	..	1	1.1	0.9	..	..	..
Levine et al (47)	3	2.6	1.2	..	..	..	—	0.9	0.0	4	2.5	1.6	..	..	..
Walrath & Fraumeni (10)	9	4.7	1.9*	30	16.0	1.9*	2	3.4	0.6	12	6.9	1.8*	—	2.5	0.0
Gallagher et al (11)	..	..	..	3	3.0	1.0	..	..	..	2	1.0	2.0	..	..	..
Logue et al (12)	..	..	..	..	..	..	..	..	..	..	..	1.1	..	..	..
Stroup et al (49)	10	3.7	2.7*	20	18.5	1.1	..	..	..	10	6.8	1.5	—	1.9	0.0
Walrath et al (67)	—	0.8	0.0	5	3.5	1.4	..	..	..	4	1.5	2.7	..	..	..
Hayes et al (63)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
White men	24	19.4	1.2	95	80.5	1.2	19	14.2	1.3	45	31.2	1.4*	3	4.0	0.8
Nonwhite men	—	0.8	0.0	16	6.9	2.3*	—	0.4	0.0	6	2.2	2.7	—	0.2	0.0
Total for professionals	60	41.0	1.5*	206	155.7	1.3*	29	22.5	1.3	107	67.0	1.6*	6	11.5	0.5
<i>Industrial workers</i>															
Fayerweather et al (40)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Marsh (35)	..	..	..	1	..	..	..	..	..	1	..	..	..	..	..
Wong (36)	3	1.6	1.9	3	3.0	1.0	1	0.9	1.1	2	1.7	1.2	2	0.8	2.4
Liebling et al (37)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Stayner et al (33)	1	2.1	0.5	8	7.3	1.1	2	1.1	1.8	4	2.4	1.7	1	0.7	1.4
Acheson et al (23, 68)	..	..	..	..	..	..	2	1.1	1.8	..	..	..	..	..	..
Coggon et al (41)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Olsen et al (44) ^b	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Malker & Weiner (13)	89	101.1	0.9	..	..	..	..	..	..	94	82.5	1.1	..	..	..
Partanen et al (31)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Bertazzi et al (50)	..	..	..	4	2.2	1.8	..	..	..	..	..	..	..	..	..
Blair et al (25)	17	21	0.8	42	48	0.9	10	12	0.8	19	24	0.8	14	10	1.4
Bond et al (43)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Hayes et al (42)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Vaughan et al (45)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Vaughan et al (62)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Roush et al (59)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Stayner et al (34)	5	7.0	0.7	15	21.9	0.7	2	3.8	0.5	9	7.9	1.1	..	..	..
Gerin et al (39)	..	..	..	167	185.6	0.9 ^b	22	22.0	1.0 ^c	..	..	..	8	16.0	0.5
Total for industrial workers	111	129.1	0.9	228	257.7	0.9	36	38.9	0.9	122	114.4	1.1	22	26.0	0.8
Number of studies with relative risks > 1.00 and total number of studies															
Professionals	6/9			7/9			2/5			11/13			1/6		
Industrial workers	0/3			1/4			1/4			2/3			1/2		

^a Data in italics are included in the summary statistics.

^b Colon and rectal cancer.

^c Melanoma.

* $P < 0.05$.

tate (CRR 1.0). Overall, fewer deaths occurred than expected for Hodgkin's disease (CRR 0.8) and for cancers of the colon (CRR 0.9) and skin (CRR 0.9).

The risk of nasal cancer was evaluated by exposure level or duration of exposure to formaldehyde (table 5). When the observed and expected numbers from the various studies were combined, no exposure-response gradient was evident from the CRR values. Of the four studies with sufficient information for an exposure-response evaluation, only one had a positive trend (42). On the other hand, for nasopharyngeal cancer, the CRR values rose to 2.1 in the high-exposure category (table 6), a trend which was statistically significant ($X = 2.02$). All three of the studies with

exposure-response data showed a rising risk of nasopharyngeal cancer with increasing exposure.

The relative risks for lung cancer by time since first exposure (latency) is shown in table 7. Only three studies of professionals had information on latency. The CRR values for lung cancer in the shorter and longer latency categories for these studies combined were 0.6 and 0.9, respectively. Risk did not vary for the embalmers by length of time since first exposure (47, 48), but it did for the anatomists (49). Among the industrial workers, the CRR was 1.1 for lung cancer for the shorter latency group and 1.2 for the longer latency group. Three studies showed higher lung cancer risks with longer latency (23, 25, 31), and three

Table 5. Relative risks for nasal cancer by level or duration of exposure to formaldehyde. (O = observed number of cases, E = expected number of cases, RR = relative risk)

Author	Unexposed			Lower level/duration			Higher level/duration			Author's X for trend
	O	E	RR	O	E	RR	O	E	RR	
Blair et al (25) ^a	—	0.2	0.0	1	2	0.5	1	1	1.0	0.59
Roush et al (59) ^b	148	148	1.0	21	26.2	0.8	9	9.0	1.0	-0.55
Hayes et al (42) ^{c, d}	48	48	1.0	8	3.6	2.2	7	2.3	3.0*	3.7*
Hayes et al (42) ^{c, e}	39	39	1.0	7	7	1.0	17	8.1	2.1*	2.41*
Vaughan et al (45) ^f	41	41	1.0	9	11.2	0.8	3	10.0	0.3	-2.09*
Total ^g	228	228.2	1.0	38	46.4	0.8	30	28.1	1.1	.

^a Lower level = >0–5.5 ppm-years, high level = ≥5.5 ppm-years.

^b Lower level = all exposed, higher level = probably exposed to high levels for at least one year.

^c On a scale of 1–9, lower level = 1–2 and higher level = ≥3 (all among those exposed to lower levels of wood dusts).

^d Exposure estimates from industrial hygienist A.

^e Exposure estimates from industrial hygienist B.

^f Lower level versus medium to high levels.

^g Using data from industrial hygienist B for Hayes et al (42).

* P ≤ 0.05.

Table 6. Relative risks for nasopharyngeal cancer by level or duration of exposure to formaldehyde. (O = observed number of cases, E = expected number of cases, RR = relative risk)

Author	Unexposed			Lower level/duration			Higher level/duration			X for trend
	O	E	RR	O	E	RR	O	E	RR	
Blair et al (28) ^a	1	0.5	2.0	2	0.5	4.0	2	0.3	7.5	0.83
Roush et al (59) ^b	126	126	1.0	21	21	1.0	7	3.1	2.3*	1.29
Vaughan et al (45) ^c	16	16	1.0	7	5.8	1.2	4	2.9	1.4	0.65
Total	143	142.5	1.0	30	27.3	1.1	13	6.3	2.1*	2.02*

^a Unexposed = <0.5 ppm-years, lower level = 0.05–<5.5 ppm-years, higher level = ≥5.5 ppm-years (all among those also exposed to particulates).

^b Lower level = probably exposed, higher levels = probably exposed to some higher levels ≥20 years before death.

^c Relative exposure scale, low = low, high = medium and high.

* P ≤ 0.05.

Table 7. Relative risk (RR) for lung cancer by time since first exposure/employment. (O = observed number of cases, E = expected number of cases)

Author	Shorter latency			Longer latency		
	O	E	RR	O	E	RR
<i>Professionals</i>						
Walrath & Fraumeni (48) ^a	39	36.1	1.1	35	34.7	1.0
Levine et al (47) ^b	19	20.9	0.9	18	18.6	1.0
Stroup et al (49) ^c	4	40.0	0.1	8	12.2	0.6
Total for professionals	62	97.0	0.6	61	65.5	0.9
<i>Industrial workers</i>						
Acheson et al (23) ^d	80	70.0	1.1	26	19.6	1.3
Blair et al (25) ^e	68	69	1.0	151	114	1.3*
Stayner et al (34) ^f	31	25.1	1.2	8	9.2	0.9
Bond et al (43) ^g	9	14.5	0.6	4	16.7	0.3
Bertazzi et al (50) ^h	14	7.3	1.9*	10	15.3	0.6
Partanen et al (31) ⁱ	13	9.8	1.3 ^h	8	5.0	1.6 ^h
Total for industrial workers	215	195.7	1.1	207	179.8	1.2

^a Shorter latency = <35 years; longer latency = ≥35 years.

^b Shorter latency = ≤10 years; longer latency = ≥20 years.

^c Joined association: shorter latency = before 1930; longer latency = after 1930.

^d Entered work force: shorter latency = before 1946; longer latency = after 1946.

^e Shorter latency = <20 years; longer latency = ≥20 years.

^f Shorter latency = total group; longer latency = ≥10 years.

^g Shorter latency = ≤15 years; longer latency = ≥15 years.

^h Adjusted for cigarette smoking.

* P ≤ 0.05.

showed higher risks with shorter latency (34, 43, 50). Risk of lung cancer by level or duration of exposure to formaldehyde is shown in table 8. Among the professionals, fewer deaths from lung cancer occurred than expected in both categories, and the relative risk was lower in the higher exposure category (CRR 0.7) than in the lower exposure category (CRR 1.0). In the studies of industrial workers there was a small, but statistically significant, excess of lung cancer among workers with shorter duration or lower levels of exposure (CRR 1.2), but not among the longer or more heavily exposed (CRR 1.0) workers. Using duration as the only measure of exposure resulted in a CRR of 1.3 for the shorter duration category and 0.8 for the longer one. The CRR values for the low and high categories based on level of exposure were identical (1.1 and 1.1, respectively), however. Neither the individual studies nor the summary statistics showed significant trends between level of formaldehyde exposure and risk of lung cancer.

Table 8. Lung cancer by level or duration of exposure to formaldehyde. (O = observed number of cases, E = expected number of cases, RR = relative risk, · = not applicable, only two categories with estimates)

Author	Unexposed			Lower level/duration			Higher level/duration			X for trend
	O	E	RR	O	E	RR	O	E	RR	
<i>Professionals</i>										
Walrath & Fraumeni (10) ^a	..	..	..	17	16.0	1.1	24	27.0	0.9	·
Walrath & Fraumeni (48) ^{b,c}	..	..	..	47	42.1	1.1	27	28.6	0.9	·
Stroup et al (49) ^d	..	..	..	6	15.0	0.4	6	26.7	0.2	·
Total for professionals	..	..	..	70	73.1	1.0	57	82.3	0.7*	·
<i>Industrial workers</i>										
Acheson et al (23) ^e	37	43	0.9	39	42	0.9	109	97	1.1	1.45
Coggon et al (41) ^f	..	..	..	296	197.3	1.5*	44	48.9	0.9	·
Blair et al (24) ^g	14	21	0.7	88	72	1.2	62	56	1.1	1.10
Stayner et al (34) ^h	..	..	..	29	21.6	1.3	10	12.5	0.8	·
Bertazzi et al (50) ⁱ	..	..	..	19	16.5	1.2	5	7.4	0.7	·
Partanen et al (31) ^{e,i}	47	47.0	1.0	10	6.6	1.5	3	2.2	1.4	1.09
Gerin et al (39) ^k	..	..	..	33	66.0	0.5	24	16.0	1.5	·
Total for industrial workers	98	111.0	0.9	514	422.0	1.2*	250	240.0	1.0	0.20
Cohort studies only (23, 24, 31, 34, 50)	98	111.0	0.9	185	158.7	1.2*	189	185.1	1.0	0.75
With estimates of level (23, 24, 31)	98	111.0	0.9	137	120.0	1.1	174	155.2	1.1	1.75
With duration only (34, 50)	..	..	..	48	38.1	1.3	15	19.9	0.8	·

^a Lower = <20 years of licensure; higher = ≥20 years of licensure.

^b Embalmers and funeral directors; embalmers only.

^c Respiratory cancer.

^d Lower = <20 years of membership; higher = ≥20 years of membership.

^e Lower = 0.1–0.5 ppm; higher = >2.0 ppm.

^f Lower = all exposed; higher = high exposure.

^g Lower = >0—<0.5 ppm-years; higher = ≥5.5 ppm-years.

^h Lower = >3 months—<3 years in duration; higher = ≥10 years in duration.

ⁱ Lower = <10 years of exposure; higher = ≥10 years of exposure.

^j Lower = 0.1–1 ppm; higher = ≥1 ppm.

^k Lower level = ≥10 years of exposure at low levels; higher level = ≥10 years of exposure at high levels.

* P ≤ 0.05.

Discussion

As noted in earlier reviews, professional and industrial workers exposed to formaldehyde have exhibited different cancer patterns (4, 5, 22, 51). The excesses for leukemia and cancers of the colon and brain observed among professionals were not seen among industrial workers. The excesses were rather consistent for leukemia (11 of 13 studies), brain cancer (six of nine studies), and colon cancer (seven of nine studies) among professionals. Studies lacking such excesses had few reported deaths (generally less than three). Diagnostic bias (52) may be a concern for these cancers, since professionals may receive better medical care than the general population which served as the reference in the investigations. Among anatomists (49), however, the relative risks for leukemia and brain cancer remained elevated when mortality rates from psychiatrists were used to generate the expected numbers, a finding suggesting that the excess risks for anatomists cannot be entirely explained by diagnostic bias or general socioeconomic bias. In the study of anatomists (49) the SMR decreased but remained elevated when expected deaths from benign tumors of the nervous system (conditions likely to be misdiagnosed) were included in the estimate of expected brain cancers, again

a finding suggesting that the excess is unlikely to be entirely due to diagnostic bias.

Industrial workers appear to have TWA values of formaldehyde similar to those of professional workers. The lack of excesses of leukemia or cancer of the brain or colon among industrial workers would seem to indicate that formaldehyde is not contributing to the excesses of these tumors. Experimental investigations also suggest that formaldehyde is unlikely to induce cancer in tissues other than those in which direct contact can occur. The formaldehyde concentration was not increased in the blood of rats exposed to 14.4 ppm (53), and (¹⁴C)- and (³H)-formaldehyde was not found in the bone marrow in labeling experiments (54). Professionals may, however, experience higher peak exposures on a more frequent basis than industrial workers. This possibility may be important if, during high peak exposures, body defenses are overwhelmed (55). In balance, these data suggest that the excesses for leukemia and brain cancer among professionals cannot be entirely explained by socioeconomic confounding or diagnostic bias, but the factors in the work environment responsible for these excesses have not been identified. Pathologists, anatomists, and embalmers differ from industrial workers in that they may be exposed to other substances used in the preserva-

tion of tissues, including dyes and stains, glycol, and xylene, as well as biologic materials (14–21). Additional investigations are needed to determine if these exposures alone or in combination with formaldehyde contribute to the cancer excesses noted among professionals.

Among industrial workers, cancers of the respiratory system have received the most attention. A small, but statistically significant, excess occurred for cancer of the lung (CRR 1.1), and an overall exposure-response gradient occurred for cancer of the nasopharynx. There was a small overall nonsignificant excess for nasal cancer (CRR 1.1), but the risk of this cancer did not increase with increasing duration or level of exposure. Several lines of evidence suggest, however, that formaldehyde may be involved in the development of this cancer in humans. First, two case-referent studies noted excess risks among persons exposed to formaldehyde (42, 44). The occurrence of an exposure-response gradient from the two independent assessments of exposure in the study from The Netherlands (42) is of particular interest. Exposure assessment is especially difficult in case-referent studies. Random exposure misclassification is to be expected, but it would tend to dilute exposure-response patterns. Similar estimates of risk from independent assessments of exposure increases one's confidence in the findings. Second, in the investigation from The Netherlands (42), squamous cell cancer was the histological type of nasal cancer most strongly associated with formaldehyde, and this was the type of cancer seen among rodents exposed to formaldehyde (1, 2). The Danish case-referent study, however, did not find that exposure to formaldehyde was particularly associated with squamous cell cancer of the nose (56). Third, hyperplasia and squamous cell metaplasia of the nasal mucosa, reported among woodworkers (57) and chemical workers exposed to formaldehyde (58), correspond to lesions observed among rodents in bioassays (1, 2) and lend biologic credibility to the hypothesis that formaldehyde is a risk factor for nasal cancer in humans. Potential confounding by other occupational factors remains a problem, however.

In the case-referent studies for nasal cancer (42, 44, 59) many workers exposed to formaldehyde may have also had exposure to wood dust, a recognized nasal carcinogen, and it is unclear whether its potential effects were entirely removed. In studies in Denmark (44) and The Netherlands (42), however, elevated risks occurred among persons who held jobs for which exposure to wood dusts was less likely. Other case-referent studies in the United States (60) and Nordic countries (61) found no association between formaldehyde exposure and nasal cancer, but they were not specifically designed to assess risks from this chemical. Several cohort studies of industrial workers or professional workers have also failed to detect excesses of nasal cancer (23, 25, 34) although the power of the studies was small.

The excesses for cancer of the nasopharynx occurred in a cohort study (relative risk 3.0) and in case-referent studies (CRR 1.2, based on two studies). In the cohort study (28) relative risks for nasopharyngeal cancer increased steadily to 7.5-fold among workers who had cumulative exposure to formaldehyde of ≥ 5.5 ppm-years and exposure to formaldehyde-containing particulates. No exposure-response relationship was found, however, among persons who were exposed to formaldehyde but not exposed to particulates. In a case-referent study (45, 62) in which exposure to formaldehyde was assessed from workplace and residential sources, the relative risks for nasopharyngeal cancer rose from 1.7 for persons with occupational exposure alone, to 2.8 for persons with residential exposures alone, to 6.7 for persons with both occupational and residential exposures (45, 62). These relative risks were adjusted for ethnic origin and cigarette smoking. In the other case-referent study (59) the relative risk of nasopharyngeal cancer rose with probable level of exposure to 2.3 for those exposed at higher levels 20 or more years before death. Contradictory results regarding nasopharyngeal cancer were obtained in other studies. No excesses occurred in most studies of professionals and no deaths from cancer of the nasopharynx were reported in the study of chemical workers in Great Britain (23) or in the investigation of garment workers in the United States (34). In these investigations, however, the expected numbers were small. The excess of nasopharyngeal cancer among black and white male embalmers in a recent study from the United States is the first report among professionals and further points to a role for formaldehyde in the origin of this tumor (63). In Denmark, a case-referent study noted an association between formaldehyde exposure and nasopharyngeal cancer among women, but not among men (44). Despite these inconsistencies, biologic plausibility (excesses for a site where direct contact may occur) and the occurrence of exposure-response patterns in studies of different designs (cohort mortality and case-referent) suggest that a causal association between formaldehyde exposure and cancer of the nasopharynx seems credible and likely. As with nasal cancer, small numbers, inconsistency among studies, and a possible independent role for particulates preclude definitively labeling formaldehyde as a nasopharyngeal carcinogen.

The findings regarding lung cancer are difficult to interpret. The significant deficits of lung cancer that occurred among anatomists and pathologists were very likely due to a lower prevalence of smoking among these health professionals (49, 64, 65) than among the general population (66). Smoking habits among embalmers and funeral directors appear, however, to resemble that of the general population. In a study of United States veterans (67) the proportion of embalmers who ever smoked cigarettes (57 %) did not differ from that of the entire study population (58 %). Smoking, therefore, does not appear to confound com-

parisons between embalmers and the general population. Embalmers, however, do not appear to experience an excess of lung cancer (CRR 1.0). In addition, among funeral directors and embalmers, the risk of lung cancer did not increase with time since first exposure.

Industrial workers had a small excess of lung cancer (CRR 1.1), but the overall relative risks increased little with latency. Neither did the risk of lung cancer increase with duration or level of exposure to formaldehyde among industrial workers, findings resembling those of studies of embalmers and funeral directors. The CRR values decreased with increasing duration of exposure and were similar in the low- and high-exposure categories.

In the studies of multiple plants in the United States (24, 25, 28, 29, 33, 34) and Great Britain (23, 68) excess mortality from lung cancer was not observed in all the plants. Among garment workers (34) in the United States, deficits were observed at two plants, whereas one had an excess. In the study of workers at 10 plants producing and using formaldehyde (24, 25) an excess of lung cancer occurred among workers with ≥ 20 years of latency for six plants, and deficits occurred for four plants. The plants with the excesses were not necessarily the plants with the highest levels of exposure. In Great Britain (23) three plants had deficits, and two had excesses. One of the plants with an excess had the highest exposure levels in the study and showed an exposure-response relationship (the SMR rising to 118 for the most heavily exposed). The other plant with an overall excess showed no such exposure-response relationship and had levels similar to those found in the other plants in the study.

In both the American and British studies of chemical workers (23–25) the lung cancer excess was largely confined to workers involved in the production of resins and molding compounds. In the American study, lung cancer was not elevated among workers exposed to formaldehyde unless they also came into contact with substances associated with the production of resins and molding compounds (24). The study of workers in an Italian resin plant also noted an excess of lung cancer, but it did not appear to be directly related to formaldehyde exposure (50). An update (69) of the Finnish cohort (31) noted an excess of cancer of the upper respiratory tract but not an excess of lung cancer.

Some investigators have speculated that the healthy worker effect may contribute to the lack of an exposure-response gradient for lung cancer (70, 71). Robins et al (70), using an analysis which controlled for this problem, concluded that the healthy worker effect was not an explanation for the failure to observe an exposure-response pattern in the Blair et al study (25). Sterling & Weinkam (71), in another reanalysis of these data, confirmed the excess of lung cancer reported by the original authors (25) but concluded that it was caused by formaldehyde. An error in the counting of deaths resulted in an inclusion of approximate-

ly three times as many deaths in the analyses as existed in the cohort (29). In a letter addressing this problem (72) Sterling & Weinkam reported an excess of lung cancer that rose with level of exposure. In these analyses, however, more deaths from lung cancer occurred than were noted in the original analysis by Blair et al (25). These new analyses (72) may have included contributing causes of death from lung cancer, but contributing causes do not appear to be included in the analyses of all cancers combined.

Based on findings from all the reviewed studies, a causal association between exposure to formaldehyde and lung cancer cannot be entirely discounted, but many of the traditional criteria for causality in epidemiologic investigations are missing. The excess risk was small among industrial workers (CRR 1.1) and was not seen consistently in all the plants studied. In some plants there were deficits. No such excess for lung cancer occurred among the embalmers. Overall, there was a slight increase in the risk of lung cancer with time since first exposure among the industrial workers, but this pattern was also inconsistent by study. Risks increased with latency in two of the three studies of professionals which included information on latency effects, but in only two of the six studies of industrial workers. A causal association was not suggested by the mortality pattern either by level or by duration of exposure. In three studies among professionals, risks were lower for the workers exposed to formaldehyde for longer durations than for those with shorter durations, and in the industry studies the risks were lower among the heavier or longer exposed workers in four of six studies. Furthermore, elevated mortality from lung cancer among workers in certain operations involving resins and molding compounds suggests that further evaluation of exposures in this process in the American, British, and Italian cohorts may help clarify the role of formaldehyde and other substances in the excess of lung cancer seen in some of these studies.

In summary, we conclude that it is likely that the excesses of nasopharyngeal cancer observed were caused by exposure to formaldehyde. The association with nasal cancer is plausible, but somewhat less persuasive than that for nasopharyngeal cancer. The absence of excesses for leukemia and cancers of the colon and brain among industrial workers suggests that the associations seen among professional workers may not be due to formaldehyde. Although a role for formaldehyde in the excess of lung cancer cannot be dismissed, inconsistencies among and within studies of industrial workers suggest that this association is not causal; however, other interpretations are possible. Formaldehyde may be an effective carcinogen only in the presence of other exposures, which were not consistent from study to study, or it may be a weak carcinogen whose effect was easily masked by the presence of lung carcinogens that varied from study to study.

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