

Extended Follow-Up of a Cohort of British Chemical Workers Exposed to Formaldehyde

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Background: Formaldehyde is mutagenic and, when inhaled at high concentrations, carcinogenic in rats. Some epidemiologic studies have linked occupational exposure to formaldehyde with cancers of the nose, nasopharynx, and lung, but the evidence for human carcinogenicity has been inconsistent and requires clarification. **Methods:** We extended by 11 years the follow-up of an existing cohort of 14 014 men employed after 1937 at six British factories where formaldehyde was produced or used. Subjects had been identified from employment records, and their jobs had been classified for potential exposure to formaldehyde. Standardized mortality ratios (SMRs) were derived using the person-years method and were compared with the expected numbers of deaths for the national population. **Results:** During follow-up through December 31, 2000, 5185 deaths were recorded, including two from sino-nasal cancer (2.3 expected) and one from nasopharyngeal cancer (2.0 expected). Relative to the national population, mortality from lung cancer was increased among those who worked with formaldehyde, particularly in men in the highest of four estimated exposure categories (>2 ppm) (SMR = 1.58, 95% confidence interval = 1.40 to 1.78), and the increase persisted after adjustment for local geographic variations in mortality (SMR = 1.28, 95% confidence interval = 1.13 to 1.44). However, there was a statistically nonsignificant decrease in the risk of death from lung cancer with duration of high exposure ($P_{\text{trend}} = .18$), and this risk showed no trend with time since first high exposure ($P_{\text{trend}} = .99$). **Conclusions:** The evidence for human carcinogenicity of formaldehyde remains unconvincing. Although a small effect on sino-nasal or nasopharyngeal cancer cannot be ruled out, a possible increase in the risk of lung cancer is a greater concern. [J Natl Cancer Inst 2003; 95:1608–15]

Formaldehyde is an important industrial chemical that has been used for more than 60 years in the manufacture of resins, adhesives, and plastics. It has also been used in the processing of anatomic and pathologic specimens, as an antimicrobial agent in cosmetics, as a fumigant in agriculture, and in the production of crease-resistant garments. Although the heaviest exposures to formaldehyde have occurred occupationally, it is also encountered residentially, where it arises from several sources, including particle board made with formaldehyde-based resins (which

are widely used in furniture) and cavity insulation with urea formaldehyde foam.

Formaldehyde is mutagenic *in vitro*, and exposures *in vivo* by gavage and inhalation have been shown to induce cytogenetic damage in tissues that are in direct contact with the chemical (1). When rats inhaled formaldehyde at concentrations of 14 ppm or higher, they developed cancer of the nose (1,2), but it is unclear whether these tumors arose through a genotoxic mechanism or as a consequence of cytotoxicity. Epidemiologic studies of occupational exposure to formaldehyde (3–5) have suggested elevated risks of cancer at various sites, including the nose and nasal sinuses, nasopharynx, lung, and brain. However, the evidence that formaldehyde is carcinogenic in humans has been inconsistent, and when last reviewed by the International Agency for Research on Cancer in 1995, the evidence was classed as “limited” (1).

To address the continuing uncertainties in risk assessment for formaldehyde, there is a need for further epidemiologic data, particularly from the chemical industry, where occupational exposures have historically tended to be highest. In Britain, a large cohort of such workers was identified by Acheson et al. (6) in the early 1980s. A previous analysis of this cohort (7) indicated an excess of lung cancer, but it was unclear whether this excess resulted from exposure to formaldehyde or from confounding by nonoccupational risk factors. Here, we have extended follow-up of the cohort by 11 years, during which almost 2000 additional deaths occurred.

SUBJECTS AND METHODS

Details of how the cohort was assembled have been published previously (6,7). The cohort was composed of 14 014 men who had been employed at six British chemical factories at a time when formaldehyde was produced or used and for which per-

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See “Notes” following “References.”

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Table 1. Distribution of cohort members by company

Company	Location	Year formaldehyde first used	Year from which personnel records were complete	Activities	No. in cohort	No. in cohort with high exposure*
Borden	North Baddesley, Southampton	About 1955	1958	Production of formaldehyde and use on site for manufacture of resins and adhesives	1909	51
Synthite	West Bromwich, West Midlands	1920s	1950	Production of formaldehyde as formalin, paraformaldehyde, and alcohols	760	261
Synthite	Mold, Clwyd, Wales	1950	1951	Production of formaldehyde as formalin, paraformaldehyde, and alcohols	459	105
British Industrial Plastics (BIP)	Oldbury, West Midlands	1937	1938	Production of formaldehyde and use on site for manufacture of resins and adhesives	4789	3416
Ciba-Geigy	Duxford, Cambridgeshire	1937	1957	Production of formaldehyde and use on site for manufacture of resins and adhesives	2624	158
British Petroleum (BP)	Barry, South Glamorgan, Wales	1948	1948	Production of resins from imported formalin	3473	0

*High level of exposure to formaldehyde estimated as greater than 2 ppm.

sonnel records were believed to be complete (Table 1). At all but one factory (British Petroleum [BP]), an attempt was made to identify all men who satisfied this criterion. At BP, where only a small proportion of the workforce was exposed to formaldehyde, ascertainment was limited to formaldehyde workers and a control group (two for each exposed man) who had worked in other parts of the plant. The original study was approved by the British Medical Association Ethics Committee, and the workforce at each factory was informed about the nature and aims of the study through their local statutory safety committee.

Identification data and occupational histories were abstracted from employment records, and each job was classified as belonging to one of five categories of exposure to formaldehyde (background, low, moderate, high, or unknown). No measurements of formaldehyde had been taken before 1970, but from later measurements and from workers' recall of irritant symptoms, it is estimated that background exposure corresponded to time-weighted average concentrations of less than 0.1 ppm; low exposure to 0.1–0.5 ppm; moderate exposure to 0.6–2.0 ppm; and high exposure to greater than 2.0 ppm. Some of the exposures may have occurred through inhalation of paraformaldehyde particles or particles of formaldehyde-based products. A separate job–exposure matrix was constructed for each factory, and a job title was not necessarily assigned the same exposure level at all factories at which it occurred. However, within each factory, each job was assigned to the same exposure category for all time periods.

In addition to formaldehyde, other hazardous materials, including styrene, ethylene oxide, epichlorhydrin, various solvents, asbestos, chromium salts, and cadmium, were handled at some of the factories. In most cases, however, any exposures to these substances would have been relatively low.

The cohort was followed for mortality and cancer incidence through December 31, 2000, principally through the National Health Service Central Register (NHSCR). For the few members of the cohort for whom tracing proved difficult, supplementary information on vital status was obtained from Social Security records. Deaths were coded according to the ninth revision of the International Classification of Diseases (ICD-9). Person-year analyses were conducted using Stata 7.0 software to derive standardized mortality ratios (SMRs), with associated 95% confidence intervals (CIs) based on the Poisson distribution. Expected numbers of deaths were calculated from national rates for England and Wales in 5-year age bands and 5-year calendar

periods. As in previous reports (6,7), some analyses also included an adjustment for local geographical variations in mortality. This adjustment involved multiplying the expected numbers of deaths from national rates by SMRs for the local authority areas in which each factory was located. The adjustment factors that were used for each factory in different time periods are shown in Table 2. The relevant local authority areas changed over time because of reorganizations of local government. Poisson regression was used for tests for trend across ordered exposure categories. All statistical tests were two-sided.

In the principal analyses, each individual was followed starting at the latest of a) January 1, 1941, b) the time from which personnel records at the factory were believed to be complete, or c) his date of first employment. He then contributed person-years at risk until the earliest of a) his date of death, b) his loss to follow-up for other reasons (e.g., emigration), or c) December 31, 2000. For men who could not be traced through the NHSCR or Social Security records, follow-up was censored at the last known date of employment. In addition to analyses of mortality by underlying cause of death, we checked cancer registrations and contributing causes of death listed on death certificates for additional cases of nasal and nasopharyngeal cancer, because these tumors were of special interest.

The number of men (14 014) included in our analysis differed slightly from that in a previous report of this cohort (14 017) (7). In our analysis, two workers previously miscoded as male were excluded, and four had previously been double-counted because they had been employed a second time by the same factory or by another factory in the study, and their records had not been linked. These losses were partially offset by the inclusion of three additional men whose date of birth (two) or sex (one) had before been unknown.

RESULTS

Within the cohort of 14 014 men, 13 865 (98.9%) were successfully traced through the NHSCR or Social Security records. Of these men, 7821 were still alive on December 31, 2000, 5185 had died (5153 with a known cause of death), and 859 had emigrated or otherwise become lost to follow-up at some time after leaving employment at the factories under study.

The overall mortality among members of the cohort was slightly higher than expected from national death rates (SMR = 1.04, 95% CI = 1.02 to 1.07), as was mortality from all cancers

Table 2. Adjustment for local variation in mortality from lung cancer and respiratory disease

Factory	Period of follow-up	Local authority	Period from which adjustment factor was derived*	Adjustment factors			
				Respiratory disease	Digestive disease	Lung cancer	Stomach cancer
Bordon	1941–1979	Romsey & Stockbridge	1969–1973†	0.66	0.76	0.95	0.66
	1980–1988	Test Valley	1980–1988	0.81	0.78	0.82	0.81
	1989–2000	Test Valley	1989–1999‡	0.81	0.69	0.88	1.00
Synthite, West Bromwich	1941–1979	West Bromwich	1969–1973†	1.65	1.53	1.30	1.48
	1980–1988	Sandwell	1980–1988	1.22	1.20	1.31	1.39
	1989–2000	Sandwell	1989–1999‡	1.27	1.23	1.30	1.45
Synthite, Mold	1941–1979	Mold	1969–1973†	1.00	0.82	1.33	0.95
	1980–1988	Delyn	1980–1988	0.91	1.00	0.92	0.86
	1989–2000	Flintshire	1989–1999‡	0.92	0.89	1.05	1.20
British Industrial Plastics (BIP)	1941–1979	Warley	1969–1973†	1.23	1.31	1.19	0.97
	1980–1988	Sandwell	1980–1988	1.22	1.20	1.31	1.39
	1989–2000	Sandwell	1989–1999‡	1.27	1.23	1.30	1.45
Ciba-Geigy	1941–1979	South Cambridgeshire	1969–1973†	1.03	0.71	0.88	0.82
	1980–1988	South Cambridgeshire	1980–1988	0.76	0.88	0.73	0.60
	1989–2000	South Cambridgeshire	1989–1999‡	0.81	0.67	0.72	0.69
British Petroleum (BP)	1941–1979	Barry	1969–1973†	1.00	0.74	0.93	1.41
	1980–1988	Vale of Glamorgan	1980–1988	0.85	0.96	0.86	0.98
	1989–2000	Vale of Glamorgan	1989–1999‡	0.95	1.02	0.89	1.02

*The adjustment factor was taken as the standardized mortality ratio (SMR) for the local authority during this period.

†1968–1978 for lung cancer.

‡In 1996, several local authorities became unitary authorities. However, numbers presented for 1989–1999 are based on 1996–1999 authority boundaries.

(SMR = 1.10, 95% CI = 1.04 to 1.16), respiratory disease (SMR = 1.12, 95% CI = 1.04 to 1.21), digestive disease (SMR = 1.19, 95% CI = 1.02 to 1.38), and injury and poisoning (SMR = 1.09, 95% CI = 0.96 to 1.24) (Table 3). A similar pattern was observed when analysis was restricted to the 1919 deaths that had occurred during the 11 years of added follow-up (data not shown). Among men who had worked in jobs with high exposure to formaldehyde (1995 deaths, overall SMR = 1.15, 95% CI = 1.10 to 1.20), the increase in mortality was greater than that in the total cohort for the diagnostic categories of cancer, respiratory disease, and digestive disease, but not for deaths from injury and poisoning. In men who had never been recorded as working in a job where formaldehyde exposure was high, mortality from all causes and from all cancers was close to that expected (SMR = 0.99 for each).

The main respiratory diseases that caused death in the cohort were chronic obstructive lung disease (374 deaths) and bronchopneumonia (145 deaths). The digestive diseases that most often caused death were chronic liver disease and cirrhosis (49 deaths) and peptic ulcer (36 deaths). The patterns of mortality from respiratory and digestive diseases, according to formaldehyde exposure category, are summarized in Table 4. The results are

presented with and without adjustment for local geographic variations in mortality and are given separately for the British Industrial Plastics (BIP) factory (where most of the high exposure to formaldehyde had occurred) and for all factories combined. For both disease categories (i.e., respiratory and digestive disease), SMRs tended to be lower after adjustment for local mortality patterns than before this adjustment and were higher in men with only low exposure to formaldehyde than in men with other exposures.

We next evaluated mortality in the cohort from specific types of cancer (Table 5). The higher-than-expected number of cancer-related deaths arose principally from increases in cancers of the stomach (150 deaths observed versus 114.4 deaths expected overall, and 63 deaths observed versus 41.3 deaths expected in men with high exposure) and lung (594 deaths observed versus 486.8 deaths expected overall, and 272 deaths observed versus 172.3 deaths expected in men with high exposure). In addition to the lung cancers, there were 10 deaths from mesothelioma (three at BIP and seven at BP). Two deaths from sino-nasal cancer were recorded (2.3 deaths expected), but neither man had been exposed to high levels of formaldehyde. A small increase in the number of deaths from pharyngeal tumors (15 deaths observed versus 9.7 deaths expected) was observed, but there was only one death from

Table 3. Mortality by cause—all factories combined

Cause of death	ICD-9 codes*	Deaths in total cohort, 1941–2000			Deaths in total cohort, 1990–2000			Deaths in men with high exposure, 1941–2000†		
		Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All causes	001–999	5185	4969.8	1.04 (1.02 to 1.07)	1919	1867.7	1.03 (0.98 to 1.07)	1995	1735.3	1.15 (1.10 to 1.20)
All cancers	140–208	1511	1375.2	1.10 (1.04 to 1.16)	572	552.8	1.03 (0.95 to 1.12)	621	474.2	1.31 (1.21 to 1.42)
Circulatory disease	390–459	2266	2306.8	0.98 (0.94 to 1.02)	815	825.2	0.99 (0.92 to 1.06)	849	815.0	1.04 (0.97 to 1.11)
Respiratory disease	460–519	661	588.3	1.12 (1.04 to 1.21)	264	244.9	1.08 (0.95 to 1.22)	285	212.5	1.34 (1.19 to 1.51)
Digestive disease	008–009, 520–579	174	146.1	1.19 (1.02 to 1.38)	70	61.8	1.13 (0.88 to 1.43)	61	49.4	1.23 (0.94 to 1.59)
Injury and poisoning	800–999	236	215.5	1.09 (0.96 to 1.24)	52	46.9	1.11 (0.83 to 1.45)	60	64.9	0.92 (0.70 to 1.19)

*ICD-9 = International Classification of Diseases, 9th edition; SMR = standardized mortality ratio; CI = confidence interval.

†High exposure to formaldehyde estimated as greater than 2 ppm. For this analysis, men were not classified as being at risk until they had worked in a high-exposure job. Four men were excluded from the analysis because of missing information on the date of starting a job.

Table 4. Mortality from respiratory and digestive diseases by exposure category, 1941–2000*

Factory	Exposure category†	Deaths from respiratory disease					Deaths from digestive disease				
		Comparison with national rates			Locally adjusted		Comparison with national rates			Locally adjusted	
		Observed	Expected	SMR (95% CI)	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Expected	SMR (95% CI)
BIP	Background	0	0.2	0 (0 to 14.78)	0.3	0 (0 to 11.85)	0	0.1	0 (0 to 57.39)	0.1	0 (0 to 45.60)
	Low	39	21.3	1.83 (1.30 to 2.50)	26.5	1.47 (1.05 to 2.01)	9	4.8	1.89 (0.86 to 3.58)	6.0	1.50 (0.69 to 2.85)
	Moderate	47	34.4	1.37 (1.00 to 1.82)	42.7	1.10 (0.81 to 1.46)	11	8.0	1.38 (0.69 to 2.47)	10.0	1.10 (0.55 to 1.97)
	High	262	189.1	1.39 (1.22 to 1.56)	235.2	1.11 (0.98 to 1.26)	57	43.6	1.31 (0.99 to 1.70)	54.6	1.04 (0.79 to 1.35)
	Unknown	22	18.5	1.19 (0.74 to 1.80)	23.1	0.95 (0.60 to 1.44)	6	4.5	1.32 (0.49 to 2.88)	5.7	1.06 (0.39 to 2.30)
				$P_{\text{trend}} = .21\ddagger$		$P_{\text{trend}} = .21\ddagger$			$P_{\text{trend}} = .41\ddagger$		$P_{\text{trend}} = .39\ddagger$
All factories	Background	127	148.3	0.86 (0.71 to 1.02)	136.0	0.93 (0.78 to 1.11)	34	37.7	0.90 (0.62 to 1.26)	32.9	1.03 (0.72 to 1.45)
	Low	152	136.5	1.11 (0.94 to 1.31)	137.1	1.11 (0.94 to 1.30)	49	35.7	1.37 (1.02 to 1.82)	33.0	1.49 (1.10 to 1.96)
	Moderate	65	57.6	1.13 (0.87 to 1.44)	64.8	1.00 (0.77 to 1.28)	15	14.1	1.06 (0.60 to 1.75)	15.2	0.99 (0.55 to 1.63)
	High	285	212.4	1.34 (1.19 to 1.51)	260.4	1.09 (0.97 to 1.23)	61	49.4	1.24 (0.94 to 1.59)	60.5	1.01 (0.77 to 1.30)
	Unknown	31	33.3	0.93 (0.63 to 1.32)	36.0	0.86 (0.58 to 1.22)	15	9.1	1.65 (0.93 to 2.73)	9.2	1.64 (0.92 to 2.70)
				$P_{\text{trend}} < .001\ddagger$		$P_{\text{trend}} = .25\ddagger$			$P_{\text{trend}} = .31\ddagger$		$P_{\text{trend}} = .40\ddagger$

*Nine men were excluded from this analysis because of missing information on the date of starting a job. SMR = standardized mortality ratio; CI = confidence interval; BIP = British Industrial Plastics.

†Background exposure to formaldehyde corresponded to estimated time-weighted average concentrations of less than 0.1 parts per million (ppm); low exposure to 0.1–0.5 ppm; moderate exposure to 0.6–2.0 ppm; and high exposure to greater than 2.0 ppm.

‡ P_{trend} from Poisson regression excluding the “unknown” exposure category.

Table 5. Mortality from cancer—all factories combined

Type/location of cancer	ICD-9 codes*	Deaths in total cohort, 1941–2000			Deaths in total cohort, 1990–2000			Deaths in men with high exposure, 1941–2000‡		
		Observed†	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Lip	140	1	0.5	2.10 (0.05 to 11.72)	1	0.1	8.30 (0.21 to 46.22)	1	0.2	5.62 (0.14 to 31.30)
Tongue	141	4	4.8	0.84 (0.23 to 2.14)	2	1.9	1.04 (0.13 to 3.75)	3	1.6	1.91 (0.39 to 5.58)
Mouth§	143–145	6	4.7	1.28 (0.47 to 2.78)	2	2.0	1.00 (0.12 to 3.60)	2	1.5	1.32 (0.16 to 4.75)
Pharynx§	146–149.1	15	9.7	1.55 (0.87 to 2.56)	8	4.0	2.02 (0.87 to 3.99)	6	3.1	1.91 (0.70 to 4.17)
Esophagus	150	57	54.7	1.04 (0.79 to 1.35)	22	28.2	0.78 (0.49 to 1.18)	23	18.0	1.28 (0.81 to 1.92)
Stomach	151	150	114.4	1.31 (1.11 to 1.54)	42	33.6	1.25 (0.90 to 1.69)	63	41.3	1.53 (1.17 to 1.95)
Small intestine§	152	2	2.6	0.77 (0.09 to 2.79)	0	0.9	0.00 (0.00 to 3.94)	0	0.9	0.00 (0.00 to 4.25)
Large intestine§	153	87	90.4	0.96 (0.77 to 1.19)	40	39.3	1.02 (0.73 to 1.39)	40	30.8	1.30 (0.93 to 1.77)
Rectum	154	72	59.7	1.21 (0.94 to 1.52)	24	22.6	1.06 (0.68 to 1.58)	26	20.7	1.26 (0.82 to 1.84)
Liver	155.0, 155.1	11	12.4	0.89 (0.44 to 1.59)	5	6.4	0.78 (0.25 to 1.82)	4	4.0	1.00 (0.27 to 2.55)
Gall bladder	156	5	6.1	0.82 (0.27 to 1.92)	1	1.8	0.57 (0.01 to 3.17)	1	2.2	0.46 (0.01 to 2.58)
Pancreas	157	57	57.7	0.99 (0.75 to 1.28)	22	22.6	0.97 (0.61 to 1.47)	18	19.8	0.91 (0.54 to 1.44)
Nose and nasal sinuses	160	2	2.3	0.87 (0.11 to 3.14)	1	0.6	1.68 (0.04 to 9.34)	0	0.8	0.00 (0.00 to 4.64)
Larynx	161	14	13.1	1.07 (0.58 to 1.79)	5	5.2	0.97 (0.32 to 2.26)	7	4.5	1.56 (0.63 to 3.22)
Lung	162	594	486.8	1.22 (1.12 to 1.32)	191	164.5	1.16 (1.00 to 1.34)	272	172.3	1.58 (1.40 to 1.78)
Bone	170	6	3.5	1.73 (0.63 to 3.76)	1	0.7	1.53 (0.04 to 8.55)	4	1.2	3.38 (0.92 to 8.65)
Soft tissue sarcoma§	171	3	4.9	0.61 (0.13 to 1.79)	1	2.1	0.47 (0.01 to 2.59)	1	1.5	0.66 (0.02 to 3.67)
Melanoma§	172	10	10.8	0.93 (0.44 to 1.71)	6	5.1	1.18 (0.43 to 2.57)	2	3.2	0.63 (0.08 to 2.26)
Other skin§	173	2	3.9	0.51 (0.06 to 1.83)	1	1.5	0.65 (0.02 to 3.61)	0	1.4	0.00 (0.00 to 2.66)
Breast	175	1	1.6	0.61 (0.02 to 3.41)	1	0.6	1.66 (0.04 to 9.25)	0	0.6	0.00 (0.00 to 6.46)
Prostate	185	80	99.4	0.80 (0.64 to 1.00)	48	57.5	0.83 (0.62 to 1.11)	30	35.0	0.86 (0.58 to 1.22)
Testis§	186	5	4.1	1.21 (0.39 to 2.82)	1	0.4	2.33 (0.06 to 12.96)	1	1.1	0.87 (0.02 to 4.86)
Other genital§	187	2	2.1	0.97 (0.12 to 3.51)	0	0.7	0.00 (0.00 to 4.99)	1	0.7	1.42 (0.04 to 7.90)
Bladder§	188	61	52.1	1.17 (0.90 to 1.50)	25	22.5	1.11 (0.72 to 1.64)	23	18.4	1.25 (0.79 to 1.88)
Kidney§	189	29	28.9	1.00 (0.67 to 1.44)	14	13.1	1.07 (0.58 to 1.79)	13	9.5	1.37 (0.73 to 2.35)
Brain and nervous system	191, 192	30	35.4	0.85 (0.57 to 1.21)	9	12.5	0.72 (0.33 to 1.37)	7	11.2	0.63 (0.25 to 1.29)
Thyroid	193	2	2.2	0.89 (0.11 to 3.23)	0	0.8	0.00 (0.00 to 4.75)	0	0.8	0.00 (0.00 to 4.81)
Hodgkin's disease	201	6	8.5	0.70 (0.26 to 1.53)	1	1.1	0.89 (0.02 to 4.94)	1	2.8	0.36 (0.01 to 2.01)
Non-Hodgkin's lymphoma§	200, 202.0, 202.1, 202.8	31	31.7	0.98 (0.67 to 1.39)	12	15.4	0.78 (0.40 to 1.36)	9	10.1	0.89 (0.41 to 1.70)
Multiple myeloma§	203.0	15	17.5	0.86 (0.48 to 1.41)	9	8.3	1.09 (0.50 to 2.07)	7	5.9	1.18 (0.48 to 2.44)
Leukemia	204–208	31	34.1	0.91 (0.62 to 1.29)	12	13.2	0.91 (0.47 to 1.59)	8	11.3	0.71 (0.31 to 1.39)

*ICD-9 = International Classification of Diseases, 9th revision; SMR = standardized mortality ratio; CI = confidence interval.

†In addition to the deaths listed in the table, deaths were observed from cancer of the parotid gland (one death), pleura (seven deaths), adrenal gland (two deaths), retroperitoneal sarcoma (one death), and cancers of other and unspecified sites (109 deaths).

‡High exposure to formaldehyde estimated as greater than 2 ppm. Four men were excluded from this analysis because of missing information on the date of starting a job.

§Because of changes in disease classification, the earliest follow-up for these cancers was from 1950.

||Because of changes in disease classification, the earliest follow-up for these cancers was from 1958.

nasopharyngeal carcinoma (2.0 expected), and the man concerned had not worked in a job with high exposure to formaldehyde. Mortality in the cohort from cancer of the brain and nervous system was lower than that in the national population.

We determined the SMRs for deaths from stomach and lung cancer for each category of exposure to formaldehyde (Table 6).

The SMRs for both diseases were highest in men who had worked in jobs with the highest exposure levels. Although the expected numbers of deaths increased after adjustment for local variations in mortality, the excess of lung cancer deaths in men with high exposure remained statistically significant (SMR = 1.28, 95% CI = 1.13 to 1.44).

Table 6. Mortality from lung and stomach cancer by exposure category, 1941–2000*

Factory	Exposure category†	Lung cancer					Stomach cancer				
		Deaths observed	Comparison with national rates		Locally adjusted		Deaths observed	Comparison with national rates		Locally adjusted	
			Deaths expected	SMR (95% CI)	Deaths expected	SMR (95% CI)		Deaths expected	SMR (95% CI)	Deaths expected	SMR (95% CI)
BIP											
	Background	0	0.2	0 (0 to 15.92)	0.3	0 (0 to 12.59)	0	0.1	0 (0 to 63.23)	0.1	0 (0 to 52.21)
	Low	23	16.4	1.40 (0.89 to 2.10)	20.6	1.12 (0.71 to 1.68)	4	4.2	0.96 (0.26 to 2.46)	4.9	0.82 (0.22 to 2.09)
	Moderate	32	27.0	1.18 (0.81 to 1.67)	34.0	0.94 (0.64 to 1.33)	6	6.6	0.91 (0.33 to 1.98)	7.9	0.76 (0.28 to 1.65)
	High	249	152.7	1.63 (1.43 to 1.85)	192.0	1.30 (1.14 to 1.47)	54	36.8	1.47 (1.10 to 1.91)	44.3	1.22 (0.91 to 1.59)
	Unknown	13	15.2	0.85 (0.45 to 1.46)	19.2	0.68 (0.36 to 1.16)	7	3.6	1.93 (0.78 to 3.98)	4.4	1.58 (0.63 to 3.25)
				$P_{\text{trend}} = .15\ddagger$		$P_{\text{trend}} = .15\ddagger$			$P_{\text{trend}} = .20\ddagger$		$P_{\text{trend}} = .23\ddagger$
All factories											
	Background	123	122.3	1.01 (0.84 to 1.20)	110.0	1.12 (0.93 to 1.33)	34	28.5	1.19 (0.83 to 1.67)	30.6	1.11 (0.77 to 1.55)
	Low	128	116.7	1.10 (0.92 to 1.30)	111.6	1.15 (0.96 to 1.36)	35	26.9	1.30 (0.91 to 1.81)	28.1	1.24 (0.87 to 1.73)
	Moderate	52	46.6	1.12 (0.83 to 1.46)	52.5	0.99 (0.74 to 1.30)	10	11.1	0.90 (0.43 to 1.66)	12.2	0.82 (0.39 to 1.51)
	High	272	172.2	1.58 (1.40 to 1.78)	212.6	1.28 (1.13 to 1.44)	63	41.3	1.53 (1.17 to 1.95)	49.2	1.28 (0.98 to 1.64)
	Unknown	19	28.6	0.66 (0.40 to 1.04)	30.6	0.62 (0.37 to 0.97)	8	6.6	1.20 (0.52 to 2.37)	7.0	1.15 (0.50 to 2.27)
				$P_{\text{trend}} < .001\ddagger$		$P_{\text{trend}} = .19\ddagger$			$P_{\text{trend}} = .28\ddagger$		$P_{\text{trend}} = .62\ddagger$

*Nine men were excluded from this analysis because of missing information on the date of starting a job. SMR = standardized mortality ratio; CI = confidence interval; BIP = British Industrial Plastics.

†Background exposure to formaldehyde corresponded to estimated time-weighted average concentrations of less than 0.1 ppm; low exposure corresponded to 0.1–0.5 ppm; moderate exposure corresponded to 0.6–2.0 ppm; and high exposure corresponded to greater than 2.0 ppm.

‡ P_{trend} from Poisson regression excluding the “unknown” exposure category.

Table 7. Mortality from lung cancer in men with high exposure to formaldehyde

Timing of exposure	BIP*					All factories					
	Deaths observed	Comparison with national rates		Locally adjusted		Deaths observed	Comparison with national rates		Locally adjusted		
		Deaths expected	SMR (95% CI)	Deaths expected	SMR (95% CI)		Deaths expected	SMR (95% CI)	Deaths expected	SMR (95% CI)	
Period of first employment in job with high level of exposure†											
	Before 1965	227	137.8	1.65 (1.44 to 1.88)	172.6	1.32 (1.15 to 1.50)	243	151.2	1.61 (1.41 to 1.82)	186.7	1.30 (1.14 to 1.48)
	After 1964	22	15.1	1.46 (0.91 to 2.21)	19.4	1.13 (0.71 to 1.72)	29	21.1	1.37 (0.92 to 1.97)	26.1	1.11 (0.74 to 1.60)
Years of employment in jobs with high level of exposure											
	<1	115	64.4	1.78 (1.47 to 2.14)	81.2	1.42 (1.17 to 1.70)	124	70.7	1.75 (1.46 to 2.09)	88.4	1.40 (1.17 to 1.67)
	1–14	99	61.3	1.62 (1.31 to 1.97)	76.7	1.29 (1.05 to 1.57)	109	70.9	1.54 (1.26 to 1.86)	86.2	1.26 (1.04 to 1.52)
	15+	33	24.1	1.37 (0.94 to 1.92)	30.4	1.09 (0.75 to 1.52)	36	27.4	1.31 (0.92 to 1.82)	34.1	1.06 (0.74 to 1.46)
	Unknown‡	2	2.8	0.71 (0.09 to 2.58)	3.5	0.58 (0.07 to 2.09)	3	3.1	0.97 (0.20 to 2.83)	3.8	0.79 (0.16 to 2.30)
				$P_{\text{trend}} = .17\§$		$P_{\text{trend}} = .18\§$			$P_{\text{trend}} = .11\§$		$P_{\text{trend}} = .13\§$
Years since first employment in job with high level of exposure											
	<10	15	10.5	1.42 (0.80 to 2.35)	12.6	1.19 (0.66 to 1.96)	17	12.2	1.40 (0.81 to 2.23)	14.6	1.17 (0.68 to 1.87)
	10–19	47	28.2	1.67 (1.22 to 2.22)	34.2	1.37 (1.01 to 1.82)	54	32.5	1.66 (1.25 to 2.17)	39.0	1.39 (1.04 to 1.81)
	20+	187	114.1	1.64 (1.41 to 1.89)	145.1	1.29 (1.11 to 1.49)	201	127.7	1.57 (1.36 to 1.81)	159.3	1.26 (1.09 to 1.45)
				$P_{\text{trend}} = .74\ $		$P_{\text{trend}} = .99\ $			$P_{\text{trend}} = .86\ $		$P_{\text{trend}} = .93\ $

*BIP = British Industrial Plastics; SMR = standardized mortality ratio; CI = confidence interval.

†High level of exposure to formaldehyde estimated as greater than 2 ppm.

‡For some men, information was missing on the dates of starting or finishing one or more jobs.

§ P_{trend} from Poisson regression excluding the “unknown” exposure category.

|| P_{trend} from Poisson regression.

Table 7 summarizes mortality from lung tumors in the subset of men who were highly exposed to formaldehyde according to period of first high exposure, duration of high exposure, and time since first high exposure. In classifying period of first high exposure, a cut point was taken at January 1, 1965, because this date had been used in earlier analyses of the same cohort (7). In general, the highest exposures to formaldehyde would be expected to have occurred during the earlier years of production, when occupational hygiene was less developed. SMRs for

deaths from lung cancer were higher in men first employed before 1965 but showed a statistically nonsignificant inverse trend with the number of years worked in high-exposure jobs ($P_{\text{trend}} = .13$) and showed no trend to increase with time since first doing such work ($P_{\text{trend}} = .93$).

The analyses were repeated, with follow-up of all subjects censored at age 85 years if it had not ended at an earlier age. The results (not shown) were virtually unchanged from those presented in Tables 3–7.

Review of cancer registrations and of the contributing causes of death reported on death certificates revealed two additional cases of sino-nasal cancer (both in individuals with high exposure to formaldehyde) but no further cancers of the nasopharynx that had not been included as causes of death in the analysis of mortality.

DISCUSSION

This study found an increase in mortality from lung cancer among men with potentially high levels of occupational exposure to formaldehyde. However, the excess of deaths from lung tumors was reduced when local geographic variations in mortality were considered and did not increase with duration of employment in high-exposure jobs or with time since first employment in a high-exposure job. Mortality was also increased for stomach cancer, but the numbers of deaths from sino-nasal and nasopharyngeal cancers were close to those expected.

The major strength of this investigation was its prolonged follow-up of a large population of workers with relatively high exposures to formaldehyde. No occupational hygiene measurements were available for the early years in which these men worked, but from descriptions of working conditions and practices, it seems likely that airborne concentrations of the compound were substantially higher than those encountered in industry today. At the factory where the largest number of heavily exposed workers was employed (BIP), formaldehyde-based resins were used in the manufacture of Mosquito aircraft during World War II, and productivity was likely to have been a higher priority than occupational hygiene.

Our study has several limitations, however. First, when follow-up of a cohort is so long (almost 60 years for some of our subjects), unrecognized losses to follow-up with missed deaths can sometimes lead to an underestimation of risks. However, when analyses were repeated with follow-up censored at age 85 years, there was no indication that bias of this sort had occurred. Second, the workers in our cohort may have been exposed to various other hazards in addition to formaldehyde in the course of their work, including asbestos and several other known or suspected carcinogens. However, the extent of such exposures is unlikely to have been sufficient to cause substantial confounding. In support of this view, among employees at the BIP factory, where the main excess of lung cancer occurred, there were only two deaths from mesothelioma, a tumor which is commonly associated with asbestos exposure. More important is the potential for confounding by non-occupational factors. Unfortunately, no information was available on aspects of individual lifestyle such as smoking habits, and the possible impact of such confounding could only be addressed indirectly.

Among the human cancers that have been linked previously with formaldehyde, tumors of the nose and nasal sinuses and of the nasopharynx have been under the most suspicion. Evidence for an association with sino-nasal cancer comes mainly from case-control studies. In a meta-analysis reported in 1997, Collins et al. (5) derived a summary relative risk estimate of 1.8 (95% CI = 1.4 to 2.3) from 11 case-control studies and of 0.3 (95% CI = 0.1 to 0.9) from nine cohort studies of industrial populations, pathologists, and embalmers. Additional results published since those analyses have followed a similar pattern. For example, one new case of sino-nasal cancer has been de-

scribed in an extended follow-up of 6039 workers at a U.S. chemical plant in Connecticut (8), and none were observed among 111 men who were exposed to formaldehyde at a plastics facility in New Jersey (9). However, an analysis of proportional cancer incidence in Denmark indicated a 2.3-fold increased risk of sino-nasal cancer in employees at 265 companies that had used or manufactured formaldehyde (10).

In our study, there was one death from sino-nasal cancer during the additional period of follow-up, but the man who died had only background exposure to formaldehyde and, over the full duration of follow-up, mortality from the disease was close to that expected. Two other cases of sino-nasal cancer were registered in men whose deaths were ascribed to other causes (melanoma and cerebrovascular disease). Both of these men had worked in jobs with high exposure to formaldehyde. Because of uncertainties about the completeness of cancer registration in the United Kingdom during the follow-up period, we do not have reliable expected numbers against which to assess this observation. However, given that the expected number of deaths from sino-nasal cancer was 2.3, a total of four observed cases, both fatal and nonfatal, is unremarkable.

The disparity between cohort and case-control studies in risk estimates for sino-nasal cancer is unlikely to reflect differences in levels of exposure to formaldehyde because, in general, exposures have been higher in the cohort studies. The discrepancy may be attributable in part to unadjusted or residual confounding by exposure to wood dust, which is strongly associated with exposure to formaldehyde in some occupations. However, in the Danish analysis of proportional cancer incidence (10), risk of sino-nasal cancer was statistically significantly increased, even in workers who were unlikely to have been exposed to wood dust. Whatever the explanation for the discrepancy, any excess risk of sino-nasal cancer from exposures to formaldehyde at the concentrations that occur in industry today is likely to be extremely small.

The suspicion that formaldehyde exposure causes nasopharyngeal cancer stems in part from a study of workers at 10 chemical plants in the United States (11), in which an SMR of 3.0 was derived based on six observed cases [although a subsequent investigation showed that one of the individuals in fact had cancer of the tonsillar fossa, and the cause of death had been misclassified on his death certificate (12)]. In addition, positive associations between formaldehyde exposure and nasopharyngeal cancers have been reported in several case-control studies (13-17). However, other investigations have given little support to these findings (5,9,10,18) and, in our study, the only death from nasopharyngeal cancer was in a man whose exposure to formaldehyde was classified as low. Overall, the epidemiologic evidence now available indicates that if formaldehyde does cause nasopharyngeal cancer, then the increased risk is small.

The last analysis of mortality in our cohort showed that, although there were 21% more deaths from lung cancer (ICD-9 codes 162-164) than expected from national rates, the excess was reduced to 12% after adjustment for local variations in mortality and was not clearly related to formaldehyde exposure (7). With extended follow-up, a similar pattern is apparent. Mortality from lung tumors (ICD-9 code 162) was increased in the cohort overall (SMR based on national rates = 1.22), and particularly among men who had worked in jobs with high levels of exposure (SMR = 1.58). However, most of the high-level exposures occurred at one factory (BIP), which was located in an

area with high background rates of lung cancer. Thus, when expected numbers were adjusted for local differences in mortality, the SMR for the high-exposure category was reduced to 1.28. Moreover, the locally adjusted SMRs for lung cancer were also elevated in men with only background (SMR = 1.12) or low exposure to formaldehyde (SMR = 1.15). There was no consistent increase in risk with duration of employment in jobs with high levels of exposure or with time since first carrying out work of this sort. Mortality was highest in those who had worked in jobs with high levels of exposure for less than 1 year (locally adjusted SMR = 1.40).

These observations suggest residual confounding by non-occupational causes of lung cancer that were more common in short-term employees. The presence of residual confounding would not be surprising, given that our method of adjusting for geographic variation in mortality was, by necessity, somewhat crude, and that such adjustment, even if more refined, would not account fully for individual differences in exposure to risk factors such as smoking. The increased mortality from respiratory disease (Table 4) is also consistent with an unusually high prevalence of smoking in the cohort, and it is notable that, at BIP, the SMR for respiratory disease was again reduced substantially after adjustment for local differences in mortality. However, the SMR for lung cancer in men with high levels of exposure (SMR = 1.28 after local adjustment) is rather large to be explained simply by a confounding effect of smoking, particularly as the prevalence of smoking in the comparison population is likely to have been high. Also, at the BIP factory, where most of the high-level exposure occurred, mortality from respiratory disease was highest for jobs with low exposures, whereas mortality from lung cancer was highest for those with high exposure. Thus, confounding by smoking may not be the full explanation for the observed excess of lung cancer deaths in the cohort.

The other major cohort study of formaldehyde exposure in the chemical and plastics industry, which was carried out in the United States, also found an increase in mortality from lung cancer (11,19), although the increase was smaller than that in our investigation. In a re-analysis of the U.S. study, one group has claimed that the risk of lung tumors increased with cumulative exposure to formaldehyde (20). However, this was not a finding in the original analysis (11,19) and has not been confirmed by others who have examined the same data (21). Several other studies of industrial populations (22,23) have also suggested an increased rate of lung cancer in workers exposed to formaldehyde, but this has not been a universal observation (10,18) and, where present, the excess has generally been small. Anatomists and pathologists who are also exposed to formaldehyde have been found to experience unusually low mortality from lung cancer (5), but this almost certainly reflects low rates of smoking.

Our cohort also had increased mortality from stomach cancer, although again the excess was reduced after adjustment for local differences in death rates. A hazard of stomach cancer from inhalation of formaldehyde is less plausible than an effect on tissues in the respiratory tract that come into direct contact with the chemical. Moreover, increased rates of stomach cancer have not been found in other cohort studies of formaldehyde workers. Therefore, it seems more likely that the excess in our study was a consequence of confounding by non-occupational factors.

Recent analysis of data from an extended follow-up of a cohort of industrial workers in the United States has suggested an association between formaldehyde and lymphatic and hematopoietic cancer, and particularly between formaldehyde and leukemia (24). Although mortality from these diseases was not increased in exposed workers overall and showed no relation to cumulative exposure, risk of death increased statistically significantly with higher peak and average intensities of exposure. In our study, however, mortality from leukemia and other lymphatic and hematopoietic cancer was lower than expected from national rates, both in the full cohort and in the subset of men with high levels of exposure (Table 5). There is no obvious explanation for this discrepancy in findings, other than that it occurred by chance.

Overall, we conclude that the evidence for human carcinogenicity of formaldehyde remains unconvincing. Whether formaldehyde exposure is associated with a small increase in the risk of sino-nasal and/or nasopharyngeal cancer cannot be ruled out from the results of our study. However, lung cancer is a much more common disease, and the possibility of a marginally elevated relative risk of lung cancer from formaldehyde exposure is of greater concern. Further follow-up of industrial cohorts, particularly those with relatively high levels of exposure to formaldehyde, may help to resolve the outstanding uncertainties. In addition, clarification may come from the study of biomarkers for tissue and DNA damage in exposed workers.

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NOTES

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