

Mortality among chemical workers in a factory where formaldehyde was used

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Abstract

Objectives—An independent and updated historical cohort mortality study was conducted among chemical plant workers to investigate further an association between exposures to formaldehyde and particulates and cancers of the nasopharynx and lung reported in an earlier National Cancer Institute study of the same plant.

Methods—Subjects were 7359 workers who were first employed between 1941 and 1984 in a factory in Wallingford, Connecticut where formaldehyde was used. Vital status was determined on 31 December 1984 for 96% of the cohort and death certificates were obtained for 93% of 1531 known deaths. Exposures of individual workers were estimated quantitatively for formaldehyde, product particulates, and non-product particulates, and qualitatively for pigment. Statistical analyses focused on 6039 white men in 1945–84. Cohort data that could not have been included in the National Cancer Institute study were also analysed separately.

Results—Mortality among long term workers (employed ≥ 1 y) was generally similar to or more favourable than that of the general population, and there was little evidence of a relation between either rates of lung cancer or standardised mortality ratios (SMRs) and several measures of exposure to formaldehyde, particulates, and pigment. For several causes including lung cancer, death rates among short term workers (employed < 1 y) were significantly increased. Short term workers did not seem to differ from long term workers for the exposures considered. Among all white men, a significant SMR of 550 (local comparison) for nasopharyngeal cancer (NPC) was based on the same four index cases identified in the earlier study of this plant. Only one case of nasopharyngeal cancer had any appreciable exposure to formaldehyde. No new cases of nasopharyngeal cancers were found among the cohort data that could not have been included in the National Cancer Institute study—that is, extended observation time and additional study members.

Conclusions—Among workers employed for at least one year, this study provides little evidence that the risk of lung cancer is associated with exposure to formaldehyde alone or in combination with particulates or pigment. The significant

increases in both the rates and SMRs for lung cancer seem to be primarily a phenomenon of short term workers, but the possibility remains that unmeasured occupational or non-occupational factors may have played a part.

(*Occup Environ Med* 1996;53:613–627)

Keywords: nasopharyngeal cancer; lung cancer; formaldehyde; particulates; historical cohort study

In 1986, Blair *et al* reported a National Cancer Institute cohort mortality study of 26 561 workers employed at some time before 1966 in one or more of 10 factories that produced or used formaldehyde in the United States.¹ Their study was prompted by earlier inhalation studies in laboratory animals that linked exposure to formaldehydes with nasal cancer in rats,^{2,3} and by previous epidemiological studies that reported some associations between exposure to formaldehyde and leukaemia and cancers of the brain, lung, buccal cavity, and pharynx.⁴ The National Cancer Institute study did not show any excess nasal tumours among workers exposed to formaldehyde and provided little evidence that mortality from cancer is associated with exposure to formaldehyde at the levels experienced. Additional review of the National Cancer Institute cohort data did show a significant excess of nasopharyngeal cancer (four observed, less than one expected) among a subcohort of 4389 workers and were employed during the 1950s in an American Cyanamid Company plant in Wallingford, Connecticut where formaldehyde was used.¹

Because of the small numbers of deaths and the inability to control for potentially confounding factors in the National Cancer Institute study, definitive conclusions could not be drawn from the findings for nasopharyngeal cancer. For example, two of the four cases occurred among short term employees with work histories of only three and seven months, and, before their work at Wallingford, three of the four cases were employed in jobs involving exposure to metal fumes or dust, two substances that have been associated with excess cancers of the nasopharynx.⁵ Despite these limitations, certain occupational exposure factors at the Wallingford plant prompted further examination of the excess of nasopharyngeal cancers. Specifically, certain work areas in the plant were associated with exposures to formaldehyde in conjunction with particulate matter derived from the paper pulp

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Accepted 10 May 1996

products that have been routinely mixed with urea, melamine, and other substances to produce a variety of plastic products. As well as paper pulp, other materials containing cellulose such as walnut and pecan shells were used throughout the plant's history to impart desirable physical characteristics to the plastic and resin products.

In the National Cancer Institute study, standardised mortality ratios (SMRs) for cancer of the buccal cavity and pharynx, cancer of the brain, and Hodgkin's disease were higher among those with exposure to particulates containing formaldehyde than among those never exposed to such dusts. An analysis of the excess of cancer of the buccal cavity or pharynx by subsite indicated that the risk for the nasopharynx was significantly increased among people exposed to particulates. However, the overall risk did not rise consistently with increasing exposure for this or any other subsite.¹

In 1987, Blair *et al* reported an additional analysis of the excess of nasopharyngeal cancer and concluded that "the pattern for nasopharyngeal cancer suggests that simultaneous exposure to formaldehyde and particulates may be a risk factor for this tumor".⁶ This conclusion was subsequently challenged on methodological and other grounds by Collins *et al*⁷ who later performed a reanalysis of the total National Cancer Institute cohort and an updated analysis of the Wallingford plant cohort.⁸ Neither of these analyses supported an association between nasopharyngeal cancer and joint exposure to formaldehyde and particulates. Although the update added five years of follow up to the Wallingford cohort, no additional cases of nasopharyngeal cancer were found.

Several extensive reanalyses of the National Cancer Institute total cohort data were subsequently performed.⁹⁻¹⁵ These analyses have shown differential mortality patterns for short term (employed < 1y) versus long term (employed \geq 1y) workers and have provided evidence that certain coexposures associated with the production of resins and moulding compounds—for example, phenol, melamine, urea, and wood dust—may play a part in the risk of lung cancer. Data limitations preclude a reliable examination of the part of coexposures in the individual plants.

In 1987, the American Cyanamid Company commissioned the University of Pittsburgh, Department of Biostatistics, to perform an updated and extended investigation of total and cause specific mortality among the workforce of the Wallingford plant with special emphasis on the association between exposures to formaldehyde and particulates and cancers of the nasopharynx and lung. Although certain epidemiological findings of this research are summarised in a brief report,¹⁶ other important findings and much of the analytical and methodological details were omitted. We report here a more comprehensive account of our findings, including a more detailed exposition of the historical exposure assessment that was performed to estimate exposures of individual workers to formalde-

hyde, particulates, and pigment. We also report new results of an analysis of the cohort data not included in the earlier National Cancer Institute study, and a comparative descriptive analysis of exposure data developed independently for the National Cancer Institute and University of Pittsburgh studies.

Methods

Operationally, the Wallingford cohort study was a collaborative effort between the University of Pittsburgh and the American Cyanamid Company. The American Cyanamid Company was responsible for the collection, coding, and computer processing of all primary study data, and the University of Pittsburgh was responsible for verifying the accuracy and completeness of the cohort data and for performing the statistical analysis and interpretation of the mortality data. Cohort tracing activities and the exposure assessment of the Wallingford plant environment were shared by the two organisations.

STUDY POPULATION

The National Cancer Institute study of the Wallingford plant included all workers ($n = 4389$) first employed from the plant's start up date in 1941 to the end of 1965, with vital status determined up to 1 December 1979. In the present study, the Wallingford cohort was independently enumerated from plant and corporate records, and the study population enlarged to include all workers who began employment between 1941 and 1984. The follow up period was also extended by five years up to 31 December 1984.

The required demographic and work history data were available for virtually all eligible study members. The completeness and accuracy of our cohort enumeration were verified with methods previously developed.^{17,18} A total of 7359 workers were found to be eligible for our Wallingford cohort, an increase of 2970 over the National Cancer Institute cohort. Work history data included 32 522 jobs representing 4322 unique department and job title combinations. Because smoking history data were available for only 30% of the cohort, they were not used in the analysis. Appendix A shows a comparison of selected Wallingford cohort data from the current study and from the National Cancer Institute study (plant 1) as developed for the reanalyses performed by Marsh *et al*.^{10,11}

COHORT TRACING

Vital status of the cohort was determined on 31 December 1984 from available plant record information as well as a variety of routine federal, state, and local sources (Social Security Administration, National Death Index, US Postal Service, Pension Benefits Company, state motor vehicle bureaux, personal contacts, and other sources). A 10% random sample of people identified as alive by the American Cyanamid Company was submitted for death clearance through other sources to verify the plant based data.

For each worker identified as dead, a death

Table 1 Distribution of total Wallingford cohort by vital status on 31 December 1984, race, and sex

Vital status	White men n (%)	Non-white men n (%)	White women n (%)	Non-white women n (%)	Total n (%)
Alive	4461 (73.5)	349 (84.1)	652 (79.3)	53 (98.1)	5515 (74.9)
Dead:	1402 (23.1)	57 (13.7)	72 (8.8)	0 (0.0)	1531 (20.8)
Death certificate	1310 (93.4)	51 (89.5)	63 (87.5)	—	1424 (93.0)
Presumed dead	92 (6.6)	6 (10.5)	9 (12.5)	—	107 (7.0)
Unknown	205 (3.4)	9 (2.2)	98 (11.9)	1 (1.9)	313 (4.3)
Total	6068 (100.0)	415 (100.0)	822 (100.0)	54 (100.0)	7359 (100.0)

certificate was obtained from the state in which the death occurred unless one had already been obtained from the American Cyanamid Company. The underlying cause of death was coded by an independent nosologist according to the international classification of diseases (ICD) rules in effect at the time of death, to assure comparability with standard population death rates.

Table 1 shows the distribution of updated Wallingford cohort by race and sex. Overall, vital status was obtained for all but 313 people (4.3%) and death certificates were found for 1424 (93%) of the 1531 identified deaths. The mortality analysis is limited to the subcohort of 6039 white men during the follow up period 1945–84 to obviate sparse data problems in the other race and sex categories and possible selection biases in studying civilian men employed during the years of the second world war.

EXPOSURE ASSESSMENT

General description of the Wallingford plant

The American Cyanamid Company Wallingford plant was built in 1941 for the production of thermosetting resins and industrial moulding compounds and has been in continuous operation since 1943. It consists of 35 buildings located on 250 acres. When the plant opened in 1941 there were 300 employees. The maximum number of employees was around 1200 in the early 1970s and in recent years the average work force has been around 700 employees. In 1943, the resins department began producing several product lines including paper product resins made from acrylamide, laminating resins made from urea, melamine, and formaldehyde and methylated resins made from melamine, formaldehyde, and various alcohols. The production of thermoplastic moulding compounds began in 1965. The thermoset moulding compounds product line consists of BEETLE, which is formulated from urea and formaldehyde and CYMEL, which is formulated from melamine and formaldehyde. These compounds are manufactured from methyl methacrylate, acrylonitrile, styrene, polybutadiene, and other acrylate monomers. The newest production facility for metal coated fibres was commissioned by the American Cyanamid Company in 1983. These materials are made by plating metals on carbon fibres and are used for lightning protection and for electromagnetic and radio frequency shielding applications.

Basic exposure estimation procedure

The exposure estimation portion of the Wallingford cohort study was based on an examination of the available sampling data and

job descriptions as well as on verbal descriptions of jobs and tasks by plant personnel, including the plant industrial hygienist. The data received by the University of Pittsburgh from the American Cyanamid Company included 156 detailed job and task descriptions, a description of past and present operations in various buildings and departments, a summary of major changes, several lists of chemicals used, and the available sampling data. Especially important in the job and task descriptions were the notations for the fraction of time a worker was expected to be performing certain tasks and the comfort level of the job as measured by dustiness and odours. These notations were an important surrogate for actual measurements.

Although several pigments used in 1955–65 were of special interest for their potential toxicity, it was not possible to specify exposure to the components of pigment from the available list of pigments used, or to estimate that exposure quantitatively; adequate measurements of airborne pigment levels were not available. Pigment exposure was assessed in terms of the presence or absence of any pigment. Because the focus of this study was on exposure to formaldehyde alone and in combination with particulates, or pigment, or both, no attempt was made to characterise other chemical exposures.

The available sampling data were sporadic measurements between 1965 and 1987 for 42 job titles (about 17% of the final 235 job classifications). The highest reported eight hour time weighted average (TWA) exposure to formaldehyde was 2.8 ppm in 1972. There were only 12 measurements in excess of 1.0 ppm TWA. The few jobs that were sampled repeatedly over the years did not show a consistent decline or increase in the measured exposure to formaldehyde. This is consistent with the American Cyanamid Company reports of few operational changes over the years, none of which influenced the measured exposures dramatically. Albeit limited, the available sampling data are consistent with a constant level of exposure over time.

The general approach used in assigning exposure was the classification of job titles by the similarity of tasks performed and the likelihood for potential exposures, as previously described.^{19,20} Exposures were initially assigned to each job and task combination by the consultant industrial hygienist on a ranked scale between background (or zero) exposure and high exposure to formaldehyde and particulate matter. These rankings provided seven classes (0–6) for formaldehyde and nine classes (0–8) for product based particulate and non-product particulate matter.

Subjective ranking of each of 156 unique job descriptions was based on potential for exposure to each agent in relation to physical proximity of jobs and duties relative to operation processes, accounting for duration, intensity, and frequency of exposure. Supporting documentation of use of personal protection equipment in response to concerns about noise and dust were also used in developing the rankings. The remaining job titles were classified accord-

ing to their similarity to the 156 job and task descriptions. An additional 79 job numbers were created to classify titles that were not comparable with any of the previously identified jobs. The resultant job classifications and exposure rankings were then sent to American Cyanamid Company to be reviewed by corporate and industrial hygienists to assess accuracy and relative potential exposure.

A range of exposures for each ranking were then assigned to the job categories. Although the assigned exposures suggest physical measurements, the exposure estimates should be considered to be relative within the study. It has been shown that on such a relative scale, the exposure estimates are satisfactory,²¹ and after calibrating the "experts", the accuracy of estimates improve substantially.²² Appendix B provides a more detailed account of the methods used to assign exposures.

The present study was designed to expand the Wallingford plant component of the National Cancer Institute study.¹ To compare the results of the present study with the National Cancer Institute study, similar exposure to formaldehyde categories were adopted, based on a modified National Cancer Institute schema. In the National Cancer Institute study, exposure to formaldehyde was classified into five categories defined as: trace (having worked at a plant that used or produced formaldehyde but with no known exposure), < 0.1 ppm, 0.1–0.5 ppm, 0.5–2 ppm, and > 2 ppm. Three minor modifications were made in the treatment of jobs with very low exposure: (a) the worker classifications such as "office help" were presumed to be exposed only to background levels of formaldehyde and such workers were assigned a zero exposure, (b) the workers who were estimated to be very indirectly exposed to formaldehyde were assigned background exposure, and (c) the estimated relative exposures were assumed to hold over time.

To summarise the exposure estimation process, 4322 job titles examined for the white male cohort were classified into 235 job numbers and assigned exposure to formaldehyde values similar, with modifications, to the scheme used in the National Cancer Institute study. Additionally, each job number specifies a set of exposure concentrations for product particulate and non-product particulate, and a unit step function for exposure to pigment.

Development of exposure indices for individual workers

The occupational history of each study member was linked to the estimated airborne exposure concentrations to estimate cumulative exposure, average intensity and duration of exposure to formaldehyde, and to the two coexposures, (product particulates and non-product particulates). Pigment exposure was assessed as duration of exposure to pigment. Exposure to formaldehyde occurring in the same job, but not necessarily simultaneously, with each of the three coexposures (formaldehyde/product particulates, formaldehyde/non-product particulates, formaldehyde/pigment) was also assessed.

For the calculation of cumulative and mean exposures, the numerical value given to each

exposure interval is the geometric midpoint of each interval. Duration of exposure to each agent was calculated by summing the years at each job in a worker's history in which a non-zero exposure to a given agent occurred. The time weighted cumulative exposure was found for each agent by multiplying the job class specific estimated mean exposure by years at that job, and summing this product across all jobs. The average intensity of exposure for each agent was found by dividing time weighted exposure by duration of exposure, where 0/0 was defined to be 0. By this definition intensity of exposure is the average intensity during periods when each worker was exposed. The class intervals for the time weighted exposure, duration of exposure, and average intensity of exposure measures were constructed a priori when possible to resemble those used for the same measures in the National Cancer Institute study.¹ Otherwise, intervals were defined to evenly distribute the observed number of deaths from lung cancer. Short and long term workers (< 1, ≥ 1 y) were defined as in the reanalysis of the National Cancer Institute cohort by Stewart *et al.*¹⁵

An alternative characterisation of exposure focused on jobs with high mean formaldehyde exposures. Duration of exposure in jobs with mean formaldehyde exposures that were ≥ 0.2 ppm and duration of exposure in jobs with mean formaldehyde exposures that were ≥ 0.7 ppm were computed. Appendix C shows the definitions of the study variables.

To assess the comparability of historical exposure data from the Wallingford plant developed independently for the National Cancer Institute and University of Pittsburgh studies, we performed both matched and unmatched descriptive analyses of selected exposure factors for white male members of both cohorts. Appendix D shows methodological details and results of the comparative analysis.

STATISTICAL ANALYSIS

Analyses of general patterns of mortality in the cohorts were performed with the occupational cohort mortality analysis program (OCMAP) developed at the University of Pittsburgh.^{23–25} Person-years at risk contributed by each study member were jointly classified by calendar period, age group, duration of employment, and the corresponding time since first employment. Person-year counts relative to non-zero time weighted exposure and duration of exposure began on the starting date of the first job in the work history that was associated with a non-zero exposure to each agent. In analyses by term of employment (short term *v* long term workers), person-years for long term workers began on the date that the first cumulative year of employment was reached. For the 313 workers lost to follow up, person-years were accumulated until the last point of verifiable vital status, which in every case was the date of the end of employment.

Expected numbers of deaths for selected causes were computed by multiplying United States mean annual age and time specific white male death rates by the person-years at risk in

the corresponding age-time intervals. To help adjust for geographic variations in mortality, expected numbers of deaths were also computed with rates for the state of Connecticut and for the combined New Haven and Middlesex counties, the local area from which the cohort was largely drawn. State and county rates were obtained from the mortality and population data system (MPDS) maintained at the University of Pittsburgh, Department of Biostatistics.²⁶ Because MPDS death rates are not available before 1950 for malignant neoplasms or before 1962 for non-cancer causes, in this study the expected cancer deaths for the period 1945–9 were estimated with MPDS data for the years 1950–4, and the expected non-cancer deaths for the period 1960–1 were estimated with MPDS data for the years 1962–4. The expected numbers of non-cancer deaths during 1948–59 were not computed with state or county rates.

Mortality excesses and deficits are expressed as standardised mortality ratios (SMRs), the ratio of observed deaths to expected deaths ($\times 100$). The SMRs were computed for subgroups of the cohort defined by age group, period, year of hire, duration of employment, time since first employment, and term of employment. Significant deviations of the SMR from 100, indicating deficit or excess risks of mortality, were identified with the Poisson probability distribution.²⁷ No formal adjustments were made for the many statistical comparisons that were made in the analysis. To facilitate the presentation of results, observed deaths and SMRs are shown with the codes (not the rules) of the ICD 8th revision (ICD-8) only.

Analysis of cohort data unique to present study

A separate analysis was performed to examine the Wallingford cohort data that by definition could not have been included in the previous National Cancer Institute study. Because individual identifiers were unavailable on our version of the National Cancer Institute cohort data file, the data not from the National Cancer Institute study were identified by selecting the workers who were hired between 1 January 1966 (the latest National Cancer Institute hire date) and 31 December 1984 (stop date of our study), and workers who were hired before 1 January 1966 and were alive on 1 January 1980 (stop date of the National Cancer Institute study). The mortality experience of workers hired in 1966–84, who could not have been included in the National Cancer Institute study, was examined between 1 January 1966 and 31 December 1984; the mortality experience of the workers hired before 1966 was examined during the additional follow up between 1 January 1980 and 31 December 1984. This analysis focused on local county comparisons of malignant respiratory diseases and was based on 1290 and 3538 white males from the two groups, respectively, who together contributed 31 400 person-years at risk.

Poisson regression modelling of cohort death rates and SMRs for lung cancer

Poisson regression modelling was used to investigate

the dependence of the internal cohort rates and the SMRs for lung cancer (including cancer of the bronchus, trachea, or lung) on combinations of the categorical exposure and potential confounding variables of interest. This approach is described elsewhere.²⁸ Briefly, the observed number of deaths in a particular cross classification is assumed to follow a Poisson distribution with a mean that depends on the person-years at risk (for internal cohort rates) or the expected numbers of deaths (for SMRs), and the effects of the classification factors. A multiplicative form of the model was assumed, so for cohort rates:

$$\log E (\text{observed deaths}) = \log (\text{person-years}) + \mathbf{a}'\mathbf{z}$$

and for SMRs:

$$\log E (\text{observed deaths}) = \log (\text{expected deaths}) + \mathbf{b}'\mathbf{z}$$

where E denotes statistical expectation, log denotes natural logarithm, \mathbf{a}' and \mathbf{b}' are vectors of regression coefficients to be estimated, and \mathbf{z} is the corresponding vector of covariates.

Parameters that allow separate effects for each age-time combination were included in every model for the cohort rates. These age-time parameters were also added to the models for the SMRs after the exposure effects were assessed, as a check on the homogeneity assumption of the SMRs across age and time intervals. Due to existing limitations in the OCMAP no more than two time dependent measures (as well as age group and period) could be analysed simultaneously, so time dependent exposures of interest were evaluated pairwise in separate models. Poisson regression models were fitted to the cohort rates and SMRs with maximum likelihood estimation in the generalised linear interactive modelling (GLIM) program.²⁹ All cells with no expected deaths were excluded from the analysis for numerical reasons.

Cohort rates and SMRs were modelled as a function of the categorical classification factors in a forward stepwise approach. The significance of each main effect (expressed as global P value) and interaction was assessed with a likelihood ratio statistic, with a P value between 0.05 and 0.10 identified as of borderline significance. Also, a test for linear trend (expressed as trend P value) was conducted on each quantitative exposure variable.

The primary Poisson regression analysis focused on 113 deaths from lung cancer among the 6039 white male study members. Some analyses were repeated on two separate subgroups of the cohort, the short term and long term workers. The 50 deaths from lung cancer among the 2590 long term workers would be expected to be more informative than data on the short term workers about risk of lung cancer associated with employment at the Wallingford plant. The very small numbers of deaths precluded Poisson regression modelling of nasopharyngeal cancer.

Results

EXPOSURE ASSESSMENT

Table 2 presents selected exposure characteristics of the white male cohort by year of hire

and term of employment. The year of hire groupings are those used by Collins *et al*⁸ to reflect periods of the Wallingford plant history that were homogeneous for processes, products, and ostensibly, worker exposure. Shown in each cell of table 2 are the number (%) of workers exposed and the median average intensity of exposure (based on exposed jobs only) among those exposed. Median average intensity of exposures are not defined for pigment, formaldehyde ≥ 0.2 ppm, and formaldehyde ≥ 0.7 ppm.

The recommended guideline for exposure to formaldehyde in a workplace has changed from a ceiling of 2 ppm as late as 1979³⁰ to the currently recommended ceiling levels 0.1 ppm by the National Institute for Occupational Safety and Health (NIOSH)³¹ and 0.3 ppm by the American Conference of Governmental Industrial Hygienists (ACGIH).³² During the 1945–84 study period, the measured formaldehyde concentrations in the Wallingford plant were generally low compared with the contemporaneously recommended exposure guidelines of 1–2 ppm, although the historical exposures are comparable or slightly in excess of the currently recommended levels.

Table 2 shows that, for the total cohort, slightly higher proportions of short term than long term workers were exposed to each of the agents formaldehyde, product particulates, non-product particulates, formaldehyde and product particulates, and formaldehyde and non-product particulates, but for each agent the median intensity of exposure for the long

term workers was at least twice as high as the corresponding median intensity of exposure for the short term workers. These same patterns were found for formaldehyde, non-product particulates, formaldehyde and product particulates, and formaldehyde and non-product particulates but not for product particulates in the separate analyses of the 1941–6 and 1947–56 year of hire subgroups. Less than a twofold differential was found in the median intensity of exposure to product particulates between the short term and long term workers in both these year of hire subgroups. Among those hired after 1956, median intensity of exposure to each of formaldehyde, product particulates, formaldehyde and product particulates, and formaldehyde and non-product particulates was at least as high for short term as long term workers. Overall and in the separate year of hire subgroups, consistently higher percentages of long term workers than short term workers were ever exposed to pigment, formaldehyde and pigment, formaldehyde ≥ 0.2 ppm, and formaldehyde ≥ 0.7 ppm. For the composite exposure variable, formaldehyde and pigment, the median intensity of exposure was identical for short and long term workers in the early and late year of hire subgroups, but over two times higher among short term workers than long term workers for those hired between 1947 and 1956. Although not shown, the median intensity of exposures of the long term workers during their first year of employment was generally similar to the intensity of exposures computed over the entire work history.

Table 2 Selected exposure characteristics of a white male cohort by year of hire and term of employment, showing median average intensity of exposures (AIE)*

	Year of hire							
	Total		1941–6		1947–56		≥ 1957	
	STW	LTW	STW	LTW	STW	LTW	STW	LTW
Workers (n)	3449	2590	504	366	1727	1053	1218	1171
STW/LTW (%)	57.1	42.9	57.9	42.1	62.1	37.9	50.9	49.1
Exposure variable†:								
F:								
Exposed (n)	2922	2057	406	268	1570	931	946	858
Exposed (%)	84.7	79.4	80.6	73.2	90.9	88.4	77.7	73.3
Median AIE (ppm)	0.07	0.16	0.02	0.11	0.02	0.15	0.20	0.18
PP:								
Exposed (n)	2653	1844	379	239	1532	876	751	729
Exposed (%)	76.9	71.2	75.2	65.3	88.2	83.2	61.7	62.3
Median AIE (mg/m ³)	0.20	0.43	0.20	0.20	0.20	0.31	1.18	0.89
NPP:								
Exposed (n)	3010	2101	399	275	1584	937	1027	889
Exposed (%)	87.3	81.1	79.2	75.1	91.7	89.0	84.3	75.9
Median AIE (mg/m ³)	0.02	0.09	0.04	0.08	0.02	0.07	0.02	0.13
Pigt:								
Exposed (n)	935	1402	70	125	256	592	609	685
Exposed (%)	27.1	54.1	13.9	34.2	14.8	56.2	50.0	58.5
F/PP:								
Exposed (n)	2635	1844	379	239	1532	876	751	729
Exposed (%)	76.9	71.2	75.2	65.3	88.2	83.2	61.7	62.2
Median AIE (ppm)	0.07	0.19	0.02	0.14	0.02	0.19	0.20	0.20
F/NPP:								
Exposed (n)	2880	2017	378	252	1565	919	937	846
Exposed (%)	83.5	77.9	75.0	68.8	90.6	87.3	76.9	72.2
Median AIE (ppm)	0.07	0.17	0.02	0.13	0.02	0.17	0.20	0.19
F/Pigt:								
Exposed (n)	868	1293	58	105	249	559	561	629
Exposed (%)	25.2	49.9	11.5	28.7	14.4	53.1	46.1	53.7
Median AIE (ppm)	0.20	0.20	0.20	0.20	0.46	0.21	0.20	0.20
F > 0.2 ppm‡:								
Exposed (n)	1547	1703	196	184	621	780	730	739
Exposed (%)	44.9	65.8	38.9	50.3	40.0	74.1	59.9	63.1
F > 0.7 ppm‡:								
Exposed (n)	328	837	59	69	180	474	89	294
Exposed (%)	9.5	32.3	11.7	18.9	10.4	45.0	7.3	25.1

*Based on exposed jobs only.

†See appendix C for definitions of variables.

‡AIE not computed for this qualitative variable.

STW = short term worker (employed < 1 year); LTW = long term worker (employed ≥ 1 year).

Table 3 Observed deaths and SMRs for selected causes of death among white male workers and three external comparison populations

Cause of death (ICD-8)	SMR			
	Observed	US	CT	County
All caused (000-999)	1225	107*	117**	114**
All malignant neoplasms (140-209)	305	110	108	105
Buccal cavity (140-145)	6	131	100	104
Oropharynx (146)	2	184	136	122
Nasopharynx (147)	4	533*	547*	550*
Hypopharynx (148)	1	141	106	82
Digestive system (150-159)	75	102	90	89
Respiratory system (160-163)	121	122*	134**	128**
Sinonasal (160)	2	381	522	372
Larynx (161)	6	147	137	154
Bronchus, trachea, lung (162)	113	120	133**	127*
Prostate (185)	16	102	100	100
Kidney (189-0-189-2)	9	127	122	112
Bladder and other urinary organs (188, 189-9)	7	97	89	86
Melanoma of skin (172-0-172-4, 172-6-172-9)	7	154	148	160
Central nervous system (191-192)	15	159	166	170
All lymphopoietic tissue (200-209)	25	89	89	91
Cerebrovascular disease (430-438)	64	98	110	111
All heart disease (390-398, 400-1, 400-9, 402, 404, 410-414, 420-429)	481	103	111*	105
Non-malignant respiratory disease (460-519)	58	85	102	104
Cirrhosis of liver (571)	38	112	110	113
Accidents (800-949)	60	78*	120	126
Suicides (950-959)	33	114	150*	159*
Unknown causes (in all causes only)	70			

*P < 0.05; **P < 0.01.

†Based on 1945-84 for cancer mortality (6039 at risk, 146 297 person-years) and 1960-84 for total and non-malignant disease mortality (5748 at risk, 110 465 person-years).

US = United States; CT = Connecticut.

There was a high degree of association between exposures to formaldehyde and product particulates, and formaldehyde and non-product particulates for the total cohort and for short and long term workers considered separately. Very few person-years were contributed by workers exposed to formaldehyde who were never exposed to product particulates or non-product particulates and very few person-years were contributed by workers exposed to product particulates or non-product particulates who were never exposed to formaldehyde. In contrast, 51.5% of the person-years among all white men were contributed by workers exposed to formaldehyde who were never exposed to pigment, but even here only 0.8% of the person-years were contributed by those exposed to pigment who were never exposed to formaldehyde. When formaldehyde exposures were restricted to ≥ 0.2 ppm and ≥ 0.7 ppm an appreciable percentage of person-years (between 28% and 66%) came from workers exposed to product particulates or non-product particulates or both who were never exposed to ≥ 0.2 or 0.7 ppm formaldehyde. Almost all of the workers exposed to pigment were exposed to ≥ 0.2 ppm formaldehyde, indicating that exposure to pigment is associated with high formaldehyde exposures.

DESCRIPTIVE MORTALITY ANALYSES

Table 3 shows the SMRs for white men for selected causes of death based on the United States, Connecticut, and local county rates. For the 70 dead workers for whom death certificates could not be located, deaths are counted only under mortality for all causes and unknown causes (ICD-8 999-9). Thus, cause specific SMRs in table 3 are slightly understated and should probably be multiplied by a factor of $1225/1155 = 1.06$.

Table 3 shows a significantly increased

SMR for total mortality based on United States, Connecticut, or local two county rates with the highest SMRs occurring relative to the state and local populations. In fact, the regional comparisons produced higher SMRs for several of the non-malignant disease categories examined, indicating that these regional death rates were lower than those for the total United States. The opposite pattern is found for the category all malignant neoplasms and for several of the site specific cancer categories examined. Based on the regional comparisons, significantly increased SMRs were found for nasopharyngeal cancer and cancers of the respiratory system and the subcategory, bronchus, trachea, lung. The excess of nasopharyngeal cancer is based on the same four index cases identified previously in the National Cancer Institute study.¹ Table 3 also shows excess mortality for cancers of the buccal cavity, oropharynx, kidney, skin, and central nervous system, although these were not significant. In the mortality tables that follow, SMRs are based exclusively on the local two county rates, which probably provide the best available adjustment for social, economic, ethnic, and lifestyle factors related to disease for these workers. Although not shown, the mortality experiences of Wallingford non-white male and white female workers were unremarkable and show no significant excesses in total or cause specific mortality and no cases of nasopharyngeal cancer.

Table 4 shows SMRs for selected causes of death for white men by term of employment and year of hire. Short term workers generally had a less favourable total and cause specific mortality experience than their longer term counterparts. For the total cohort, short term workers had significant excesses in total mortality and mortality due to ischaemic heart disease and non-malignant respiratory disease, whereas long term workers had corresponding mortality experiences only slightly higher than the white men of the local two county area. The short term workers account for most of the total and site specific cancer excesses for the total white male cohort (table 3). Among short term workers, significant excesses of site specific cancers were found for the lung, melanoma of the skin, and the central nervous system; no excesses were found among long term workers for melanoma of the skin or cancers of the central nervous system, and the SMR of 119 for lung cancer among long term workers was not significantly increased. The excess of nasopharyngeal cancer (table 3) was maintained among both short and long term workers.

Table 4 also shows that the differential mortality experience of short and long term workers was generally maintained in the three year of hire subcohorts examined, although many of the largest excesses were found among those hired between 1947 and 1956. For this subcohort, significantly increased SMRs were found among short term workers for nearly all of the cause of death categories examined compared with slightly increased SMRs among the long term workers. For lung cancer, a significant excess was found for the short term workers overall and the 1947-56

Table 4 Observed deaths and SMRs for selected causes of death among white male short and long term workers by year of hire

Cause of death (ICD-8)		Year of hire							
		Total		1941-6		1947-56		≥ 1957	
		OBS	SMR†	OBS	SMR†	OBS	SMR†	OBS	SMR†
All causes (000-999)	STW	706	124**	167	105	487	138*	52	91
	LTW	519	103	145	103	295	110	79	79
All malignant neoplasms (140-209)	STW	175	115	45	102	119	124*	11	92
	LTW	130	95	30	72	76	105	24	101
Buccal cavity and pharynx (140-149)	STW	10	164	0	—	9	229*	1	218
	LTW	5	91	1	61	3	102	1	107
Nasopharynx (147)	STW	2	515	0	—	2	768	0	—
	LTW	2	596	0	—	2	1049*	0	—
Bronchus, trachea, lung (160-163)	STW	63	134*	15	117	46	151*	2	56
	LTW	50	119	12	105	29	126	9	118
Kidney (189-0-189-2)	STW	8	185	4	341	4	144	0	—
	LTW	1	27	0	—	1	50	0	—
Melanoma of skin (172-0-172-4, 172-6-172-9)	STW	7	288*	3	543*	3	191	1	317
	LTW	0	—	0	—	0	—	0	—
Central nervous system (191, 192)	STW	12	245**	2	172	9	283*	1	177
	LTW	3	78	1	111	1	46	1	113
Ischaemic heart disease (410-414)	STW	228	116*	56	96	160	128*	12	85
	LTW	186	104	50	94	110	116	26	86
Non-malignant respiratory disease (excluding influenza and pneumonia) (460-469, 475-479, 487-519)	STW	27	155*	6	111	18	168	3	233
	LTW	14	86	10	204	4	45	0	—
Unknown causes (in all causes only)	STW	49	—	—	—	—	—	—	—
	LTW	21	—	—	—	—	—	—	—

*P < 0.05; **P < 0.01.

†Based on 1945-84 for cancer mortality and 1960-84 for total and non-malignant disease mortality.

STW = short term worker (employed < 1 y); LTW = long term worker (employed ≥ 1 y).

year of hire subgroup of short term workers. There was a deficit for the short term workers hired after 1956, based on two deaths. The 18% to 26% excesses in the SMRs for lung cancer for the long term workers hired after 1946 were not significant. All four nasopharyngeal cancers occurred among workers hired between 1947 and 1956, resulting in a significant SMR of 1049 for the long term workers and a non-significant increased SMR of 768 for the short term workers.

Table 5 shows selected characteristics and estimated exposures for the four index cases of nasopharyngeal cancer. Exposure to formaldehyde always occurred in the presence of product particulates or non-product particulates, and only case 3 had any appreciable exposure to formaldehyde. None of the cases had any exposure to pigment.

ANALYSIS OF COHORT DATA UNIQUE TO THE PRESENT STUDY

For the combined data not from the National Cancer Institute white male cohort, table 6 shows the SMRs for selected malignant respiratory disease categories for the 1966-84 fol-

low up period. The data not from the National Cancer Institute study contributed two of the six cancers of the buccal cavity, one of the two sinonasal cancers, and 27 of the 113 lung cancers found among the total white male cohort. Based on local county rates, the findings for buccal cavity and lung cancer represent deficits in mortality, whereas the one sinonasal cancer death represents a non-significant 7.28-fold excess in mortality. The data not from the National Cancer Institute study yielded no additional nasopharyngeal cancer deaths compared with 0.20 deaths expected.

POISSON REGRESSION ANALYSIS OF RATES AND SMRS FOR LUNG CANCER

Table 7 shows the Poisson regression models relating mortality from lung cancer to duration of exposure to formaldehyde (≥ 0.2 ppm) for the total cohort and for the short and long term workers considered separately. Table 7 shows for each exposure category the observed number of lung cancer deaths, the externally adjusted SMR, the unadjusted ratio of SMRs (category specific SMR to the baseline cate-

Table 5 Selected characteristics of deaths due to nasopharyngeal cancer (all white men)

Case No.	Estimated exposure levels*						Year of hire	Year of term	Year of death	Age at death (y)	Duration of employment (y)	Time since first employment (y)	Underlying cause of death	
	F†‡	PP†§	NPP†§	Pig	F/(PP or NPP)†‡	F/Pig								
1:	DUR	0.625	0.625	0.625	0	0.625	0	1950	1950	1967	56.6	0.6	18.0	Epidermoid cancer of nasopharynx
	TWE	0.084	0.047	0.084	0	0.084	0							
	AIE	0.134	0.075	0.134	0	0.134	0							
2:	DUR	0.252	0.216	0.252	0	0.252	0	1949	1950	1969	42.2	0.3	19.2	Metastatic epidermoid cancer of nasopharynx
	TWE	0.007	0.043	0.011	0	0.007	0							
	AIE	0.027	0.200	0.045	0	0.027	0							
3:	DUR	17.879	16.153	17.879	0	17.879	0	1955	1973	1976	64.2	17.9	21.3	Carcinoma of nasopharynx
	TWE	10.821	3.007	46.423	0	10.821	0							
	AIE	0.605	0.186	2.596	0	0.605	0							
4:	DUR	4.279	4.088	3.463	0	4.279	0	1951	1955	1977	52.4	4.3	25.5	Nasopharyngeal carcinoma with regional and cranial metastases
	TWE	0.684	0.417	0.538	0	0.684	0							
	AIE	0.160	0.102	0.155	0	0.160	0							

*See appendix C for definitions of variables.

†DUR (y).

‡TWE (ppm-y), AIE (ppm).

§TWE (mg/m³-y), AIE (mg/m³).

Table 6 Observed and expected deaths and SMRs for selected cancer sites for white male cohort data not from the National Cancer Institute study* 1966-84, local two county comparison

Cause of death (ICD-8)	Observed	Expected	SMR
Buccal cavity and pharynx (140-149)	2	2.95	68
Nasopharyngeal (147)	0	0.20	—
Sinonasal (160)	1	0.14	728
Bronchus, trachea, lung (162)	27	28.32	95

*Workers hired 1966-84 and workers hired before 1 January 1966 who were alive as of 1 January 1980.

gory SMR), and the estimated risk ratios derived from the Poisson regression models for the SMRs and cohort rates. The models of cohort death rates were adjusted for age, time period, year of hire, and the time since first employment. Comparable models fitted to the SMRs excluded the modelled adjustment for age and time period.

Table 7 shows the estimated risk ratios for the total cohort and for the short and long term workers, considered separately, as a function of duration of exposure to formaldehyde

at ≥ 0.2 ppm. For the total cohort, significant heterogeneity in the estimated risk ratios was found for both the rates and the SMRs, with estimated risk ratios of ≥ 1.5 for all exposure categories above the baseline. Although there was a significant linear trend component to these estimates, the risk ratios did not increase monotonically with increasing exposure. The short term workers show a highly significant positive gradient in estimated risk ratios for both rates and SMRs. The estimated risk ratios of 6.03 and 5.37 based on the SMRs and rates, respectively, for short term workers employed for half to one year in jobs with exposure to formaldehydes of at least 0.2 ppm were based on seven deaths. Among the long term workers, neither the heterogeneity nor the linear trend was significant, and the estimated risk ratios for the 0.5-5.0 exposure category were close to baseline levels.

Table 8 presents risk ratio estimates for several measures of average intensity of exposure

Table 7 Summary of unadjusted and adjusted mortality measures for duration (y) of exposure to formaldehyde ≥ 0.2 ppm, cancer of the lung in the Wallingford white male cohort, 1945-84 by term of employment

Duration of exposure to formaldehyde (≥ 0.2 ppm)	Observed deaths	SMR*	Unadjusted ratio† of SMRs	Adjusted estimates of risk ratio					
				SMR based‡	Global P value	Trend P value	Cohort rate based§	Global P value	Trend P value
Total cohort:									
0	41	93	1.00	1.00	0.05	0.02	1.00	0.03	0.01
< 0.5	34	166	1.78	1.74			1.64		
0.5-4.9	22	145	1.56	1.57			1.54		
≥ 5	16	170	1.83	1.80			2.21		
Short term workers:					< 0.01	< 0.01		< 0.01	< 0.01
0	27	95	1.00	1.00			1.00		
< 0.5	29	169	1.78	1.81			1.85		
0.5-1.0	7	530	5.58	6.03			5.37		
Long term workers:					0.42	0.18		0.25	0.17
0	14	90	1.00	1.00			1.00		
< 0.5	5	149	1.66	1.65			1.48		
0.5-4.9	15	108	1.20	1.18			1.01		
≥ 5.0	16	170	1.89	1.81			1.96		

*SMR internally adjusted for age group and calendar time period.

†Relative to baseline category.

‡All models adjusted for year of hire and time since first employment in Poisson regression.

§All models adjusted for age, time period, year of hire and time since first employment in Poisson regression.

Table 8 Summary of unadjusted and adjusted mortality measures for selected exposure models, cancer of the lung in the short and long term Wallingford white male cohort, 1945-84

Exposure variable*	Observed deaths	SMR†	Unadjusted ratio‡ of SMRs	Adjusted estimates of risk ratio			
				SMR based§	Global P value	Cohort rate based¶	Global P value
Short term workers:							
AIE (F):						< 0.01	< 0.01
< 0.1	30	96	1.00	1.00		1.00	
≥ 0.1	33	211	2.20	2.25		2.23	
AIE (F/PP):						< 0.01	< 0.01
< 0.1	31	98	1.00	1.00		1.00	
≥ 0.1	32	210	2.14	2.17		2.17	
AIE (F/NPP):						< 0.01	< 0.01
< 0.1	31	102	1.00	1.00		1.00	
≥ 0.1	32	208	2.04	2.16		2.13	
AIE (F/Pig):						0.07	0.09
< 0.1	49	122	1.00	1.00		1.00	
≥ 0.1	14	209	1.71	1.81		1.75	
Long term workers:							
AIE (F):						0.79	0.85
< 0.1	23	106	1.00	1.00		1.00	
≥ 0.1	27	132	1.24	1.09		1.06	
AIE (F/PP):						0.72	0.83
< 0.1	21	102	1.00	1.00		1.00	
≥ 0.1	29	135	1.32	1.13		1.08	
AIE (F/NPP):						0.16	0.24
< 0.1	19	94	1.00	1.00		1.00	
≥ 0.1	31	148	1.57	1.64		1.49	
AIE (F/Pig):						0.16	0.23
< 0.1	25	100	1.00	1.00		1.00	
≥ 0.1	25	146	1.46	1.65		1.53	

*Refer to appendix C for definitions of variables.

†SMR internally adjusted for age group and calendar period.

‡Relative to baseline category.

§All models adjusted for year of hire and time since first employment in Poisson regression.

¶All models adjusted for age, time period, year of hire and time since first employment in Poisson regression.

Table 9 Summary of Poisson regression modelling of SMRs and cohort rates for lung cancer

Variable*	All workers		Long term workers		Short term workers	
	SMR	Cohort rate	SMR	Cohort rate	SMR	Cohort rate
Year of hire	NS	G = 0.05	NS	NS	—	—
Duration of employment	NS	NS	NS	NS	—	—
Time since first employment	NS	G = 0.01	NS	NS	—	—
DUR (F)†	NS	NS	NS	NS	—	—
DUR (F ≥ 0.2 ppm)†	G = 0.05, T = 0.02	G = 0.03, T = 0.01	NS	NS	G < 0.01, T < 0.01	G < 0.01, T < 0.01
DUR (F ≥ 0.7 ppm)†	NS	NS	NS	NS	—	—
DUR (PP)†	NS	T = 0.08	NS	T = 0.10	—	—
DUR (NPP)†	NS	NS	NS	NS	—	—
DUR (Pig)†	G = 0.02	G = 0.05	NS	NS	—	—
TWE (F)†	NS	NS	NS	NS	—	—
TWE (F/PP)†	NS	T = 0.08	NS	NS	—	—
TWE (F/NPP)†	NS	NS	NS	NS	—	—
TWE (F/Pig)†	NS	NS	NS	NS	—	—
TWE (F)/TWE (PP)	NS	NS	NS	G = 0.10	—	—
TWE (F)/TWE (NPP)	NS	NS	G = 0.09	G = 0.05	—	—
TWE (F)/DUR (Pig)	NS	NS	G = 0.09	G = 0.07	—	—
TWE (PP)/TWE (F)	NS	NS	NS	NS	—	—
TWE (NPP)/TWE (F)	NS	NS	NS	NS	—	—
DUR (Pig)/TWE (F)	G = 0.02	G = 0.03	NS	NS	—	—
AIE (F)	G < 0.01	G = 0.01	NS	NS	G < 0.01	G < 0.01
AIE (F/PP)	G < 0.01	G = 0.01	NS	NS	G < 0.01	G < 0.01
AIE (F/NPP)	G < 0.01	G < 0.01	NS	NS	G < 0.01	G < 0.01
AIE (F/Pig)	G = 0.03	G = 0.05	NS	NS	G = 0.07	G = 0.09

*Refer to appendix C for definitions of variables.

†Trend test performed for this variable.

G = Global test P value; T = trend test P value; NS = not significant at 0.10 level.

separately for short and for long term workers. Again, in contrast to long term workers, short term workers show larger and significant estimated risk ratios for SMRs and rates for those exposed to the baseline category < 0.1 ppm compared with those exposed to ≥ 0.1 ppm for intensity of exposure to formaldehyde, intensity of exposure to formaldehyde and product particulates, and intensity of exposure to formaldehyde and non-product particulates. The estimated risk ratios were consistently more than doubled for the short term workers exposed at more than 0.1 ppm to these agents. Risk ratios of 1.81 and 1.75 were estimated for short term workers exposed to intensities of exposure to formaldehyde and pigment ≥ 0.1 ppm based on SMRs (P = 0.07) and rates (P = 0.09), respectively; the corresponding estimates of 1.65 and 1.53 for the long term workers were not significantly increased (P > 0.15 for each).

Table 9 presents a summary of our Poisson regression modelling of lung cancer SMRs and rates for this Wallingford cohort. To decide which adjustment factors to include in subsequent models involving the exposure variables, the SMRs and cohort rates were first modelled as a function of the year of hire, duration of employment, and time since first employment. For the total white male cohort, there was significant heterogeneity in the cohort rates for year of hire (with estimated risk ratios of 1.0, 1.45, and 0.71 for the year of hire categories 1941–6, 1947–56, and 1957–84, respectively). Significantly increased risk was associated with increasing time since first employment, with estimated risk ratios of 1.0, 2.21, and 3.99 for the categories < 20, 20–9, and ≥ 30 years, respectively. None of these effects were even of marginal significance in the models for the SMRs or the long term workers. With the exception of the models involving two time dependent exposure measures, all subsequent models were adjusted for both year of hire and time since first employment.

Next, duration of exposure to each agent and time weighted exposure to formaldehyde with

and without consideration of each coexposure were modelled separately. Table 7 has already shown the results for duration of exposure to ≥ 0.2 ppm formaldehyde. For the total white male cohort, significant heterogeneity was found in both the SMRs and the cohort rates as a function of duration of exposure to pigment, with estimated risk ratios of 1.0, 1.99, and 0.98 for the SMRs for a duration of exposure to pigment of 0, < 0.5, and ≥ 0.5 years, respectively, and corresponding risk ratios for the cohort rates of 1.0, 1.87, and 1.08. A trend of borderline significance was found in the cohort rates for duration of exposure to product particulates and time weighted exposure to formaldehyde and product particulates, with estimated risk ratios of 1.0, 1.1, 1.27, and 1.74 for duration of exposure to product particulates, and estimated risk ratios of 1.0, 1.04, 1.45, and 1.55 for time weighted exposure to formaldehyde and product particulates. A similar trend with duration of exposure to product particulates was also found in the cohort rates for the long term workers, with estimated risk ratios of 1.0, 1.15, 1.11, and 1.83 for duration of exposure to product particulates of 0, < 0.5, 0.5–4.9, and ≥ 5 years, respectively.

In the next set of models, time weighted exposure to formaldehyde was modelled jointly with time weighted exposure to each of the other coexposures in separate models. The P values for this set of models refer to the first variable listed. For example, for long term workers and time weighted exposure to formaldehyde and time weighted exposure to product particulates, G = 0.10 is the global P value for time weighted exposure to formaldehyde given that time weighted exposure to product particulates is in the model. This analysis was adjusted for year of hire but not for time since first exposure. Among the long term workers, there was some evidence of heterogeneity in the cohort rates as a function of time weighted exposure to formaldehyde when adjusted for time weighted exposure to product particulates, for time weighted exposure to non-product particulates, and for

duration of exposure to pigment ($P \leq 0.10$ for each). None of these effects increased monotonically with increasing time weighted exposure to formaldehyde. For example, when adjusted for time weighted exposure to product particulates, the estimated risk ratios for the long term workers at the four levels of time weighted exposure to formaldehyde (0, < 0.05 , $0.05-1$, and > 1 ppm-y) were 1.0, 2.58, 0.81 and 1.34, respectively. The corresponding estimates were 1.0, 5.36, 2.30, and 4.67 adjusted for time weighted exposure to non-product particulates, and 1.0, 2.64, 0.99, and 1.97 adjusted for duration of exposure to pigment. Similar results were obtained for the SMR models for the long term workers, except that the heterogeneity with time weighted exposure to formaldehyde when adjusted for time weighted exposure to product particulates was not significant at the 0.10 level.

Table 9 also shows the P values for each of the coexposures adjusted for time weighted exposure to formaldehyde. Significant heterogeneity in the SMRs and cohort rates was found only for duration of exposure to pigment in the total white male cohort. The estimated risks were similar to those given earlier for duration of exposure to pigment without adjustment for time weighted exposure to formaldehyde, with almost twofold increases for duration of exposure to pigment of < 0.5 years relative to the 0 and ≥ 0.5 year categories. The last section of this table summarises the results given in table 8.

Poisson regression modelling was performed on short term workers only for those models where a significant main effect of exposure to formaldehyde was found in the total cohort (duration of exposure to ≥ 0.2 ppm formaldehyde, average intensity of exposure to formaldehyde, average intensity of exposure to formaldehyde and to product particulates, average intensity of exposure to formaldehyde and to non-product particulates, and average intensity of exposure to formaldehyde and pigment (the last two columns of table 9)). Virtually all of the significant findings for lung cancer among the total cohort can be attributed to significant findings among the short term workers.

Discussion and conclusions

Many historical cohort studies, including the one reported here, have shown unusual mortality patterns for non-malignant and malignant disease among short term workers.^{15 33} Differential mortality patterns found among short term workers can be due to risks acquired elsewhere—for example—avocations or earlier employment—to non-occupationally related differences in behaviour or lifestyle—for example, tobacco and alcohol consumption—or to occupationally related differences in job type or exposure—for example, newly hired employees assigned to “dirtier”, less desirable jobs.³⁴⁻³⁶ For these reasons, very short term workers are frequently excluded from studies of occupational cohorts or else considered separately.

Based on our new exposure assessment of

the Wallingford plant, work histories of the short term and long term workers could be compared relative to several measures of exposure to formaldehyde, product particulates, non-product particulates, and pigments. We found little evidence that short term white male workers held different jobs than those who went on to work for longer periods of time in this plant, or that the jobs they held had higher exposures to any of the agents considered. The same conclusion was reached by Stewart *et al*¹⁵ after a similar analysis by Blair *et al*¹ of the cohort data. One exception to this general pattern occurred among workers initially hired between 1947 and 1956. For this subgroup, the median average intensity of exposure to formaldehyde in the presence of pigment exposure was 0.46 ppm for the 14.4% of exposed short term workers compared with 0.21 ppm for the 53.1% of exposed long term workers. Significant excesses in mortality for all cancers combined and for many of the specific cancer sites were found for the short term workers in the 1947–56 year of hire subcohort.

Few differences were found between short and long term workers for exposures to the agents considered. Demographic differences between the long term workers and the short term workers were slight: long term workers tended to be born longer ago, hired more recently, and hired at somewhat older ages than the short term workers. Our findings of higher SMRs among short term workers for many categories of disease related to smoking (lung cancer, ischaemic heart disease, and non-malignant respiratory disease) suggest a difference in smoking habits between short and long term workers in the Wallingford cohort. Over 60% of the short term workers in this cohort were actually employed at this plant for less than three months.

Robins *et al*¹² considered whether the slight excesses and the apparent lack of exposure-response between exposure to formaldehyde and lung cancer in the study of Blair *et al*¹ could be explained by the healthy worker survivor effect, which is defined as the tendency of workers at increased risk of death to end employment early. Based on the proposed G-null tests, Robins *et al*¹² found no evidence that the healthy worker effect was biasing the findings of Blair *et al*¹ for lung cancer mortality. In the present study, because the occupational exposures for the short term workers seem to be generally similar to those of long term workers, we have no reason to suspect that the healthy worker effect is introducing major biases. However, significant positive effects have been identified for the short term workers in the present study. The presence of a healthy worker effect could mean that we are underestimating the risk associated with exposure among short term workers.

In this update, no additional cases of nasopharyngeal cancer were found in the Wallingford plant cohort despite our independent enumeration of an expanded cohort with an additional five years of follow up. The four cases were the same index cases identified in the original National Cancer Institute study, whose suspected clustering in this one plant

served as a major impetus for our study. Although these four cases of nasopharyngeal cancer did represent a significant excess greater than fivefold, the very small numbers of deaths from nasopharyngeal cancer precluded a more detailed investigation of possible aetiological factors. Although all four cases had at least some exposure to both formaldehyde and particulates (as did over 80% of the white male cohort), only one case had any appreciable exposure to formaldehyde. The potential for diagnostic misclassification of nasopharyngeal cancer has been considered elsewhere.^{37,38}

A major portion of this investigation was directed at the question of whether the significant 27% excess in lung cancer mortality among the total white male cohort was in any way related to occupational factors at the Wallingford plant. Our Poisson regression modelling of internal cohort rates and SMRs showed that virtually all of the evidence of a relation between exposure to formaldehyde (with or without coexposures) and lung cancer occurred within the cohort of short term workers. Among the long term workers there was no clear evidence of an association between mortality from lung cancer and any occupational factors with the possible exception of cumulative exposure to formaldehyde when evaluated jointly with each of the three coexposure agents (table 9). Although monotone trends were not found with increasing time weighted exposure to formaldehyde in any of these analyses, consistently greater than twofold risk ratios were found for time weighted exposure to formaldehyde in each category above the baseline when adjusted for time weighted exposure to non-product particulates. The analysis of time weighted exposure to formaldehyde adjusted for time weighted exposure to non-product particulates is sensitive to the collinearity between these two exposures: only 2.3% of the white male person-years in this study involved exposure to non-product particulates and not to formaldehyde, and 1.2% of the white male person-years involved exposure to formaldehyde but not to non-product particulates.

At least a portion of the non-significant 19% excess of lung cancer in long term white male workers may be linked to exposures to agents not studied here that were used or produced at the Wallingford plant. Recent reanalyses of the total National Cancer Institute formaldehyde worker cohort, which includes the Wallingford plant, have found significant positive associations between risk of lung cancer and cumulative exposure to formaldehyde in the presence of several other coexposures including antioxidants, hexamethylenetetramine, melamine, phenol, and urea.⁹⁻¹¹

The composition of this workforce is such that the cohort is relatively uninformative about the risks associated with exposures of long duration as the long term workers comprised only 43% of the white male cohort. Because less than one third of these long term workers were employed for more than five years in the Wallingford plant, this study lacks

power to detect trends with increasing exposure. A plateau effect was found for many of the exposures, with the risk ratios generally increased for levels of exposure above the baseline, but with no apparent trend.

In conclusion, this study provides little evidence that the risk of lung cancer is associated with exposure to formaldehyde alone or in combination with exposures to particulates or pigment among workers employed for at least one year in this plant. The excess risk of lung cancer found in the total white male cohort seems to be primarily a short term worker phenomenon, but the possibility remains that unmeasured occupational or non-occupational factors may have played a part.

Appendix A: Comparison of selected Wallingford cohort data from current study and NCI study

Characteristic	Current study	NCI study (plant 1)*
Cohort definition	All employees hired 1941-84	All employees hired 1940-66
Cohort size	7359	4389
Primary analysis subcohort	White men, 1945-84 study period	White men (excluding unknown job type), 1943-79 study period
Subcohort size	6039	3659
Total deaths	1396	787
Lung cancer deaths	113	59

*NCI study data as developed for Marsh *et al* reanalyses.^{10,11}

Appendix B: Exposure assignment procedures used in current study

Given the scarcity of measurements, our initial preference in assigning exposure was to assign exposures strictly on a ranked basis, between background and a highest rank, without attributing a physically meaningful number to each level. Although this approach would have been reasonable, because the National Cancer Institute study had some numbers attached to their estimates, we were concerned that our estimates would seem "less rigorous". Keeping in mind that each estimate is subjective, the details of our process are elucidated below. The estimation process for formaldehyde is detailed; the same procedures were used to estimate the other exposures considered.

There were detailed job assignment and employment sheets for 156 jobs. In these sheets, details of tasks done by the holder of that job title were outlined. Also there were entries for dustiness, noisiness, safety, and similar concerns. These 156 classes and the additional job classes created to classify the job titles that did not fit the original classes are referred to as job numbers. Table B-1 shows the job or task ranking criteria. The exposure assignment procedure based on the attributes listed in the table was first applied to the original job number list, and an exposure rank for each job number was developed. The job titles that appeared in the employment records were culled to extract those that fitted the descriptions of these job numbers exactly. The remaining job titles were then examined to identify similar groups, who were assigned additional job numbers. The plant personnel verified the appropriateness of including each previously unassigned job title into one of these new job numbers. Exposures were assigned to these new job numbers based on the ranking table, and the employment records were culled again. After several iterations of generating new job numbers, less than 20 as yet unclassified job

Table B-1 Exposure classification levels

Rank	Range (ppm)	Description
0	< 0.01	Background exposure
1	0.01–0.05	Mostly background with occasional presence in the manufacturing areas—for example, supervisor
2	0.05–0.1	The jobs that dealt with the product end with possibly trace amount of the pollutant
3	0.1–0.5	All jobs in the middle stages of operation with some potential for high but short duration of exposure to formaldehyde
4	0.5–1	Jobs that dealt with pure formaldehyde or slurries containing formaldehyde only part of the day with potentially high but short duration of exposure to formaldehyde several times a day
5	1–5	Jobs that dealt directly with pure formaldehyde or slurries containing high formaldehyde concentrations most of the day and had frequent high but short duration formaldehyde exposure potential
6	> 5	Jobs that dealt directly with pure formaldehyde or slurries containing high formaldehyde concentrations most of the day and frequently showed symptoms of eye, nose, or throat irritation

titles were sent to the plant personnel to classify. Because they were unable to decode these titles, average department exposures were assigned to these job titles. The exposure potentials for the components studied were assigned to each job title that appeared in the employment record according to the assigned job number.

Also, there were some exposure measurements, mostly for workers with highest exposure potential. Although these measurements were *not* used in the reconstruction of exposures, they were used as a part of validation. The measured exposure values ranged between < 0.02 to about 6 ppm. Most of the measured values were < 1 ppm eight hour time weighted average (TWA). In fact, only nine out of 298 TWA measurements available were > 1 ppm and only one out of nine was > 3 ppm. The average of this highest measurement and the four other TWA measurements for the same job was < 1 ppm.

The exposure classification intervals were chosen to maximise comparability with the National Cancer Institute study. If, however, a substantial portion of the measured exposures had been > 2 ppm, an attempt to reconstruct detailed exposures temporally beyond the available data might have been justified. The data available for this study do not support any further refinement of the classification intervals, and a reconstruction of exposures was not considered necessary.

The measured exposures for several job titles were compared with the estimated exposures based on the job and task descriptions as part of a subjective evalu-

ation. The initial estimates were calibrated with the available exposure measurement data in re-evaluation rounds. In this method, artificially altered exposure values for 15 job titles with measured exposure values (test exposures) were mixed with the estimated exposures for 15 job titles without measured exposure values. One third of the test exposure estimates were constructed to be too low and one third too high compared with the measured values. This set was sent to our plant contacts for review. Their corrected test exposures were in complete agreement with the measured values. Although the plant personnel may have been aware of the sampling results or may have had access to these results, their influence on the calibration is unlikely as the PITT investigator of the current study possessed all the original documents.

For several job titles, the available air monitoring data measured could be used to check the validity of the classification scheme by use of all the available measured concentration data to obtain an arithmetic mean for the corresponding ranks. The mean calculated for each rank fell in the intervals assigned for that rank. Although this crude validity check does not provide a full verification of the estimation method, no gross errors were identified. The job class specific classifications were reviewed by plant personnel, who disagreed with or corrected < 10% of data. None of the corrections pertained to a major class of workers, and the values suggested by the plant personnel were then accepted.

Appendix D: Descriptive analysis of selected Wallingford plant historical exposure data developed for the current study and for the National Cancer Institute study

Methods for Comparative Analysis

The analysis compares individual Wallingford worker exposure values for formaldehyde with and without regard to particulate exposure, as developed independently for the current study and the National Cancer Institute study.¹ The analysis was performed in both a matched and unmatched fashion and was limited to white males.

Matched analysis—Here an effort was made to locate all white male study members who appeared on both cohort files. Because individual identifiers were unavailable on our version of the National Cancer Institute file, common members were located by matching records on exact date of birth and exact

Appendix C: Definitions of classification factors (covariates) used in the Poisson regression modelling of cohort rates and SMRs for mortality from lung cancer

Covariate	Symbol	Levels	
		n	Definition
Age group	—	2	< 65, ≥ 65 (y)
Calendar period	—	3	1945–69, 1970–79, 1980–84
Year of hire	—	3	1941–46, 1947–56, 1957–84
Time since first employment	—	3	< 20, 20–29, ≥ 30 (y)
Duration of employment	—	3	< 5, 5–19, ≥ 20 (y)
Cumulative formaldehyde exposure	TWE (F)	4	0, < 0.05, 0.05–1.0, ≥ 1.0 (ppm-y)
Cumulative formaldehyde and product particulates	TWE (F/PP)	4	0, < 0.05, 0.05–1.0, ≥ 1.0 (ppm-y)
Cumulative formaldehyde and non-product particulates	TWE (F/NPP)	4	0, < 0.05, 0.05–1.0, ≥ 1.0 (ppm-y)
Cumulative formaldehyde and pigment	TWE (F/Pig)	2	0, > 0
Cumulative product particulate exposure	TWE (PP)	4	0, < 0.01, 0.01–0.25, ≥ 0.25 (mg/m ³ -y)
Cumulative non-product particulate exposure	TWE (NPP)	4	0, < 0.01, 0.01–0.25, ≥ 0.25 (mg/m ³ -y)
Duration of exposure to formaldehyde	DUR (F)	4	0, < 0.5, 0.5–5.0, ≥ 5.0 (y)
Duration of exposure to product particulates	DUR (PP)	4	0, < 0.5, 0.5–5.0, ≥ 5.0 (y)
Duration of exposure to non-product particulates	DUR (NPP)	4	0, < 0.5, 0.5–5.0, ≥ 5.0 (y)
Duration of exposure to pigment	DUR (Pig)	3	0, < 0.5, ≥ 0.5 (y)
Duration of exposure to formaldehyde ≥ 0.2	DUR (F ≥ 0.2)	4	0, < 0.5, 0.5–5.0, ≥ 5.0 (y)
Duration of exposure to formaldehyde ≥ 0.7	DUR (F ≥ 0.7)	3	0, < 0.5, ≥ 0.5 (y)
Average exposure to formaldehyde*	AIE (F)	2	< 0.1, ≥ 0.1 (ppm)
Average exposure to formaldehyde and product particulates*	AIE (F/PP)	2	< 0.1, ≥ 0.1 (ppm)
Average exposure to formaldehyde and non-product particulates*	AIE (F/NPP)	2	< 0.1, ≥ 0.1 (ppm)
Average exposure to formaldehyde and pigment*	AIE (F/Pig)	2	< 0.1, ≥ 0.1 (ppm)

*Based on exposed jobs only.

date of hire. Although the matched analysis is limited to a subset of the two Wallingford cohorts, it does provide the most direct comparison of the exposures estimated in the two studies.

Before matching, the two white male cohort files were made as comparable as possible by defining a common Wallingford cohort as:

- All white male workers hired between plant start up (around 1941) and 31 December 1965
- Exclude workers who died before 1945
- Mortality follow up to the end of 1979
- Exposure values were computed from date of hire to date of end of employment or 31 December 1979

To meet these criteria the following changes were made to the present cohort file:

- Exclude workers hired after 1965
- Workers employed after 31 December 1979 were censored on 31 December 1979

The matching on exact dates of birth and hire resulted in the numbers of study members (table D-1):

Possible reasons for the discrepancies include:

- Discrepancies in birth and hire dates
- Differences in cohort inclusion criteria relative to job title, work area, etc
- Different records available or missing at the plant site during the time of the two cohort enumerations

The matched analysis was based on the 2990 records present in both files. It is not known whether the reasons for the discrepancies are in any way related to formaldehyde exposures at the plant.

Table D-1 Results of matched analysis

	In present file	Not in present file	Total
In National Cancer Institute file	2990	666	3656
Not in National Cancer Institute file	1758	—	1758
Total	4748	666	5414

Table D-1a Results of matched analysis (n = 2990)

	Present study		
	Exposed to F	Unexposed to F	Total
NCI study:			
Exposed to F	2519	216	2735
Unexposed to F	12	243	255
Total	2531	459	2990

Table D-1b Results of matched analysis (n = 2990)

	Present study		
	Exposed to F/Part	Unexposed to F/Part	Total
NCI study:			
Exposed to F/Part	2466	213	2679
Unexposed to F/Part	30	281	311
Total	2496	494	2990

Table D-2 Results of matched analysis (n = 2990)

	DOE		DUR (F)		DUR (F)/Part		TWE (F)		TWE (F)/Part		AIE (F)		AIE (F)/Part	
	NCI	Present	NCI	Present	NCI	Present	NCI	Present	NCI	Present	NCI	Present	NCI	Present
Min	0.08	0.08	0	0	0	0	0	0	0	0	0	0	0	0
25%	0.33	0.31	0.21	0.15	0.18	0.14	0.21	0	0.19	0	0.60	0.02	0.56	0.02
50%	1.36	1.16	0.75	0.57	0.61	0.52	0.73	0.05	0.59	0.05	1.00	0.07	0.98	0.08
75%	8.23	7.63	4.69	3.64	3.50	2.98	3.80	0.47	2.89	0.40	1.16	0.20	1.15	0.20
Max	38.16	37.84	37.95	36.32	37.95	34.00	45.28	22.68	34.92	22.68	2.06	0.70	2.06	0.70
Mean	6.19	5.97	4.63	3.95	3.91	3.30	3.32	0.63	2.75	0.63	0.87	0.12	0.85	0.12
SD	9.03	8.99	7.72	7.07	6.98	6.16	5.52	1.65	4.76	1.65	0.41	0.14	0.42	0.14
Corr	0.99		0.90		0.72		0.79		0.72		0.33		0.29	

NCI = National Cancer Institute; Min = minimum value; 25% = 25th percentile value; 50% = 50th percentile value (median); 75% = 75th percentile value; Max = Maximum value; Mean = Arithmetic mean; Corr = Correlation coefficient (Pearson); Refer to appendix C for definitions of exposure variables.

Unmatched analysis—In this analysis exposure values were computed separately for the 3656 study members in the National Cancer Institute file and the 4748 study members in the current study file, under the assumption that these cohorts were comparably defined. Although it is known that these cohorts contain a relatively large number of different members, this analysis does relate more closely to the actual cohorts that were studied.

For each study member the following exposure indicators were computed across the entire work history, where particulate exposure refers to exposure to either product or non-product particulates:

- Duration of employment regardless of exposure (DOE)
- Duration of exposure
 - To formaldehyde (DUR(F))
 - To formaldehyde in the presence of particulates (DUR(F)/Part)
- Cumulative exposure (time weighted)
 - To formaldehyde (TWE(F))
 - To formaldehyde in the presence of particulates (TWE(F)/Part)
- Average intensity of exposure computed across exposed jobs only
 - To formaldehyde (AIE(F))
 - To formaldehyde in the presence of particulates (AIE(F)/Part)

Results

Matched analysis—Tables D-1a and D-1b show the distribution of the 2990 pairs according to qualitative exposure to F and F/Part. Overall, the agreement is good between the two studies. For exposure to F and F/Part there is a greater frequency of pairs classified as exposed by National Cancer Institute and unexposed by the present study compared with the opposite classification.

Table D-2 shows selected summary statistics for the exposure indicators computed in the two studies. In general, the agreement is excellent for DOE and DUR(F), good for DUR(F)/Part, TWE(F) and TWE(F)/Part and poor for AIE(F) and AIE(F)/Part. The median AIE(F) and AIE(F)/Part values from National Cancer Institute are more than ten times larger than the corresponding values from the present study.

Unmatched Analysis—Table D-3 shows selected summary statistics for the exposure indicators computed in the two studies. It is more difficult to assess comparability here due to the different study members in each file. Nevertheless, the basic patterns observed in the matched analysis (table D-2) are evident.

Table D-4 shows the distribution of study members by qualitative exposure status to F and F/Part. As in the matched analysis, the overall level of agreement is good, with a somewhat larger percentage of study members assigned to F and F/Part exposures in the National Cancer Institute study.

This project was supported by a contract between the University of Pittsburgh and the American Cyanamid Company. We gratefully acknowledge the assistance and cooperation of Dr James Collins, Larry Drapela, and Judy Saipher, as well as other American Cyanamid Company employees and former employees who participated in this research effort. In

Table D-3 Results of unmatched analysis NCI (n = 3656), present study (n = 4748)

	DOE		DUR (F)		DUR (F)/Part		TWE (F)		TWE (F)/Part		AIE (F)		AIE (F)/Part	
	NCI	Present	NCI	Present	NCI	Present	NCI	Present	NCI	Present	NCI	Present	NCI	Present
Min	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25%	0.34	0.15	0.22	0.04	0.18	0.04	0.22	0	0.19	0	0.60	0.02	0.57	0.02
50%	1.41	0.64	0.77	0.31	0.63	0.29	0.76	0.02	0.61	0.02	1.00	0.05	0.98	0.05
75%	8.67	4.55	5.02	2.15	3.76	1.85	3.89	0.29	3.14	0.26	1.16	0.20	1.15	0.20
Max	38.16	38.15	37.95	36.32	37.95	34.00	45.28	22.68	40.52	22.68	2.16	0.70	2.16	0.70
Mean	6.25	4.88	4.70	3.20	4.02	2.67	3.38	0.51	2.83	0.50	0.88	0.11	0.85	0.12
SD	9.03	8.38	7.82	6.51	7.07	5.66	5.55	1.44	4.84	1.43	0.42	0.14	0.42	0.14

NCI = National Cancer Institute; Min = minimum value; 25% = 25th percentile value; 50% = 50th percentile value (median); 75% = 75th percentile value; Max = maximum value; Mean = arithmetic mean; refer to appendix C for definitions of exposure variables.

Table D-4 Results of unmatched analysis: National Cancer Institute (n = 3656), present study (n = 4748)

	Exposure to F		Exposure to F/Part	
	Ever exposed n (%)	Never exposed n (%)	Ever exposed n (%)	Never exposed n (%)
National Cancer Institute study	3351 (91.7)	305 (8.3)	3284 (89.8)	372 (10.2)
Present study	3953 (83.3)	795 (16.7)	3897 (82.1)	851 (17.9)

particular, we acknowledge the assistance of Dr Lorraine Lucas who also contributed many helpful comments on the manuscript. We also acknowledge the work of the University of Pittsburgh staff: Stephen Sefcik, Michele LaValley, Howard Lebow, and Linda Kobus.

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