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# Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde

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**Objectives:** To assess the possible relationship between formaldehyde exposure and mortality risk from pharyngeal cancer (PC), in particular nasopharyngeal cancer (NPC). **Methods:** Subjects were 7328 workers employed at a plastics-producing plant (1941–1984). Vital status for 98% of the cohort and cause of death for 95% of 2872 deaths were determined. Reconstructed exposures to formaldehyde, particulates and pigment were used to compute several exposure measures. Standardized mortality ratios (SMRs) were computed for several demographic, work history and formaldehyde exposure variables. In a nested case-control study, seven cases of NPC and 15 cases of other PC were matched on race, sex, age and year of birth to four controls from the cohort. Among interviewed subjects, lifetime smoking history was determined using respondents or proxies for all but one control subject. **Results:** Statistically significant 2.23-fold and fivefold excesses for PC and NPC, respectively, were observed. Fivefold range NPC excesses were observed for both short (< 1 year) and long-term workers and were concentrated among workers hired during 1947–1956. Only three NPC cases were exposed to formaldehyde for longer than one year, and each had low average intensity of formaldehyde exposure (0.03–0.60 ppm). Only a few exposure measures revealed some evidence of an association with all PC or NPC. For all PC combined, adjustment for smoking and year-of-hire in the case-control study generally corroborated findings from the cohort study. **Conclusions:** Overall, the pattern of findings suggests that the large, persistent nasopharyngeal and other PC excesses observed among the Wallingford workforce are not associated with formaldehyde exposure, and may reflect the influence of nonoccupational risk factors or occupational risk factors associated with employment outside the Wallingford plant. *Toxicology and Industrial Health* 2002; **18**: 257–268.

**Key words:** case-control study; chemical workers; cohort study; formaldehyde; nasopharyngeal cancer; occupational diseases; particulates; pharyngeal cancer; pigment

## Introduction

Since the early 1980s, when inhalation studies in laboratory animals showed that exposure to formaldehyde could cause nasal cancer in rats (Swenberg *et al.*, 1980; Albert *et al.*, 1982), the

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carcinogenic potential of formaldehyde in humans has been the subject of extensive research and controversy. While one review and two meta-analyses of the available epidemiologic evidence concluded that nasopharyngeal cancer (NPC) is associated with formaldehyde exposure (International Program on Chemical Safety, 1989; Blair *et al.*, 1990; Partanen, 1993), a recent meta-analysis of 47 studies concluded that the available studies do not support a causal association (Collins *et al.*, 1997). Other reviews have concluded that insufficient evidence exists for a causal relation between formaldehyde exposure and cancer risk (Purchase and Paddle, 1989; McLaughlin, 1994). The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a 'probable' (2A) human carcinogen based on limited human evidence and sufficient animal evidence (International Agency for Research on Cancer, 1995).

Our study involves workers from a plastics producing facility in Wallingford, CT, operated by Cytec Industries, Inc., since 1941. It is one of ten formaldehyde using or producing plants in the US included in an ongoing National Cancer Institute (NCI) cohort mortality study (Blair *et al.*, 1986). In 1987, the University of Pittsburgh, Department of Biostatistics (UPitt) began an independent, extended investigation of total and cause-specific mortality among a cohort of Wallingford workers hired between 1941 and 1984 to examine possible associations between exposures to formaldehyde and/or particulates and pigment and cancers of the lung and pharynx, which were elevated in the NCI study (Blair *et al.*, 1986; 1987). In particular, four of seven NPC deaths identified in the combined ten-plant NCI study occurred among white male Wallingford workers, resulting in a statistically significant 3.18-fold excess based on standardized comparisons with US mortality rates (Blair *et al.*, 1986).

In 1994, we confirmed the mortality excess for NPC based on the same four cases reported by NCI (Blair *et al.*, 1986) and found no new NPC cases in the extended 1980–1984 follow-up period (Marsh *et al.*, 1994). Using historical exposure estimates derived from an independent exposure assessment of the Wallingford plant, we also examined the association between selected cancer sites (NPC and lung cancer) and exposure to formaldehyde alone

or in combination with particulates or pigment (Marsh *et al.*, 1996). These analyses revealed little evidence of a causal association between formaldehyde exposure and lung cancer or NPC.

Subsequent 1995 and 1998 follow-ups of the Wallingford cohort focused on NPC and other cancers of the upper respiratory tract and included the updating of work histories and associated formaldehyde exposure. The 1998 follow-up also included a new nested case-control study of NPC and other pharyngeal cancers (PCs). We report here results of the 1998 follow-up.

## Methods

### Historical cohort study

#### *Study population*

Our original study population included 7359 workers employed at Wallingford between 1941 and 1984. The 1984 follow-up focused on 6040 white males at risk during 1945–1998 (Marsh *et al.*, 1996). This 1998 follow-up included all Wallingford workers at risk during 1945–1998 ( $n = 7328$  or 99.6% of the total population). Table 1 shows the cohort consists mostly of white males (82%), and the majority (54%) worked less than one year. More than 1300 workers (18%) were employed for ten or more years, and more than 60% of the total cohort has now been followed for 30 or more years. The year of hire categories in Table 1 reflect four distinct phases of the plant's history that are roughly correlated with exposure levels to formaldehyde and particulates (1941–1946 highest, 1966–1984 lowest) (Marsh *et al.*, 1996).

#### *Exposure assessment*

The work histories of all study members actively employed beyond the 1984 follow-up were updated through 1995, as were exposures to formaldehyde, particulates (product and nonproduct) and pigment using the historical exposure reconstruction methods used in the original study (Marsh *et al.*, 1996). Work histories and exposures were not updated beyond 1995 for the 1998 update. In brief, the exposure estimation 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. A total of 4332 job titles were classified

**Table 1.** Selected demographic and work history characteristics of Wallingford cohort.

| Characteristic                 | Number | Percent |
|--------------------------------|--------|---------|
| <b>Race/Sex</b>                |        |         |
| White male                     | 6040   | 82.4    |
| White female                   | 819    | 11.2    |
| Nonwhite male                  | 415    | 5.7     |
| Nonwhite female                | 54     | 0.7     |
| Total                          | 7328   | 100.0   |
| <b>Year of hire</b>            |        |         |
| 1941–1946                      | 1112   | 15.2    |
| 1947–1956                      | 3050   | 41.6    |
| 1957–1965                      | 1338   | 18.3    |
| 1966–1984                      | 1828   | 24.9    |
| <b>Age at entry into study</b> |        |         |
| < 25                           | 3287   | 44.9    |
| 25–34                          | 2272   | 31.0    |
| 35–44                          | 1124   | 15.3    |
| 45+                            | 645    | 8.8     |
| <b>DOE</b>                     |        |         |
| < 1 month                      | 1069   | 14.6    |
| 1–11.9 months                  | 2905   | 39.6    |
| 1–9 years                      | 2022   | 27.6    |
| 10–19 years                    | 656    | 9.0     |
| 20+ years                      | 676    | 9.2     |
| <b>TSFE (years)</b>            |        |         |
| < 10                           | 441    | 6.0     |
| 10–19                          | 880    | 12.0    |
| 20–29                          | 1437   | 19.6    |
| 30+                            | 4570   | 62.4    |
| <b>Vital status (12/31/98)</b> |        |         |
| Alive                          | 4341   | 59.2    |
| Deceased                       | 2872   | 39.2    |
| with cause of death            | 2735   | (95.2)  |
| without cause of death         | 137    | (4.8)   |
| Unknown                        | 115    | 1.6     |

into 235 groups by similarity of tasks performed and the likelihood for potential exposures as previously described (Esmen, 1979; Corn and Esmen, 1979). The available sampling data were sporadic measurements between 1965 and 1987. Exposures were initially assigned to each job and task on a ranked scale between background (or zero) exposure and high exposure to formaldehyde and particulate matter. Supporting documentation on use of personal protection equipment were used in developing the rankings. These rankings provided seven classes for formaldehyde, and nine classes for product particulate and nonproduct particulate. A range of exposures for each ranking was then assigned to the job categories. For formaldehyde, the classification scheme chosen maximized comparability with that developed in the NCI study (Blair *et al.*, 1986). Pigment exposure was assessed as presence or absence of any pigment.

Our exposure assessment revealed that the median average intensity of exposure (AIE) to formaldehyde for the 5665 exposed workers (0.138 ppm) was lower than the current Occupational Safety and Health Administration (OSHA) standard of 0.75 ppm (OSHA, 1992). The median formaldehyde AIE was slightly higher for the 5104 workers exposed to formaldehyde in jobs with nonproduct particulate exposure (0.20 ppm) and among the 2523 workers exposed to formaldehyde in jobs with pigment exposure (0.20 ppm). Slightly higher proportions of short- rather than long-term workers were exposed to each of the formaldehyde, product particulate and nonproduct particulate, and the combined formaldehyde/(product particulate or nonproduct particulate). However, for each of these measures, the median AIE of long-term workers was at least twice as high as that for short-term workers.

As noted earlier (Marsh *et al.*, 1996), our estimates of median AIE to formaldehyde with and without coexposure to particulates are more than ten times lower than corresponding values estimated for the same Wallingford workers in the NCI study (Blair *et al.*, 1986). This difference may be explained by the fact that the NCI used data from several facilities to estimate exposures in a single facility, including Wallingford, whereas our assessment was based exclusively on Wallingford exposure data. Our lower median AIE is also supported directly by our observation that only nine of 298 available eight-hour time-weighted average (TWA) exposure measurements from Wallingford were greater than 1 ppm and only one of the nine was greater than 3 ppm. The average of this highest measurement and the four other TWA measurements for the same job was less than 1 ppm.

#### ***Vital status tracing and cause of death ascertainment***

All study members without a confirmed cause of death at the end of the 1984 follow-up were traced for deaths through December 31, 1998, utilizing the protocol of Schall *et al.* (Schall *et al.*, 1997; 2001). Underlying cause of death codes were obtained from the National Death Index Plus system or from death certificates obtained from state health departments. Death certificates were coded to the underlying cause of death by a nosologist using the

International Classification of Diseases (ICD) rules in effect at time of death. Table 1 shows that 2872 or 39% of the cohort was identified as deceased and cause of death was obtained for 2735 or 95%. Only 115 or 1.6% of the cohort remains untraced.

## Statistical analyses

### *Analysis of general mortality patterns*

Mortality analyses were limited to malignant neoplasms of the upper and lower respiratory tract and were performed using the Occupational Cohort Mortality Analysis Program (OCMAP-PLUS) (Marsh *et al.*, 1998). Person-years at risk contributed by each study member were jointly classified by race, sex, age group, calendar time, year of hire, duration of employment (DOE) and the time since first employment (TSFE).

We computed expected numbers of deaths, using as standard populations the total US and the local two county area (Middlesex and New Haven Counties) from which the Wallingford workforce was largely drawn. Population-weighted county rates were obtained from the Mortality and Population Data System (MPDS) maintained by the University of Pittsburgh (Marsh *et al.*, 2000). To account for geographic variability, the analyses focused primarily on the local county comparisons (Doll, 1985). Standardized Mortality Ratios (SMRs) and their 95% confidence intervals (CI) were computed for the Wallingford cohort and selected subgroups. Statistically significant deviations of the SMR below and above 1.00 were identified using Poisson probabilities (Breslow and Day, 1987).

### *Analysis in relation to occupational exposure*

For all PC combined and the subcategory NPC, we computed SMRs by occupational exposure to formaldehyde through 1995 (the latest available data) with and without considering coexposures to particulates and pigment. Quantitative formaldehyde exposure measures included duration of exposure, AIE, and cumulative exposure. Other exposure measures considered were: 1) exposure to formaldehyde occurring in the same job, but not necessarily simultaneously, with particulates or pigment; 2) duration of formaldehyde exposure in jobs with average mean formaldehyde exposure, i)

greater than 0.2 ppm; and ii) greater than 0.7 ppm.<sup>1</sup> Methodological details of the exposure measures considered are described elsewhere (Marsh *et al.*, 1996).

## Nested case-control study of NPC and other PC

During the 1945–1998 study period, 22 PC deaths were identified among the Wallingford cohort and included as cases in the nested case-control study. These deaths included the specific sites: oropharynx ( $n=5$ ), nasopharynx ( $n=7$ ) and hypopharynx ( $n=3$ ), as well as deaths coded to the residual category, 'pharynx, unspecified' ( $n=7$ ). Nineteen cases were white males, two were nonwhite males and one was a white female. All seven NPC cases were white males. Although NPC is the site of primary *a priori* interest, other pharyngeal sites were included as cases because: 1) these sites are anatomically contiguous to the nasopharynx, and therefore they are potential target sites of formaldehyde and/or particulate exposures; and 2) mortality excesses for these sites were observed in the NCI study (Blair *et al.*, 1986; 1987) and our 1995 update. Sinonasal cancer deaths were not included as cases because: 1) the sinonasal region of the upper respiratory tract may not be a target site for formaldehyde exposure (Collins *et al.*, 1997; Heck *et al.*, 1989); and 2) the histologic, preneoplastic and etiologic features of sinonasal cancer are distinct from those head and neck cancers arising in contiguous sites (i.e., PC) (Roush, 1996).

Each case was matched on race, sex, age and year of birth (within two years) to four controls from the remaining living and deceased members of the cohort. We attempted to obtain information on lifetime smoking history and relevant exposures outside of Wallingford through structured telephone interviews with the respondent or a knowledgeable informant (usually a surviving family member). We successfully interviewed 15 or 68% of the 22 PC cases, including five (71%) of the seven NPC cases and ten (67%) of the 15 'other PC' cases. Interviews were obtained for 76% of 88 targeted

<sup>1</sup>Our previous Wallingford exposure assessment assigned formaldehyde exposure levels to 162 homogeneous department/job title combinations. Assigned exposures were the geometric means from one of eight formaldehyde exposure categories (Marsh *et al.*, 1996). 0.2 and 0.7 ppm are the geometric means of the two exposure categories close to the current OSHA standard of 0.75 ppm (OSHA, 1992).

controls, including 17 (61%) of 28 targeted NPC controls and 50 (83%) of 60 targeted 'other PC' controls. Among subjects with interview data, basic information on cigarette smoking history (ever/never smoking – all forms of tobacco) was obtained for all but one 'other PC' control. All 15 interviewed PC cases were reported as 'ever' smokers compared with 48 (71.6%) of the 67 interviewed controls. Information on relevant non-Wallingford exposures was limited by a large percentage of 'unknown' responses.

The statistical analysis of the case-control data included multivariate modeling of estimated odds ratios (OR) using exact conditional logistic regression (Breslow and Day, 1980; Cytel Software, 1993). Due to sparse data, modeling was not performed separately for NPC. For ORs showing a positive monotonic or nearly monotonic trend with increasing level of formaldehyde exposure, we computed trend test *P*-values. Because work history and exposure data were available at the cohort level, models included all 22 cases and 88 matched controls. For smoking history, we formed a separate category ('unknown') for subjects who were not contacted or were contacted but responded 'unknown'. Other variables were categorized as in the cohort analysis (Table 4). The 'unexposed' category was used as the baseline of the OR if the number of observed cases was at least five, otherwise, the unexposed and lowest exposure categories were combined to construct a more stable baseline category. Due to the small number of cases in some subcategories of the variables considered, certain risk sets (a case and its matched controls) for a given study factor were uninformative for estimating ORs. This contributed to some *P*-values close to 1.0 and/or very large 95% CIs for ORs. In the presence of many uninformative risk sets, the OR was estimated using a less robust 'median unbiased estimator (MUE)' approach (Cytel Software, 1993).

## Results

### Cohort study

Table 2 presents for the combined 1945–1998 study period, observed deaths and US and local rate-based SMRs for subcategories comprising the

upper and lower respiratory tracts. Based on local county rates, a statistically significant 1.52-fold excess was observed for the combined buccal cavity and pharynx category. This includes a statistically significant 2.23-fold excess for PC combined and a statistically significant fivefold excess based on seven deaths for NPC, the primary site of *a priori* interest.<sup>2</sup> Similar, though not statistically significant, excesses of 1.80-, 1.52- and 1.89-fold were observed for cancers of the oropharynx, hypopharynx and 'pharynx-unspecified site', based on five, three and seven deaths, respectively.

For the combined respiratory system cancer category, Table 2 shows a statistically significant 1.22-fold excess (county comparison) based on 278 observed deaths. A not statistically significant 3.06-fold excess based on three deaths was observed for sinonasal cancer, including a statistically significant 10.96-fold excess based on two deaths for the subcategory 'other specified sinus' (includes the ethmoid, frontal and sphenoidal sinuses) and a statistically significant 1.21-fold excess based on 262 deaths for cancer of the bronchus, trachea, lung. US rate-based SMRs for the buccal cavity and PC categories were generally higher than those based on local rates; those for respiratory system cancer were generally lower. SMRs in the 1985–1998 update period were generally similar to those observed in the previous 1945–1984 period.

Table 3 shows county rate-based SMRs for all PC and NPC according to selected work history and formaldehyde exposure measures. Short- and long-term workers experienced similarly elevated SMRs for both cancer categories. Most PC and NPC cases occurred among workers hired between 1947 and 1956, resulting in the largest and statistically significant SMRs of 3.24 and 8.13, respectively. SMRs for neither PC nor NPC were associated with DOE, while SMRs for all PC increased with increasing TSFE. Twenty of the 22 PC cases and all seven NPC cases had some exposure to formaldehyde, resulting in statistically significant SMRs of 2.42 and 6.03, respectively.

<sup>2</sup>During the 1985–1998 update period, we observed an additional three deaths from NPC and six deaths from 'other PC'. The 1985–1998 SMR for NPC was 4.89 (based on 0.61 expected deaths) and statistically significant. In the previous 1945–1984 follow-up, a similar, statistically significant SMR for NPC of 5.08 was observed (four observed versus 0.79 expected deaths).

**Table 2.** Observed deaths and SMRs for selected cancer site categories, Wallingford Cohort, 1945–1998, US and local county comparisons (no. at risk = 7328, person-years = 240997).

| Cause of death (ICDA 9th revision codes)           | Observed | United States |            | Local County |            |
|--|----------|---------------|------------|--------------|------------|
|  |          | SMR           | 95% CI     | SMR          | 95% CI     |
| All malignant neoplasms (140–208)                  | 757      | 1.08          | 1.00–1.15  | 1.06         | 0.99–1.14  |
| Buccal cavity and pharynx (140–149)                | 31       | 1.80**        | 1.22–2.55  | 1.52*        | 1.03–2.15  |
| Lip (140)  | 1        | 3.23          | 0.08–18.00 | 7.75         | 0.19–43.19 |
| Tongue (141)                                       | 3        | 0.76          | 0.16–2.22  | 0.61         | 0.13–1.78  |
| Major salivary glands (142)                        | 0        | –             | 0–3.18     | –            | 0–3.06     |
| Gum and other mouth unspecified (143, 145)         | 3        | 1.20          | 0.25–3.51  | 1.01         | 0.21–2.95  |
| Floor of the mouth (144)                           | 2        | 2.07          | 0.25–7.48  | 1.48         | 0.18–5.35  |
| Pharyngeal (146–149)                               | 22       | 2.63**        | 1.65–3.98  | 2.23**       | 1.40–3.38  |
| Oropharynx (146)                                   | 5        | 2.17          | 0.71–5.07  | 1.80         | 0.58–4.19  |
| Nasopharynx (147)                                  | 7        | 4.94**        | 1.99–10.19 | 5.00**       | 2.01–10.30 |
| Hypopharynx (148)                                  | 3        | 2.25          | 0.46–6.58  | 1.52         | 0.31–4.43  |
| Pharynx, unspecified (149.0)                       | 7        | 2.11          | 0.85–4.35  | 1.89         | 0.76–3.89  |
| Respiratory system (160–165)                       | 278      | 1.12          | 0.99–1.26  | 1.22**       | 1.08–1.38  |
| Sinonasal (160)                                    | 3        | 3.10          | 0.64–9.07  | 3.06         | 0.63–8.93  |
| Nose (internal) and nasal cavities (160.0)         | 0        | –             | 0–33.42    | –            | 0–47.99    |
| Eustachian tube and middle ear (160.1)             | 0        | –             | 0–148.66   | –            | 0–128.04   |
| Maxillary Sinus (160.2)                            | 0        | –             | 0–8.01     | –            | 0–7.97     |
| Other specified sinus (160.3, 160.4, 160.5, 160.8) | 2        | 16.94*        | 2.05–61.20 | 10.96*       | 1.33–39.58 |
| Sinus site unspecified (160.9)                     | 1        | 5.59          | 0.14–31.16 | 7.17         | 0.18–39.95 |
| Larynx (161)                                       | 13       | 1.50          | 0.80–2.57  | 1.59         | 0.84–2.71  |
| Bronchus, trachea, lung (162)                      | 262      | 1.11          | 0.98–1.25  | 1.21**       | 1.06–1.36  |

\* $P < 0.05$ .

\*\* $P < 0.01$ .

Overall, for both PC and NPC, Table 3 shows little consistent evidence of increasing mortality risks with increasing levels of the measures considered. Excess deaths were observed in both the baseline and nonbaseline categories of all the measures and many are statistically significant. For PC, only DOE in jobs with formaldehyde exposures  $> 0.2$  ppm revealed limited evidence of an association with mortality risk. For NPC, we observed limited evidence of an association with increasing duration of exposure to formaldehyde, cumulative exposure to formaldehyde or DOE in jobs with formaldehyde exposures  $> 0.2$  ppm or  $> 0.7$  ppm. Our findings for formaldehyde were not materially altered when coexposures to particulates or pigment were considered (data not shown).

### Case-control study

Table 4 summarizes the exact conditional logistic regression modeling results for all PC combined. Shown for each model are the observed number of cases, the estimated OR and 95% CI, and the global test  $P$ -value (test of main effect). Among the potential confounding variables considered in the univariate models, only smoking history and year of hire were statistically significant predictors of case-control status (borderline for smoking-global

$P = 0.055$ ). The estimated OR for workers who ever smoked was 8.03, which is higher than the risks observed for PCs in other case-control studies. (Blot *et al.*, 1998; Yu *et al.*, 1996). The 7.62-fold risk for the ‘unknown’ category suggests that most of these subjects were probably smokers. Year of hire showed the strongest association (global  $P = 0.026$ ) with PC, with workers hired in 1947–1956 having a 10.07-fold risk of PC compared with workers hired 1941–1946.

Table 4 reveals limited evidence of an increasing trend in ORs for PC with increasing levels of DOE in jobs with formaldehyde exposure greater than 0.2 ppm (Dur (formaldehyde  $> 0.2$  ppm)) (trend test  $P = 0.210$ ). Only one of the formaldehyde exposure variables considered in the univariate models (cumulative exposure to formaldehyde in the presence of pigment) was a statistically significant predictor (global  $P = 0.012$ ) of PC risk; however, there was no evidence of a trend in risk with increasing exposure (data not shown).

Most of the models adjusted for smoking and year of hire yielded similar OR estimates as the corresponding unadjusted models suggesting generally weak confounding effects of smoking and year of hire. Adjusted models revealed some evidence of an increasing trend in ORs with

**Table 3.** Observed deaths and SMRs for all PC and NPC, total Wallingford cohort, 1945–1998, local county comparison, by selected work history and formaldehyde exposure indicators.

| Work history/exposure indicator                        | All pharyngeal cancer ( <i>n</i> = 22) |        |            | Nasopharyngeal cancer ( <i>n</i> = 7) |         |            |
|--|--|--------|------------|---------------------------------------|---------|------------|
|  | Observed                               | SMR    | 95% CI     | Observed                              | SMR     | 95% CI     |
| Short-term workers (< 1 year) <sup>a</sup>             | 12                                     | 2.35*  | 1.22–4.11  | 4                                     | 5.35*   | 1.46–13.71 |
| Long-term workers (1+ years)                           | 10                                     | 2.10*  | 1.01–3.86  | 3                                     | 4.59    | 0.95–13.42 |
| Year of hire   |  |        |            |                                       |         |            |
| 1941–1946  | 1                                      | 0.46   | 0.01–2.56  | 0                                     | –       | 0–13.10    |
| 1947–1956  | 18                                     | 3.24*  | 1.92–5.12  | 6                                     | 8.13**  | 2.98–17.69 |
| 1957+  | 3                                      | 1.41   | 0.29–4.12  | 1                                     | 2.63    | 0.07–14.64 |
| DOE (years) (all workers)                              |  |        |            |                                       |         |            |
| < 1  | 12                                     | 2.34*  | 1.21–4.09  | 4                                     | 5.33*   | 1.45–13.64 |
| 1–9  | 5                                      | 1.89   | 0.61–4.42  | 1                                     | 2.62    | 0.06–14.57 |
| 10+  | 5                                      | 2.36   | 0.76–5.50  | 2                                     | 7.49    | 0.91–27.06 |
| TSFE (years)   |  |        |            |                                       |         |            |
| < 20   | 4                                      | 1.41   | 0.38–3.61  | 2                                     | 5.01    | 0.61–18.08 |
| 20–29  | 7                                      | 2.32   | 0.93–4.78  | 3                                     | 8.72*   | 1.80–25.48 |
| 30+  | 11                                     | 2.75*  | 1.37–4.92  | 2                                     | 3.04    | 0.37–11.00 |
| Formaldehyde exposure measures                         |  |        |            |                                       |         |            |
| Exposure to formaldehyde                               |  |        |            |                                       |         |            |
| Unexposed  | 2                                      | 1.24   | 0.15–4.49  | 0                                     | –       | 0–15.41    |
| Exposed  | 20                                     | 2.42** | 1.48–3.74  | 7                                     | 6.03**  | 2.42–12.42 |
| Duration of exposure to formaldehyde (years)           |  |        |            |                                       |         |            |
| Unexposed  | 2                                      | 1.24   | 0.15–4.49  | 0                                     | –       | 0–15.41    |
| > 0– < 1   | 11                                     | 2.35*  | 1.17–4.21  | 4                                     | 5.84*   | 1.59–14.94 |
| 1–9  | 4                                      | 1.81   | 0.49–4.63  | 1                                     | 3.17    | 0.08–17.68 |
| 10+  | 5                                      | 3.65*  | 1.18–8.52  | 2                                     | 12.46*  | 1.51–45.02 |
| Cumulative exposure to formaldehyde (ppm – years)      |  |        |            |                                       |         |            |
| Unexposed  | 2                                      | 1.24   | 0.15–4.49  | 0                                     | –       | 0–15.41    |
| > 0– < 0.004   | 6                                      | 3.31   | 1.22–7.21  | 1                                     | 3.97    | 0.10–22.10 |
| 0.004–0.219  | 7                                      | 2.06   | 0.83–4.24  | 3                                     | 5.89*   | 1.22–17.22 |
| 0.22+  | 7                                      | 2.30   | 0.92–4.73  | 3                                     | 7.51*   | 1.55–21.93 |
| AIE to formaldehyde (ppm)                              |  |        |            |                                       |         |            |
| Unexposed  | 2                                      | 1.24   | 0.15–4.49  | 0                                     | –       | 0–15.41    |
| > 0– < 0.03  | 6                                      | 2.02   | 0.74–4.40  | 1                                     | 2.41    | 0.06–13.44 |
| 0.03–0.159   | 7                                      | 3.82** | 1.54–7.88  | 4                                     | 15.27** | 4.16–39.10 |
| 0.16+  | 7                                      | 2.03   | 0.82–4.19  | 2                                     | 4.13    | 0.50–14.91 |
| Formaldehyde > 0.2 or > 0.7 ppm measures               |  |        |            |                                       |         |            |
| Exposure to formaldehyde > 0.2 ppm                     |  |        |            |                                       |         |            |
| Unexposed  | 8                                      | 1.72   | 0.74–3.39  | 2                                     | 3.01    | 0.36–10.87 |
| Exposed  | 14                                     | 2.68** | 1.46–4.49  | 5                                     | 6.79**  | 2.21–15.85 |
| Duration of exposure to formaldehyde > 0.2 ppm (years) |  |        |            |                                       |         |            |
| Unexposed  | 8                                      | 1.72   | 0.74–3.39  | 2                                     | 3.01    | 0.36–10.87 |
| > 0– < 1   | 6                                      | 2.19   | 0.80–4.77  | 2                                     | 4.81    | 0.58–17.37 |
| 1–9  | 3                                      | 1.68   | 0.34–4.90  | 1                                     | 4.04    | 0.10–22.51 |
| 10+  | 5                                      | 7.35** | 2.39–17.16 | 2                                     | 27.61** | 3.34–99.73 |
| Exposure to formaldehyde > 0.7 ppm                     |  |        |            |                                       |         |            |
| Unexposed  | 16                                     | 2.12** | 1.21–3.45  | 4                                     | 3.64    | 0.99–9.31  |
| Exposed  | 6                                      | 2.55   | 0.94–5.56  | 3                                     | 9.98**  | 2.06–29.17 |
| Duration of exposure to formaldehyde > 0.7 ppm (years) |  |        |            |                                       |         |            |
| Unexposed  | 16                                     | 2.12** | 1.21–3.45  | 4                                     | 3.64    | 0.99–9.31  |
| < 1  | 4                                      | 2.58   | 0.70–6.61  | 2                                     | 9.51*   | 1.15–34.37 |
| 1+   | 2                                      | 2.50   | 0.30–9.03  | 1                                     | 11.07   | 0.28–61.67 |

<sup>a</sup> Does not include short-term experience of long-term workers.

increasing duration of exposure to formaldehyde (trend test  $P = 0.434$ ), and increasing duration of exposure to formaldehyde > 0.2 ppm (trend test

$P = 0.163$ ). The findings for formaldehyde in the adjusted models were not materially altered when coexposures to particulates or pigment were con-

**Table 4.** Case-control study: estimated OR for all PC, univariate and bivariate models<sup>a</sup>.

| Variable <sup>b</sup>  | Observed cases | Univariate (no adjustments) |                              | Adjusted for smoking and year of hire |                              |
|--|----------------|-----------------------------|------------------------------|---------------------------------------|------------------------------|
|  |                | OR (95%CI)                  | <i>P</i> -value <sup>c</sup> | OR (95%CI)                            | <i>P</i> -value <sup>c</sup> |
| <b>Smoking status</b>  |                |                             |                              |                                       |                              |
| Never smoker   | 0              | 1.00                        |                              |                                       |                              |
| Ever smoker  | 15             | 8.03 <sup>d</sup> (1.22–∞)  | –                            | –                                     |                              |
| Unknown or not contacted   | 7              | 7.62 <sup>d</sup> (1.01–∞)  | 0.055                        | –                                     | –                            |
| <b>Year of hire</b>  |                |                             |                              |                                       |                              |
| 1941–1946  | 1              | 1.00                        |                              |                                       |                              |
| 1947–1956  | 18             | 10.07 (1.04–511.07)         |                              | –                                     | –                            |
| 1957+  | 3              | 2.55 (0.09–201.06)          | 0.026                        |                                       |                              |
| <b>Worker type</b>   |                |                             |                              |                                       |                              |
| Short-term workers (< 1 year) <sup>a</sup>                       | 12             | 1.00                        |                              | 1.00                                  |                              |
| Long-term workers (1+ years)                                     | 10             | 0.86 (0.28–2.53)            | 0.811                        | 1.01 (0.30–3.24)                      | 0.999                        |
| <b>DOE (years)</b>   |                |                             |                              |                                       |                              |
| < 1  | 12             | 1.00                        |                              | 1.00                                  |                              |
| 1–9  | 5              | 0.82 (0.20–2.87)            |                              | 0.91 (0.22–3.22)                      |                              |
| 10+  | 5              | 0.93 (0.21–3.54)            | 0.951                        | 1.37 (0.20–8.86)                      | 0.934                        |
| <b>TSFE (years)</b>  |                |                             |                              |                                       |                              |
| < 20   | 4              | 1.00                        |                              | 1.00                                  |                              |
| 20–29  | 7              | 0.85 (0.16–5.78)            |                              | 0.23 (0.01–2.68)                      |                              |
| 30+  | 11             | 0.74 (0.11–5.86)            | 0.999                        | 0.24 (0.003–5.69)                     | 0.474                        |
| <b>Formaldehyde exposure measures</b>                            |                |                             |                              |                                       |                              |
| <b>Exposure to formaldehyde</b>                                  |                |                             |                              |                                       |                              |
| Unexposed  | 2              | 1.00                        |                              | 1.00                                  |                              |
| Exposed  | 20             | 1.88 (0.38–18.51)           | 0.524                        | 3.04 (0.36–145.58)                    | 0.433                        |
| <b>Duration of exposure to formaldehyde (years)</b>              |                |                             |                              |                                       |                              |
| < 1  | 13             | 1.00                        |                              | 1.00                                  |                              |
| 1–9  | 4              | 0.86 (0.17–3.32)            |                              | 1.01 (0.19–4.42)                      | 0.615                        |
| 10+  | 5              | 1.52 (0.34–6.23)            | 0.745                        | 2.23 (0.34–14.97)                     | (0.434)                      |
| <b>Cumulative exposure to formaldehyde (ppm – years)</b>         |                |                             |                              |                                       |                              |
| < 0.004  | 8              | 1.00                        |                              | 1.00                                  |                              |
| 0.004–0.219  | 7              | 0.71 (0.20–2.43)            |                              | 0.89 (0.22–3.56)                      |                              |
| 0.22+  | 7              | 0.79 (0.18–3.20)            | 0.824                        | 0.81 (0.13–4.34)                      | 0.999                        |
| <b>AIE to formaldehyde (ppm)</b>                                 |                |                             |                              |                                       |                              |
| < 0.03   | 8              | 1.00                        |                              | 1.00                                  |                              |
| 0.03–0.159   | 7              | 1.71 (0.47–6.10)            |                              | 1.80 (0.45–7.47)                      |                              |
| 0.16+  | 7              | 0.99 (0.27–3.55)            | 0.549                        | 0.86 (0.17–3.74)                      | 0.509                        |
| <b>Formaldehyde &gt; 0.2 or 0.7 ppm exposure measures</b>        |                |                             |                              |                                       |                              |
| <b>Exposure to formaldehyde &gt; 0.2 ppm</b>                     |                |                             |                              |                                       |                              |
| Unexposed  | 8              | 1.00                        |                              | 1.00                                  |                              |
| Exposed  | 14             | 1.35 (0.45–4.25)            | 0.625                        | 1.27 (0.35–4.88)                      | 0.776                        |
| <b>Duration of exposure to formaldehyde &gt; 0.2 ppm (years)</b> |                |                             |                              |                                       |                              |
| Unexposed  | 8              | 1.00                        |                              | 1.00                                  |                              |
| > 0 – < 1  | 6              | 1.02 (0.26–3.79)            |                              | 1.13 (0.24–5.29)                      |                              |
| 1–9  | 3              | 1.19 (0.17–6.26)            | 0.422                        | 1.38 (0.18–9.03)                      | 0.287                        |
| 10+  | 5              | 3.28 (0.56–20.45)           | (0.210)                      | 9.49 (0.55–701.35)                    | (0.163)                      |
| <b>Exposure to formaldehyde &gt; 0.7 ppm</b>                     |                |                             |                              |                                       |                              |
| Unexposed  | 16             | 1.00                        |                              | 1.00                                  |                              |
| Exposed  | 6              | 1.60 (0.15–9.77)            | 0.633                        | 1.30 (0.08–21.59)                     | 0.999                        |
| <b>Duration of exposure to formaldehyde &gt; 0.7 ppm (years)</b> |                |                             |                              |                                       |                              |
| Unexposed  | 16             | 1.00                        |                              | 1.00                                  |                              |
| < 1  | 4              | 0.76 (0.17–2.69)            |                              | 0.52 (0.08–2.45)                      |                              |
| 1+   | 2              | 1.48 (0.14–9.42)            | 0.787                        | 1.11 (0.06–11.31)                     | 0.639                        |

<sup>a</sup> Controls individually matched to cases on exact age, year of birth ( $\pm 2$  years), race and sex; controls sampled from risk sets derived from cohort.

<sup>b</sup> If unexposed category of exposure variable included < 5 cases, the baseline category and lowest exposure category were combined.

<sup>c</sup> Global test *P*-value of main effect; trend test *P*-value shown in parentheses if ORs display a positive monotonic (or nearly monotonic) trend.

<sup>d</sup> Estimate based on less robust MUE.

sidered (data not shown). In unadjusted and adjusted models, workers who had some exposure to formaldehyde had an elevated PC risk compared with unexposed workers, but long-term workers ( $\geq 1$  year) showed a reduced or nearly equal risk compared to short-term workers.

## Discussion and conclusions

The Wallingford historical cohort study provides an important epidemiological resource for evaluating long-term health effects of occupational exposure to formaldehyde, alone or in combination with exposures to particulates and pigment. It also offers a valuable contrast to the larger ten-plant NCI study, which produced much larger exposure formaldehyde estimates for the Wallingford plant (Blair *et al.*, 1986). Strengths of the Wallingford cohort study include a large cohort with a high proportion of older workers, long observation period and sufficient statistical power to detect meaningful excesses for many cause of death categories. Other strengths include excellent follow-up and cause of death ascertainment rates, and the availability of detailed work histories linked to quantitative and qualitative historical exposure estimates for individual workers. A particular strength of this latest update was the new nested case-control study, which enabled risk estimates for all PC combined to be adjusted for potential confounding by smoking history, an unmeasurable variable at the cohort level.

The Wallingford study also has several limitations that impact on the interpretation of the results. One limitation of the cohort study is that more than 50% of the cohort worked at Wallingford for less than one year, which increases the likelihood that unmeasurable, non-Wallingford occupational exposures may have confounded exposure-response relationships in this study. Also, the cohort and nested case-control studies were limited by the small number of PC cases, in particular, NPC cases, which led to low statistical power to detect other than large mortality excesses. The nested case-control study was also limited by the inability to acquire information on potential confounding factors, such as exposure to relevant occupational or nonoccupational risk factors outside the Wallingford plant (Hildesheim and Levine, 1993).

As in the original cohort study (Marsh *et al.*, 1996), this latest update of the Wallingford cohort

and case-control studies provides evidence both for and against a possible association between formaldehyde exposure and mortality risks from PC. This contrasting evidence is discussed below and summarized in Table 5. The evidence that supports a possible association includes: 1) Three additional NPC cancers and six other PC deaths were observed in the 1985–1998 update period; 2) the excess mortality risk for NPC remains in the update period and overall at a statistically significant fivefold level. Excesses of this magnitude are unlikely to be related solely to uncontrolled potential confounding factors, and the use of local county rates reduces the likelihood of bias due to uncontrolled geographic variations in NPC mortality rates; 3) excess risks for other PC sites remain in the 1.5–2.0-fold range; 4) in the cohort and case-control studies, mortality risks for all PC combined (and for NPC in the cohort study) were highest among workers hired during the 1947–1956 period when formaldehyde exposures were known to be higher than later periods. This may reflect the influence of occupational factors at the Wallingford plant that were present at that time or in earlier time periods; alternatively, other factors not accounted for may also be operating; 5) the cohort and case-control studies revealed some evidence of increasing risks for all PC combined with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 ppm; and 6) the cohort study revealed some evidence of increasing NPC risks with increasing duration and cumulative exposure to formaldehyde with and without the presence of particulates, and with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 or 0.7 ppm.

Evidence in this latest update that does not support a possible association includes: 1) For most of the many formaldehyde exposure variables considered in the cohort study, elevated SMRs for all PC combined and NPC were observed in the unexposed and lower exposure categories, as well as the higher exposure categories. Similarly, the case-control analysis of all PC combined revealed elevated ORs for both the lower and higher exposure categories of the same exposure variables; 2) SMRs for all PC combined and NPC were greater among short-term ( $< 1$  year) than long-term workers, a possible reflection of relevant

**Table 5.** Summary of epidemiological evidence for and against an association between formaldehyde exposure and mortality risks from PC, including NPC.

| Evidence for an association   | Evidence against an association  |
|---|--|
| Three additional NPC cancers and six other PC deaths were observed in the 1985–1998 update period.  | For most of the formaldehyde exposure variables considered in the cohort and case-control studies, elevated SMRs for all PC combined and NPC were observed in the unexposed and lower exposure categories as well as the higher exposure categories. |
| The excess mortality risk for NPC remains in the update period and total study period at a statistically significant, fivefold level  | The limited evidence that supports a possible association was not observed consistently across the many formaldehyde exposure measures considered.   |
| Excess risks for other PC sites remain in the 1.5–2.0-fold range.   | SMRs for all PC combined and NPC were greater among short-term (< 1 year) than long-term workers, a possible reflection of relevant exposures received before or after employment at Wallingford.  |
| In the cohort and case-control studies, mortality risks for all PC combined (and for NPC in the cohort study) were highest among workers hired during the 1947–1956 period when formaldehyde exposures were known to be higher than later periods.  | The patterns of findings relative to year of hire (mortality risks for PC and NPC highest among workers hired 1947–1956) may reflect the influence of occupational factors associated with employment before the Wallingford plant.                  |
| The cohort and case-control studies revealed some evidence of increasing risks for all PC combined with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 ppm.   | For most of the 22 PC cases, the very brief periods of Wallingford employment afforded little opportunity for etiologically relevant exposures.  |
| The cohort study revealed some evidence of increasing NPC risks with increasing duration and cumulative exposure to formaldehyde with and without the presence of particulates, and with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 ppm or 0.7ppm.  | A manual review of time period-specific job codes for the 22 PC cases revealed no unusual pattern of jobs compared with a similar review of job codes for the controls used in the case-control study  |
| Conclusion: The short employment periods of most of the cases coupled with patterns of findings relative to year of hire suggests that the NPC and other PC excesses may reflect the influence of occupational factors associated with employment outside the Wallingford plant and/or to non-occupational factors such as those associated with the unknown responses in the case-control study. |  |

exposures received before or after employment at Wallingford; 3) for most of the 22 PC cases, the very brief periods of Wallingford employment afforded little opportunity for etiologically relevant exposures. Only three of the seven NPC cases and six of the 13 other PC cases were exposed to formaldehyde longer than one year, and each had low average intensity of formaldehyde exposure (ranging from 0.02 to 0.60 ppm); 4) the limited evidence that supports a possible association was not observed consistently across the many exposure measures considered; 5) a manual review of time period-specific job codes for the 22 PC cases revealed no unusual pattern of jobs compared with a similar review of job codes for the controls used in the case-control study; and 6) the short employment periods of most of the cases coupled with patterns of findings relative to year of hire suggests that the NPC and other PC excesses may reflect the influence of occupational factors associated with employment before the Wallingford plant and/or to nonoccupational factors, such as those associated with the unknown responses in the case-control study. As noted earlier (Marsh *et al.*,

1996), three of the four original NPC cases were employed before their work at Wallingford in jobs involving exposure to metal fumes or dust, two potential risk factors for NPC (Blot *et al.*, 1998).

In conclusion, although the latest update of the Wallingford cohort study and the new nested case-control study revealed some evidence that supports a possible association between formaldehyde exposure and PC risk, this evidence is outweighed by more compelling evidence that does not support such an association. Overall, the pattern of findings suggests that the large, persistent nasopharyngeal and other PC excesses observed among the Wallingford workforce may reflect the influence of nonoccupational risk factors or occupational risk factors associated with employment outside the Wallingford plant.

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