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Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers

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Abstract

Objective. To investigate further the possibility that the large nasopharyngeal cancer (NPC) mortality excess among a cohort of formaldehyde-exposed workers may be related to occupational factors external to the study plant.
Methods. Subjects were 7345 workers employed at a plastics-producing plant (1941–1984) in Wallingford, Connecticut evaluated independently as part of a National Cancer Institute cohort study. Vital status for 98% of the cohort and cause of death for 95% of 2872 deaths were determined through 2003. Reconstructed worker exposures to formaldehyde were used to compute unlagged and lagged exposure measures. We computed standardized mortality ratios (SMRs) based on US and local county rates. In a nested case–control study we evaluated mortality risks from NPC and from all other pharyngeal cancers combined (AOPC) in relation to formaldehyde exposure while accounting for potential confounding or effect modification by smoking or external (non-Wallingford) employment. Job applications, Connecticut commercial city directories and a previous survey were used to assign subjects to three external job groups.
Results. We observed no new deaths from NPC and one additional AOPC death (pharynx unspecified) yielding, respectively, SMRs of 4.43 (7 deaths, 95% CI = 1.78–9.13) and 1.71 (16 deaths, 95% CI = 1.01–2.72). Five of seven NPC cases worked in silver smithing (including brass plating and other jobs related to silver or brass) or other metal work (including steel working and welding), and this type of work was relatively rare in the remaining study population (OR = 14.41, 95% CI = 1.08–82.1). For AOPC, we found a moderate increase in risk for other metal work (OR = 1.40, 95% CI = .31–5.1). Interaction models suggested that NPC and AOPC risks were not elevated in subjects exposed only to formaldehyde.
Conclusions. The results of our nested case–control study suggest that the large nasopharyngeal cancer mortality excess in the Wallingford cohort may not be due to formaldehyde exposure, but rather reflects the influence of external employment in the ferrous and nonferrous metal industries of the local area that entailed possible exposures to several suspected risk factors for upper respiratory system cancer (e.g., sulfuric acid mists, mineral acid, metal dusts and heat). Our findings may also help to explain why the associations with formaldehyde and nasopharyngeal cancer reported in the 1994 update of the 10-plant NCI formaldehyde cohort study were unique to the Wallingford plant (Plant 1 in NCI study). Further updates of the NCI formaldehyde cohort study should include co-exposure data on silver smithing and other metal work for all study plants to help explain the unique findings for nasopharyngeal cancer in Plant 1 compared with the other nine plants.

Keywords: Formaldehyde; Sulfuric acid; Mineral acid; Metal dust; Silver smithing; Pharyngeal cancer; Nasopharyngeal cancer; Chemical workers; Occupational diseases; Cohort study; Case–control study

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1. Introduction

In 2004, an International Agency for Research on Cancer (IARC) working group categorized formaldehyde as a human carcinogen (Group 1) (IARC, 2006). A key part of the epidemiologic evidence evaluated by IARC was the suggested causal association with formaldehyde exposure and death from nasopharyngeal cancer (NPC) reported in the National Cancer Institute (NCI) historical cohort of industrial workers exposed to formaldehyde (Hauptmann et al., 2004). A reanalysis of the NCI data by Marsh and Youk (2005) showed that NCI's findings for NPC were driven entirely by anomalous findings for one of 10 study plants (Plant 1). That is, six of 10 observed NPC deaths occurred in Plant 1 and the remaining four cases occurred in four of the other nine plants studied by NCI. This led to a large, statistically significant 10.3-fold excess in NPC deaths (SMR = 10.3, 95% CI = 3.8–22.5) for formaldehyde-exposed workers in Plant 1 that contrasted sharply with a 35% deficit in NPC deaths (SMR = 0.65, 95% CI = .08–2.3) for exposed workers in Plants 2–10. NCI also reported a statistically significant exposure-response relationship with peak formaldehyde exposure[1] and NPC (Hauptmann et al., 2004) that was later shown to be driven entirely by the anomalous Plant 1 findings (Marsh and Youk, 2005). In a second reanalysis of the NCI data, Marsh et al. (2007) demonstrated statistically that NCI failed to account explicitly for an important interaction structure between plant group (Plant 1 vs. Plants 2–10) and the peak formaldehyde exposure variable and that this prohibited a generalization of formaldehyde effects within and beyond the NCI cohort.

Since the 1980s, in response to the original findings of the NCI formaldehyde cohort study (Blair et al., 1986), the University of Pittsburgh, Department of Biostatistics has conducted an independent historical cohort mortality study of Plant 1, a plastics producing facility in Wallingford, Connecticut. While our original analysis and subsequent updates of the Wallingford cohort have confirmed the large NPC mortality excess noted by NCI, we have found no consistent evidence of a causal association with formaldehyde exposure and NPC (Marsh et al., 1994, 1996, 2002). Our previous 1998 mortality follow-up, which included a new nested case–control study of pharyngeal cancers, concluded that the Wallingford NPC mortality excess was most likely related to occupational or non-occupational risk factors external to Plant 1 (Marsh et al., 2002). This conclusion was based partly on mostly anecdotal information that some NPC cases were employed before their work at the Wallingford facility in manufacturing jobs involving exposure to metal fumes or dust, two potential risk factors for NPC (Lam and Tan, 1984; Zheng et al., 1992; IARC, 1995; Chang and Adami, 2006). These anecdotal reports were compelling from an epidemiological standpoint, given their concordance with the manufacturing history of the local Wallingford area. In the 19th and early 20th centuries, the Wallingford area was replete with silversmith shops, silverware production and brass plating companies, in addition to iron and steel casting and production facilities. In fact, nearby Meriden, Connecticut was known as the "Silver City of the World" producing the largest volumes of silver and silver-plated wares in the world (McKain, 1954; Gillespie, 1992).

We report here findings of our 2003 mortality follow-up of the Wallingford cohort and update of the nested case–control study. The focus of this update was to investigate NPC mortality risks in relation to occupational risk factors external to the Wallingford plant.

2. Methods

2.1. Historical cohort study

2.1.1. Study population

Our original study population included 7359 workers employed at Wallingford between 1941 and 1984. The previous 1998 follow-up included 7328 workers at risk during 1945–98 (Marsh et al., 2002). This 2003 follow-up included 7345 workers at risk during 1945–2003.[2] Table 1 shows the distribution of subjects by key study factors. The cohort consists mostly of white males (82.4%), and the majority (54.4%) worked less than one year. More than 1300 workers (17.8%) were employed for 10 or more years and 70% of the cohort has now been followed for 30 or more years.

2.1.2. Vital status tracing and cause of death ascertainment

All study members without a confirmed cause of death at the end of the 1998 follow-up were traced for deaths through December 31, 2003 utilizing the protocol of Schall et al. (1997, 2001) as modified by Buchanich et al. (2005). 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. We identified 3516 or 47.9% of the cohort as deceased and obtained cause of death for 3347 or 95.2%. Only 104 or 1.4% of the cohort remained untraced.

[1] Peak formaldehyde exposure was defined by NCI as a 4-level categorical variable (0, .0–<2.0, 2.0–<4.0 and 4.0+ppm). Subjects accrued person-years in peak exposure categories up to the highest peak attained, then all remaining person-years were accrued in the highest peak category regardless of subsequent changes in peak exposure. This approach has been challenged on methodological grounds by Marsh and Youk (2005).

[2] The number of subjects varies slightly from follow-up to follow-up as updated vital status information often affects cohort eligibility. For example, we determined that six of the original subjects had died between 1941–44 (including 1 brain cancer, 1 liver cancer, 1 coronary artery disease, 1 stricture of the urethra, 1 drowning and 1 unknown cause), and 8 subjects who terminated employment before 1945 were lost to follow-up.

Table 1
Selected demographic and work history characteristics of Wallingford cohort

Characteristic	Number	Percent
Race/sex		
White male	6055	82.4
White female	821	11.2
Nonwhite male	415	5.7
Nonwhite female	54	0.7
Total	7345	100.0
Year of hire		
1941–46	1129	15.4
1947–56	3050	41.5
1957–65	1338	18.2
1966–84	1828	24.9
Age at entry into study		
<25	3296	44.9
25–34	2274	31.0
35–44	1127	15.3
45+	648	8.8
Duration of employment		
<1 mo.	1076	14.7
1–11.9 mos.	2915	39.7
1–9 yrs.	2041	27.6
10–19 yrs.	542	7.3
20+ yrs.	771	10.5
Time since first employment		
<10 yrs	296	4.0
10–19	566	7.7
20–29	1346	18.3
30+	5137	70.0
Vital status (12/31/2003)		
Alive	3725	50.7
Deceased	3516	47.9
With cause of death	(3347)	(95.2)
Without cause of death	(169)	(4.8)
Unknown	104	1.4

2.1.3. Exposure assessment

The work histories of all study members actively employed beyond the 1998 follow-up were updated through 2003, as were individual worker exposures to formaldehyde, using the historical exposure reconstruction methods described in detail in the original study and 1998 update (Marsh et al., 1996, 2002). We did not attempt to update the original exposure characterization for product and non-product particulates or pigment, as previous updates revealed no evidence that these co-exposures were associated with pharyngeal cancer *per se* or acted as important confounders or effect modifiers of the formaldehyde-pharyngeal cancer associations under study.

During the total study period the median average intensity of exposure (AIE) to formaldehyde for the 5649 exposed workers (0.138 ppm) was lower than the current OSHA permissible exposure level (PEL) of 0.75 ppm (OSHA, 1992). Slightly higher proportions of short- than long-term workers were exposed to formaldehyde, but the median AIE of long-term workers was more than twice as high as short-term workers (0.168 vs. 0.079 ppm) (data not shown). Our median AIE to formaldehyde is more than seven times less than the corresponding median AIE of 1.023 ppm estimated for the 4261 Plant 1 workers in the NCI study[3] (Blair et al., 1986; Hauptmann et al., 2004). Possible reasons for this difference were discussed elsewhere (Marsh et al., 2002).

Quantitative formaldehyde exposure measures computed for individual subjects included duration of exposure, average intensity of exposure, and cumulative exposure. Methodological details of the exposure measures and categorizations considered are described elsewhere (Marsh et al., 1996, 2002). The exposure classification for this update (1995–2003) was based on 228 time-weighted average (TWA)-based formaldehyde personal exposure measurements of various job titles across the Wallingford plant.

2.1.4. Statistical analyses

Mortality analyses were limited to malignant neoplasms of the upper and lower respiratory tract with emphasis on pharyngeal cancer, in particular, nasopharyngeal (NPC). 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). Person-years were accrued from hire date until date of death, the end of the study period (12/31/2003) or date of termination (subjects lost to follow-up only). 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., 2004). 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).

2.2. Nested case–control study

2.2.1. Identification of cases and selection of controls

Details of the nested case–control study were described in our previous update (Marsh et al., 2002). In brief, cases were 22 subjects who died from pharnygeal cancer during 1945–98 (oropharynx ($n = 5$), nasopharynx ($n = 7$), hypopharynx ($n = 3$), "pharynx, unspecified" ($n = 7$)). Each

[3] The NCI study included 4261 Plant 1 workers hired between plant start up and December 31, 1966; whereas our larger independent study included 7345 workers hired through 1984.

case was matched on exact age (at the date of death of the case) race, sex, and year of birth (±2 years) to four controls from the remaining living and deceased members of the cohort. We also selected four replacement controls for each case that were used only if all attempts to locate an original control failed.[4] All controls were selected randomly from pools of eligible controls. Through structured telephone interviews with the respondent (controls only) or a knowledgeable informant (usually a surviving family member), we obtained lifetime smoking history for five of the seven NPC cases, 10 of 15 other pharyngeal cancer cases and 66 of 88 targeted controls. Our earlier attempt to obtain information on relevant non-Wallingford occupational and non-occupational exposures was largely unsuccessful, resulting in a large percentage of ''unknown'' responses (Marsh et al., 2002). In this 2003 update, we identified one additional death from pharyngeal cancer (coded as ''pharynx, unspecified''), bringing the total number of cases to 23. Four original and four replacement controls were selected for this new case using the algorithm described above.

2.2.2. Assessment of employment histories external to Wallingford plant

To investigate further the possibility that the NPC excess at Wallingford may be related to external occupational (or non-occupational) exposures, we made another attempt to obtain information on the non-Wallingford employment histories of the seven cases and all original and replacement controls. Our search included jobs held during Wallingford employment as some workers held second jobs. We also sought external employment histories for the 16 other pharyngeal cancer cases and matched controls to enable comparison with the previous study. Sources of external employment included: (1) survey data from the original nested case–control study, (2) pre-employment application forms obtained from the Wallingford personnel department and (3) occupational data obtained from Connecticut commercial city directories. City directories have been used successfully in several case–control studies as a source of occupational data (Roush et al., 1980, 1982; Teta et al., 1983; Steenland et al., 1987; Rosenbaum et al., 1993), including two Connecticut-based studies: a study of scrotal carcinoma in Connecticut metalworkers (Roush et al., 1982) and a study of mesothelioma in Connecticut (Teta et al., 1983). Rosenbaum et al. (1993) provides an overview of the methodology used to search and match subjects to city directories. Our search of the Connecticut city directories covered the years from 1907 to 1991 (the last available date) and focused primarily on the towns of Wallingford and Meriden.[5]

Our searching efforts were aided by a professional Connecticut-based genealogist who utilized on-line subscription databases, such as www.ancestry.com, that list the social security death index, phone books, marriage and birth records and WWI and II draft cards. The online sources were used to help narrow down areas to locate an individual. Subjects were searched without knowledge of case–control status from age 18 until date of death or the last available city directory year. Table 2 shows that at least one data source provided information for 100% of NPC cases and their replacement controls and 93% of the original NPC controls. Likewise, at least one data source provided information for more than 93% of AOPC cases and all controls. The most complete source of data for both case series and associated controls was the Wallingford job application; the least complete was the survey data from the 1998 update. Every job identified from the city directories and applications had employer's name and almost all included job title; about one-half of jobs obtained from the survey only had job title. Using the combined data from all three sources we developed a non-Wallingford employment history for cases and matched controls that included employer's name, location and job title or some combination of the three. Unknown companies were researched to identify the type of industry. Using the non-Wallingford employment histories and our *a priori* knowledge of the manufacturing history of the Wallingford area, we formed two external job groups as follows: ''silver smithing'' (including brass plating or other jobs related to silver or brass) and ''other metal work'' (including steel working and welding). We also attempted to form other external job groups based simply on a high prevalence of associated jobs. This produced only one additional group, ''military service'' (any kind). A fourth group, ''woodworking or wood dust exposure'', was considered, but the small number of cases and matched controls (only one AOPC case and 15 total controls) assigned to this group precluded statistical analysis.

Approximately 11% of all jobs were in silver smithing or other metal work; an additional 15% of all jobs were in military service. For purposes of statistical analysis, cases and controls were categorized as ''ever'' or ''never'' employed in any of the three external job groupings if any mention was made of an employer related to that job grouping, regardless of job title, or as ''unknown'' if no data on exter-

[4] One original NPC control and one original and one replacement AOPC control were found to be ineligible.

[5] Wallingford was chosen since it was the location of the plant. Meriden was selected due to frequent findings of ''removed to Meriden'' in the Wallingford City Directory findings. Other towns were selected based on their general proximity to Wallingford and included Branford /North Branford/Pine Orchard/Short Beach/Stony Creek; New Haven/West Haven/Woodbridge; Guilford/Clinton/Madison; New Britain/Berlin/Kensington; Southington; Hamden/Cheshire/North Haven; Portland; Middletown; Durham/Haddam/ Middlefield. The towns examined are within a range of 15 miles to the north and east of Wallingford, 12.5 miles to the south, and 10 miles to the west.

Table 2
General availability of information on external job groups by source of data*

Source	Cases ($n = 7$)		Original controls ($n = 27$)		Replacement controls ($n = 28$)		Total ($n = 62$)	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Nasopharyngeal cancer (NPC)								
Wallingford application	7	100	23	85	26	92	56	90
Survey (1998 Update)	5	71	13	48	4	14	22	36
CT City Directory	6	86	13	48	16	57	35	56
Pre Wallingford	4	57	10	37	14	50	28	45
Post Wallingford	4	57	8	30	11	39	23	37
At least one source	7	100	25	93	28	100	60	97

Source	Cases ($n = 16$)		Original controls ($n = 63$)		Replacement controls ($n = 63$)		Total ($n = 142$)	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
All other pharyngeal cancer (AOPC)								
Wallingford application	13	81	55	87	58	92	126	89
Survey (1998 Update)	6	37	28	44	19	30	53	37
CT City Directory	11	69	37	59	37	59	85	60
Pre Wallingford	8	50	30	48	32	51	70	49
Post Wallingford	6	38	26	41	23	37	55	39
At least one source	15	94	60	95	62	98	137	97

* Percentages are based on number of cases or controls shown in parentheses and are not mutually exclusive across sources.

nal employment was available from at least one of the three sources. The categorization of external job groupings was blinded to case or control status. Because the city directories allowed multiple job entries for the same time period, and the applications and survey data were often undated, no effort was made to ascertain agreement between the sources.

2.2.3. Statistical analyses

The statistical analysis of the matched case–control data was performed separately for NPC and for all other pharyngeal cancers (AOPC) combined and included modeling of estimated odds ratios (OR) using exact conditional logistic regression (Breslow and Day, 1980; Cytel Software, 2003). We also broke the matching and performed age-stratified analyses to corroborate modeling results. Demographic and exposure variables were first considered univariately as categorical variables to identify patterns of univariate associations with outcome variables and possible sparse data problems. Variables were categorized as in the original case–control study (Marsh et al., 2002). For smoking history (available for cases and a limited number of controls from the 1998 update), we formed a separate category ('unknown'') for subjects who were not contacted or were contacted but responded ''unknown.'' All exposure variables for cases and controls were computed as of the date of death of the corresponding case. Possible exposure–response associations were evaluated with a forward stepwise approach to adjust for potential confounders. Effect modification was assessed if warranted by statistically significant main effects. For NPC, we also computed ORs in relation to formaldehyde exposure lagged 15 years as done in the NCI study (Hauptmann et al., 2004). We assessed the statistical significance of each main effect (expressed as a global p-value) with a likelihood ratio statistic. For the exposure variables, we also conducted a test for linear trend (expressed as a trend p-value).

Due to the small number of cases in some subcategories of the variables considered, certain risk sets for a given study factor were uninformative for estimating ORs. This contributed to some p-values close to 1.0 and/or very wide 95% CIs for ORs. In the presence of many uninformative risk sets, the OR was estimated using a less robust median unbiased point estimator (MUE) approach (Hirji et al., 1988, 1989; Cytel Software, 2003). In some cases, estimators were deemed inestimable. All statistical tests on ORs and SMRs were done at the .05 significance level and no formal adjustment was made for multiple comparisons.

3. Results

3.1. Cohort study

Based on local county rates, we observed a statistically significant 1.54-fold excess for the combined buccal cavity and pharynx category (Table 3). This includes a statistically significant 2.10-fold excess for all pharyngeal cancer combined and a statistically significant 4.43-fold excess for NPC based on seven observed and 1.58 expected deaths.[6] Similar, though not statistically significant, excesses of 1.71-fold, 1.43-fold and 1.88-fold were observed for cancers of the oropharynx, hypopharynx and ''pharynx-unspecified

[6] During the 5-year, 1999–2003 update period, we observed no additional deaths from NPC and only one additional death from an other pharyngeal cancer site (coded as ''pharynx, unspecified''). In the previous 1945–98 follow-up, a larger, statistically significant local county rate-based SMR for NPC of 5.00 was observed based on the same seven deaths.

Table 3
Observed and expected deaths and SMRs for selected cancer site categories, Wallingford cohort, 1945–2003, US and local county comparisons (No. at Risk = 7345, Person-years = 268,205)

Cause of death (ICDA 9th Revision Codes)	Obs	United States			Local County		
		Exp	SMR	95% CI	Exp	SMR	95% CI
Buccal cavity & pharynx (140–149)	36	20.23	1.78*	1.25–2.46	23.44	1.54*	1.08–2.13
Lip (140)	1	0.35	2.83	.07–15.78	0.14	7.08	.18–39.45
Tongue (141)	5	4.62	1.08	.55–2.53	5.45	0.92	.30–2.14
Major salivary glands (142)	1	1.45	0.69	.02–3.86	1.52	0.66	.02–3.65
Gum and other mouth unspecified (143, 145)	4	2.94	1.36	.37–3.50	3.39	1.18	.32–3.02
Floor of the mouth (144)	2	1.05	1.91	.23–6.92	1.42	1.41	.17–5.07
Pharyngeal (146–149)	23	9.66	2.38**	1.51–3.57	10.93	2.10**	1.33–3.16
Oropharynx (146)	5	2.56	1.95	.63–4.56	2.92	1.71	.56–4.00
Nasopharynx (147)	7	1.61	4.34**	1.74–8.94	1.58	4.43**	1.78–9.13
Hypopharynx (148)	3	1.45	2.07	.43–6.03	2.10	1.43	.29–4.17
Pharynx, unspecified (149.0)	8	3.98	2.01	.87–3.96	4.26	1.88	.81–3.70
"All other pharyngeal" (146, 148, 149)[a]	16	8.08	1.98*	1.17–3.15	9.35	1.71*	1.01–2.72
Respiratory system (160–165)	341	309.98	1.10	.99–1.22	285.17	1.20**	1.07–1.33
Sinonasal (160)	3	1.127	2.66	.55–7.77	1.138	2.64	.54–7.71
Nose(internal) and nasal cavities (160.0)	0	0.13	—	0–28.74	0.08	—	0–44.90
Eustachian tube and middle ear (160.1)	0	0.03	—	0–132.56	0.03	—	0–123.34
Sinus (160.2, 160.3, 160.4, 160.5, 160.8, 160.9)	3	0.90	3.34	.69–9.74	0.93	3.22	.67–9.43
Larynx (161)	15	10.44	1.44	.80–2.37	9.91	1.51	.85–2.50
Bronchus, trachea, lung (162)	322	296.65	1.09	.97–1.21	273.08	1.18**	1.05–1.32

[a] Special category formed as all pharyngeal minus nasopharyngeal.
* $p < .05$.
** $p < .01$.

site," based on five, three and eight observed deaths, respectively. For the special category, "all other pharyngeal cancer (AOPC)" that comprises all pharyngeal cancers but NPC, we observed a statistically significant 1.71-fold excess based on 16 deaths.

For the combined respiratory system cancer category, Table 3 shows a statistically significant 1.20-fold excess (county comparison) based on 341 observed deaths. A not statistically significant 2.64-fold excess based on three deaths was observed for sinonasal cancer, including a not statistically significant 3.22-fold excess based on three deaths for sinus cancer, and a statistically significant 1.18-fold excess based on 322 deaths for cancer of the bronchus, trachea or lung. US rate-based SMRs for the buccal cavity and pharyngeal cancer categories were generally higher than those based on local rates; those for respiratory system cancer were generally lower. SMRs in the 1999–2003 update period were generally similar to those observed in the previous 1945–98 period (Marsh et al., 2002).

3.2. Case–control study

Among study factors considered as potential confounders, smoking history, silver smithing and the combined group, silver smithing or other metal work, were statistically significant predictors of NPC mortality (Table 4), and thus used to further adjust ORs in other models. Four of the seven NPC cases had non-Wallingford employment in silver smithing, yielding a large, statistically significant 14.41-fold increase in NPC risk compared to workers without such employment history (OR = 14.41; 95% CI = 1.30–757.8; global $p = 0.024$). Likewise, five NPC cases had non-Wallingford employment in silver smithing or other metal work yielding a smaller but statistically significant 7.31-fold risk for NPC (OR = 7.31; 95% CI = 1.08–82.1; global $p = 0.047$). NPC risk did not appear to be related to military service. The OR estimates for the three external job groups in Table 4 were consistent with those obtained from the age-standardized analysis of the case–control data with the matching broken.[7] Table 5 shows that the adjusted OR models for NPC revealed evidence of an increasing trend in ORs with increasing duration and cumulative exposure to formaldehyde; however, none of the category-specific ORs nor trends in ORs were statistically significant. We observed no evidence of increasing NPC risk with increasing average intensity of exposure.

Four AOPC cases had non-Wallingford employment in other metal work, yielding a not statistically significant 1.40-fold increase in AOPC mortality compared with workers without such employment history. None of the cases had non-Wallingford employment in silver smithing and five had military service leading to a reduction in risk (OR = 0.40). None of the external job groups considered was a statistically significant predictor of AOPC risk. OR models for AOPC revealed no evidence of important main effects or trends for any of the formaldehyde measures considered (data not shown).

[7] For example, 4 of 7 NPC cases (57%) vs. 7 of 55 controls (13%) worked in silver smithing (Mantel-Haenszel OR = 9.76, 95% CI = 1.3–94.5); 5 of 7 NPC cases (71%) vs. 13 of 55 controls (24%) worked in silver smithing or other metal work (Mantel-Haenszel OR = 7.24, 95% CI = 1.05–83.9).

Table 4
Case–control study of nasopharyngeal cancer (NPC): number of cases and controls and estimated odds ratios (OR) for potential confounding factors[a], 1945–2003

Study factor	Cases	Controls	OR (95% CI)	p-value[b]
Smoking status				
Never smoker	0	6	1.00	.022
Ever smoker	5	11	3.04[d] (.33–∞)	
Unknown or not contacted	2	38	0.38[d] (.03–∞)	
Year of hire				
1941–46	0	11	1.00	.187
1947–56	6	32	2.72[d] (.33–∞)	
1957+	1	12	Inestimable	
Worker type				
Short-term workers (<1 yr)[c]	4	32	1.00	.999
Long-term workers (1+ yrs)	3	23	1.06 (.14–6.8)	
Duration of employment (yrs)				
<1	4	32	1.00	.999
1–9	1	12	0.68 (.01–7.9)	
10+	2	11	1.45 (.24–8.9)	
Time since first employment (yrs)				
<20	2	10	1.00	.678
20–29	3	23	0.62 (.06–8.2)	
30+	2	22	0.58[d] (0–9.3)	
Silver smithing				
Never	3	46	1.00	.024
Ever	4	7	14.41 (1.30–757.8)	
Unknown	0	2	3.31[d] (0–42.4)	
Other metal work				
Never	4	45	1.00	.360
Ever	3	8	3.61 (0.50–22.7)	
Unknown	0	2	5.04[d] (0–68.0)	
Silver smithing or other metal work				
Never	2	40	1.00	.047
Ever	5	13	7.31 (1.08–82.1)	
Unknown	0	2	7.15[d] (0–104.4)	
Military service				
Never	3	24	1.00	.999
Ever	4	29	1.12 (.17–8.5)	
Unknown	0	2	3.35[d] (0–44.5)	

[a] Controls individually matched to cases on exact age, race, sex and year of birth (±2 years); controls sampled from risk sets derived from cohort.
[b] Global test p-value of main effect.
[c] Does not include short-term experience of long-term workers.
[d] Estimate based on less robust median unbiased estimator.

Table 6 shows the results of our interaction models for NPC with and without further adjustment for smoking history. The conventional two-factor interaction model uses ''neither factor'' as the baseline category, but because this factor included no observed cases for NPC, we also fit models using ''formaldehyde only'' as baseline. The conventional interaction model with no further adjustments revealed that subjects with exposure to both factors had a 3.26-fold risk of dying from NPC compared with subjects with neither factor; whereas, subjects exposed only to formaldehyde had no elevated risk of NPC. The separate effect of the combined silver smithing or other metal work group was inestimable. Further adjustment for smoking revealed essentially the same pattern of findings for NPC, but the global p-value was statistically significant ($p = .044$). We observed essentially the same pattern of findings for NPC using formaldehyde only as the baseline, with and without further adjustment for smoking, although with somewhat more robust estimation given the non-zero number of baseline cases.

Our interaction models for AOPC generally produced more robust risk estimates due to the larger number of cases and a pattern of findings similar to those observed for NPC. For example, the conventional baseline model further adjusted for year of hire revealed a 4.32-fold risk (based on MUE) for subjects with silver smithing or other metal work only; whereas, subjects exposed only to formaldehyde had no elevated risk of AOPC. Here, subjects with

Table 5
Case–control study of nasopharyngeal cancer (NPC): number of cases and controls and estimated odds ratios (OR) for formaldehyde exposure measures[a], 1945–2003

Exposure measure	Cases	Controls	No further adjustments		Further adjusted for smoking and the combined silver smithing or other metal work job group	
			OR (95% CI)	*p*-value[b]	OR (95% CI)	*p*-value[b]
Exposure to formaldehyde						
Unexposed	0	8	1.00		1.00	
Exposed	7	47	1.51[c] (.20–∞)	.407	2.87[c] (.21–∞)	.242
Duration of exposure to formaldehyde (yrs)						
<1	4	35	1.00		1.00	
1–9	1	11	0.79 (.01–9.2)	.725	1.81 (.03–36.4)	.823
10+	2	9	1.96 (.15–19.5)	(.619)	2.72 (.16–145.6)	(.423)
Cumulative exposure to formaldehyde (ppm-years)						
<.004	1	16	1.00		1.00	
.004–.219	3	21	2.17 (.16–118.9)	.794	1.65 (.03–173.1)	.507
.22+	3	18	2.52 (.19–136.5)	(.476)	5.91 (.16–950.3)	(.358)
Average intensity of exposure to formaldehyde (ppm)						
<.03	1	24	1.00		1.00	
.03–.159	4	6	10.85 (1.01–560.3)	.058	11.41 (.80–668.5)	.136
.16+	2	25	1.88 (.09–118.3)	(.841)	2.18 (.09–133.8)	(.626)

[a] Controls individually matched to cases on exact age, race, sex and year of birth (±2 years); controls sampled from risk sets derived from cohort.
[b] Global test *p*-value of main effect; trend test *p*-value shown in parentheses.
[c] Estimate based on less robust median unbiased estimator.

Table 6
Case–control study: numbers of cases and controls and estimated odds ratios (OR) for nasopharyngeal cancer (NPC), Interaction models[a] with and without further factor adjustment, 1945–2003

Model	Cases	Controls	No further adjustments		Further adjusted for smoking	
			OR (95% CI)	*p*-value[b]	OR (95% CI)	*p*-value[b]
Nasopharyngeal cancer (NPC)						
Neither factor	0	7	1.00	.057	1.00	.044
Formaldehyde only	2	35	0.37[c] (.03–∞)		0.30[c] (.02–∞)	
Silver smithing or other metal work only	0	1	Inestimable		Inestimable	
Both factors	5	12	3.26[c] (.38–∞)		2.36[c] (.22–∞)	
Formaldehyde only	2	35	1.00		1.00	
Silver smithing or other metal work only	0	1	13.37[c] (0–521.3)		2.28[c] (0–88.9)	
Both factors	5	12	7.34 (1.02–85.9)		9.20 (.91–436.5)	
Neither factor	0	7	2.72[c] (0–37.9)		3.28[c] (0–58.8)	

[a] Controls individually matched to cases on exact age, race, sex and year of birth (± 2 years); controls sampled from risk sets derived from cohort.
[b] Global test *p*-value of main effect.
[c] Estimate based on less robust median unbiased estimator.

both exposure factors had a decreased risk for AOPC due to the heavy influence of the subjects with formaldehyde exposure only (10 of 16 cases). Neither of the interaction models for AOPC was statistically significant (data not shown).

4. Discussion

From the first NCI reports in the 1980s (Blair et al., 1986, 1987), through the recent NCI update (Hauptmann et al., 2004), the question, "What is different or unusual about Plant 1 (Wallingford) that has led to the large, statistically significant NPC mortality excess?" has remained a frustrating enigma. With the possible exception of relatively higher particulate exposures due to the nature of its plastics producing operations, the subjects, formaldehyde exposures, co-exposures and other factors within the Wallingford plant are similar to the remaining nine NCI study plants, and any known plant-specific differences in potentially confounding factors (e.g., age, time, race, sex, pay category) were controlled through study design or analytically. As noted in a recent review by Chang and Adami (2006), some basic results from our Wallingford study also do not support a causal association with NPC mortality risk. These included the very short periods of Wallingford employment (4/7 NPC cases worked less than one year, 5/7 worked less than five years), the low average intensity of formaldehyde exposure (median of 7 cases was 0.14 ppm) and the statistically significantly elevated NPC SMRs in both short-term (< 1 yr) and long-term (1 + yrs) workers (SMR = 5.35 and 4.59, respectively) (Marsh et al, 2002). Also, the short work duration and relatively older age at

hire (average = 29 years) of the NPC cases allowed many years of opportunity for relevant occupational exposures in non-Wallingford jobs. Thus, based on both analytical and anecdotal evidence observed across several updates of our study, we hypothesized that the anomalous findings for NPC in Wallingford were most likely related to occupational or non-occupational risk factors external to Wallingford. However, until the current update, which enabled the convergence of old and new job information for NPC cases and their matched controls, we were unable to quantify the suspected anecdotal evidence and test this hypothesis.

Initially, attempts were made to evaluate exposures to particulates (dust) as contributing to or causing the NPC excess in the NCI cohort, as wood dust has been linked to nasal cancer and NPC (Mould and Bakowski, 1976; Hardell et al., 1982; Lam and Tan, 1984; Ng, 1986; Kawachi et al., 1989; Vaughan and Davis, 1991; Sriamporn et al., 1992; Demers et al, 1995; IARC, 1995; Armstrong et al., 2000; Hildesheim and Levine, 1993; Yu and Yuan, 2005; Chang and Adami, 2006). For example, in 1987 Blair et al. reported an additional analysis of NPC and concluded that simultaneous exposure to formaldehyde and particulates may be a risk factor for NPC. This conclusion was later challenged on methodological and other grounds by Collins et al. (1987, 1988) who performed a reanalysis of the total NCI cohort and an updated analysis of the Wallingford cohort. Neither of these analyses supported an association with NPC and joint formaldehyde and particulate exposure.

In our independent study of Wallingford, we have found no evidence of an association with exposures to product or non-product particulates and NPC with and without concurrent exposures to formaldehyde (Marsh et al., 1994, 1996, 2002), and for this reason, we did not consider particulate exposure in the current update. Hauptmann et al. (2004) considered particulate co-exposures in the most recent NCI update, but complete collinearity of exposure to formaldehyde and particulates among nine of 10 NPC cases precluded statistical analysis. Other co-exposures and jobs considered as potential confounders by NCI and us included: dyes and pigments (Marsh et al., 1994, 1996, 2002; Hauptmann et al., 2004), antioxidants, asbestos, carbon black, hexamethylenetetramine, melamine, phenol, plasticizers, urea and benzene, or working as a chemist or laboratory technician (Hauptmann et al., 2004) and cigarette smoking (Marsh et al., 2002). None of these co-exposures has helped to explain the NPC excess in the overall NCI study or in the Wallingford plant.

Despite the presence of a statistically significant main effect for silver smithing on NPC risk, silver smithing or other metal work (with or without further adjustment for smoking) did not appear to be important confounders for formaldehyde exposure. This indicates that external employment in silver smithing or other metal work was not substantially correlated with formaldehyde exposure level at Wallingford. Thus, workers at all levels of formaldehyde exposure were affected similarly by the large main effects of these two external job groups. This coupled with the evidence that silver smithing or other metal work dominated the prediction of NPC risk in our interaction models may explain why we have observed in this and previous updates elevated risks of NPC for workers in all categories of formaldehyde exposure.

Our new findings by external job group call into question the nature of the exposures and potential health risks associated with these industries. The operations related to the ferrous and non-ferrous metal industry present in the Wallingford/Meriden area can be categorized into three groups. One group including molding, casting, grinding and machining operations is known to produce mostly metal fumes and some dusts (Brown, 1998). The second group of operations is annealing and pickling. Pickling involves removing fluxes and flux residues from metal surfaces by the use of an appropriate solution. In silver, brass, bronze and ferrous metal forming industries, pickling solutions generally involve mineral acids. Especially in the silver and other non-ferrous metal operations such as nickel, brass, imitation gold and copper, the general pickling solution is a 10–25% hot sulfuric acid solution with 5–10% potassium dichromate. In ferrous pickling, hydrochloric and nitric acid as well as sulfuric acid may be involved (Brown, 1998). The third group of operations comprises chemical surface treatment, polishing, silver plating, etching, and other surface deposition operations. Here, in addition to exposure to sulfuric acid, nitric acid and hydrofluoric acid mists, occupational exposure to strong alkali, such as sodium hydroxide mists, and various metal-cyanides are possible. Exposures to strong alkali mists are irritating to the mucous membranes and may have a similar effect as mineral acid (Brown, 1998).

Many exposures and job types associated with the three groups of operations in the ferrous and non-ferrous metals industry have been linked with increased risks of upper respiratory cancer, although the evidence is not unequivocal. For example, in 1992 IARC classified occupational exposures to strong inorganic-acid mists containing sulfuric acid as carcinogenic to humans (Group 1) based on sufficient epidemiological evidence. In particular, mineral acid and sulfuric acid mists and vapors have been associated with increased risks of upper respiratory tract cancers, including nasopharynx (NPC) (Ho et al., 1999; Li et al., 2006), larynx (Soskolne et al., 1984, 1992; Forastiere et al., 1987; IARC, 1992; Coggon et al., 1996; Steenland, 1997; Steenland et al., 1998; Sathiakumar et al., 1997), and aerodigestive (Coggon et al., 1996). Soskolne et al. (1984) found a positive association between sulfuric acid and all upper respiratory cancer sites combined that was strongest for laryngeal cancer. Exposures to metal dusts have been linked to increased risks for NPC (Armstrong et al., 2000) and laryngeal cancer (Shangina et al., 2006), and industrial heat exposure has been linked to NPC (Armstrong et al., 2000). Recently, Shangina et al. (2006) found hypopharyngeal cancer risk was significantly associated with exposure to mild steel dust and iron compounds and

fumes. Epidemiology studies that have evaluated cancer risks in relation to occupation or job type also have found increased risks for: laryngeal cancer among metal manufacturing workers (Goldberg et al., 1997); NPC among primary metal workers and machinists (Huebner et al, 1992), and hammersmiths, welders, flame cutters, metal grinders, polishers, tool sharpeners and machine tool operators (Zheng et al., 1992); and sino-nasal among workers in basic metal industries (Olsen, 1988) and metal and foundry workers (Combra et al., 1992).

Our case–control findings for NPC and AOPC in relation to external employment coupled with the epidemiologic evidence reviewed above suggests the possibility that external employment in the ferrous and non-ferrous metal industries in the Wallingford area may have played some role in all the increased upper respiratory cancer risks observed in the Wallingford cohort. With the exceptions of cancer of the tongue and gum, local county rate-based SMRs were elevated for all upper respiratory cancer sites, including the nasal sinuses that do not seem to be penetrated by formaldehyde exposures (Heck et al., 1989). The fact that sulfuric acid exposure has also been linked to excess lung cancer risks (IARC, 1992) may also help to explain the small, but statistically significant, overall excess for cancer of the bronchus, trachea and lung found in the total Wallingford cohort.

The possibility that external employment in local Connecticut metal industries had a more widespread effect on respiratory cancer risks in the Wallingford cohort is supported indirectly by the essentially null findings in the NCI study for respiratory cancer sites other than NPC. In their latest update, NCI found little or no excess risks among workers exposed to formaldehyde for cancers of the buccal cavity (SMR = 1.01), nose and nasal cavity (SMR = 1.19), larynx (SMR = 0.95) and lung (SMR = 0.97) (Hauptmann et al., 2004). We do not know at this time whether workers from any of the nine remaining NCI study plants (Plant Nos. 2–10) had opportunity for external employment in industries associated with potential exposures to risk factors for lower and upper respiratory cancer. However, if such opportunities existed in one or more of the other NCI study plants, they would likely be less than those known to be associated with the extensive and long-standing ferrous and non-ferrous metal industries historically present in the Wallingford, Connecticut area.

A fundamental limitation of our cohort study was trying to study cancer sites, such as NPC, that are exceedingly rare in the general population. For example, U.S. white, male, age-adjusted mortality rates for NPC during the years 1969–2002 ranged from about 3 to 5 deaths per million population at risk per year. Such low rates, even in a moderately sized cohort in which 70% of subjects were followed for 30 or more years, led to very small numbers of expected and observed deaths and many imprecise and sometimes inestimable estimates of mortality risk. In light of this imprecision, we relied primarily on the patterns and consistency of point estimates of NPC and AOPC risks to guide our interpretation of results rather than the absolute values of the point estimates and their statistical significance. Key limitations of our nested case–control studies of NPC and AOPC were the incomplete collection of non-Wallingford job information and the absence of detailed information on the types of jobs and exposures associated with the data that was collected. Our categorization of cases and controls into silver smithing or other metal work was based primarily on self-reported company names and assumptions made about the nature of the industries or manufacturing processes involved with those companies. We did not know, however, whether a given case or control was actually exposed to any of the chemical agents commonly found in these industries that are suspected risk factors for upper respiratory cancer. We also made no attempt to calculate duration of employment, time since first employment or other characteristics of the jobs in the external job groups, which did not allow us to evaluate the timing of these exposures with respect to the development of NPC or AOPC.

Despite this lack of knowledge about specific external exposures, the pattern of case–control findings for NPC and AOPC is suggestive of an association between these cancer sites and the known exposure potentials. This evidence is strengthened by the nearly complete and equal coverage of eligible years of external employment (i.e., from age 18 until year of death or last year of city directory availability) for both NPC and AOPC cases and their matched controls, and the blinded searching of city directories relative to case–control status, which should have helped to obviate differential misclassification bias from our assignment of subjects into external job groups.

Other strengths of the Wallingford study included: a complete, independent and expanded enumeration of a study population from one of 10 plants included in the NCI formaldehyde cohort study, excellent vital status tracing and cause of death acquisition rates, sufficiently long observation times to evaluate long-term health effects, substantial portion of workers followed for 30 or more years, availability of historical individual worker-level estimates of exposures to formaldehyde, external mortality comparisons using both national and local county standard populations, modeling of internal cohort rates to obviate selection bias due to the healthy worker effect and nested case–control studies of NPC and AOPC that included smoking histories and a new, systematic and comprehensive characterization of occupational histories external to the Wallingford plant.

5. Conclusions

The results of our nested case–control study suggest that the large nasopharyngeal cancer mortality excess in the Wallingford cohort may not be due to formaldehyde exposure, but rather reflects the influence of external employment in the ferrous and non-ferrous metal industries of

the local area that entailed possible exposures to several suspected risk factors for upper respiratory system cancer (e.g., sulfuric acid mists, mineral acid, metal dusts and heat). Our findings may also help to explain why the associations with formaldehyde and nasopharyngeal cancer reported in the 1994 update of the 10-plant NCI formaldehyde cohort study were unique to the Wallingford plant (Plant 1 in NCI study). Further updates of the NCI formaldehyde cohort study should include co-exposure data on silver smithing and other metal work for all study plants to help explain the unique findings for nasopharyngeal cancer in Plant 1 compared with the other nine plants.

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