FORMALDEHYDE AND CANCERS OF THE PHARYNX, SINUS AND NASAL CAVITY:

I. OCCUPATIONAL EXPOSURES

II. RESIDENTIAL EXPOSURES

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ABSTRACT

A population-based case-control study was undertaken in 13 counties of western Washington to determine if occupational formaldehyde exposure was related to cancer of the oro- and hypopharynx (OHPC, N=205), nasopharynx (NPC, N=27) or sinus and nasal cavity (SNC, N=53). Controls were selected by random digit dialing (N=552). A telephone interview inquired about lifetime occupational history as well as a number of potential confounding factors, including smoking and drinking. Approximately half (N=143) of case interviews were with next-of-kin. Occupational formaldehyde exposures were assessed by application of a job-exposure matrix developed for this study which classified unique job codes into four categories based on judgement of likelihood and intensity of formaldehyde exposure. Exposure scores were calculated by weighting the number of years in a formaldehyde-associated job by the assigned exposure level. The effects assuming a 15-year induction period were also investigated. Logistic regression was used to estimate exposure odds ratios (OR) while taking into account multiple risk factors for each site.

No significant associations were found between occupational formaldehyde exposure and any of the cancer sites under study. However, relative risk estimates associated with the highest exposure score categories were elevated for OHPC (OR = 1.3, 95% Confidence Interval = 0.6 - 3.1) and NPC (OR = 2.1, 95% CI = 0.4 - 10.0) when an induction period was accounted for. When only live interviews were considered, the odds ratios for OHPC and NPC increased to 1.7 and 3.1 respectively. Several limitations in the study tend to conservatively bias the results and must be taken into account in its interpretation.

INTRODUCTION

The carcinogenicity and mutagenicity of formaldehyde in non-human species is well established (Swenberg, 1980; Consensus Workshop, 1984). The long-term effects of chronic exposure in humans, however, are much less clear. Much of the evidence is based on mortality studies, either of historical cohort or proportional design. Most recently, Blair et al. (In Press) reported a slightly elevated number of deaths among formaldehyde-exposed workers for cancers of the lung and nasopharynx. Additional studies, reviewed by Scott and Margosches (1985) and by the Consensus Workshop on Formaldehyde (1984), have inconsistently suggested associations with cancer of the brain, and with leukemia. They have been severely limited, however, in their ability to detect possible increased risk of less common cancers.

Case-control studies of formaldehyde and respiratory cancers have also yielded conflicting results. Partanen et al. (1985) found a non-significant 40% excess of respiratory cancer among Finnish woodworkers. Hayes et al. (1986) and Olsen et al. (1984) reported approximately two- and three-fold increases in risk for sinonasal cancer respectively, whereas Hernberg (1983) found no association. Olsen also reported no association with nasopharyngeal cancer.

Formaldehyde is a common chemical in the environment, ranking 26th in chemical production in the United States (EPA, 1981). Approximately 1.6 million persons are exposed in the U.S. workplace every year in over 200 occupations (NIOSH, 1981). Industrial hygiene surveys demonstrate a wide variation of levels in the workplace, with some workers experiencing peak levels of as much as 18 ppm (NIOSH, 1981). Similar levels were found in Scandinavian occupational surveys (Niemela, 1981).

The present case-control study was undertaken to determine whether exposure to formaldehyde in the work setting is associated with an increased risk of pharyngeal or sinonasal cancer. A separate report from this study examines associations found with exposures in residential settings (Vaughan, In Press).

METHODS

The investigation took place in a 13 county area in western Washington state with an estimated population of 2.7 million. It is a diverse environment, containing both urban and rural areas and a variety of ethnic and cultural groups. The major urban areas include the port cities of Seattle, Everett, and Tacoma. Less than 10% of the population is nonwhite, with roughly equal number of blacks and Asian and Pacific Islanders. Fewer than 1% of the population is comprised of American Indians, Aleut and Eskimo peoples. Airplane manufacture and wood products are dominant industries in the area. It is via the wood products industry that a major proportion of occupational exposures to formaldehyde occur.

Cases were identified by the Cancer Surveillance System (CSS) of the Fred Hutchinson Cancer Research Center, a population-based cancer registry operated as part of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. The CSS identifies 98 to 99% of all incident cases of cancer occurring among residents of the 13 counties. Case identification is accomplished through medical record review in all 58 area hospitals as well as routine surveillance of private radiotherapy and pathology facilities and state death certificates.

Included in this study were all incident cases of pharyngeal and sinonasal cancer (International Classification of Disease codes 146-149 and

160) occurring to persons between the ages of 20 and 74 who were resident in the study area. Eligible diagnosis dates were from 1979 through 1983 for sinonasal cancer, and from 1980 through 1983 for pharyngeal cancer.

Controls were identified via random digit dialing (Waksberg, 1978). Phone numbers were randomly generated from a list of working exchanges for the area. Each number generated was called up to nine times at different times of the day and week in order to determine if the number was a residence, and if so, whether an eligible person resided in the household. Controls were selected to be similar in age and sex to the cases. If more than one eligible control resided in a household, only one was randomly selected to be interviewed.

Information on medical, smoking, alcohol, residential and occupational histories were collected in a structured telephone interview lasting approximately 30 minutes. If a case was deceased, attempts were made through physicians' offices and death certificates to locate and interview the closest next-of-kin (NOK), preferably the spouse.

Overall, 415 cases were identified as potentially eligible for the study. Of these, 59 (14%) could not be located or were deceased with no known next-of-kin, and 61 (15%) were not interviewed due to physician or subject refusal. Of the 295 (71%) subjects successfully interviewed, 5 were later determined to be ineligible on the basis of age (greater than 74 years old at the diagnosis date) and 5 had primary sites out of the scope of the study. Therefore the following numbers of cases were available for analysis: oro- and hypopharyngeal cancer (OHPC) (including unspecified pharyngeal sites) - 205, nasopharyngeal cancer (NPC) - 27, and sinonasal cancer (SNC) - 53. Since cases diagnosed as early as 1979 were included in

the study while interviewing did not begin until late 1983, approximately half (N = 143) of the case interviews were with NOK.

Of households contacted for control selection, 96% were successfully screened. Of the 690 households in which an eligible household member resided, 573 (83%) completed the interview. Twenty-one control interviews were later excluded on the basis of ineligible age, leaving 552 available for analysis.

Characteristics of the eligible cases and controls are described in Table 1. Compared to the live interviews, cases for whom a NOK interview was necessary were more likely to be older, male and to have a diagnosis of OHPC. Cases with squamous cell carcinoma, the predominant cell type, were more likely to have died before they could be interviewed, in contrast to lymphoma cases, of which most were live interviews. The non-respondents tended to be somewhat younger, but of similar distribution with respect to sex, site and histology when compared to the interviewed cases.

Occupational formaldehyde exposure was assessed by means of a job-exposure linkage system. This is a table which includes two elements: a job (consisting of a three-digit occupation code and a three-digit industry code classified according to the 1980 U.S. Census system), and an estimate of formaldehyde exposure in that job. We first classified each unique job into three categories based on our judgement of the likelihood that it involved formaldehyde exposure: unlikely, possible or probable. We then classified each job with probable exposure into two levels according to the intensity of exposure. Finally, these estimates of likelihood and intensity were combined into a summary variable with four categories: high (probable exposure to high levels), medium (probable exposure to low levels), low (possible exposure at any level), and background.

The linkage system was first created by the investigators using: a) available industrial hygiene data from multiple sources, b) formaldehyde exposures documented as part of the National Occupational Hazard Survey of 1970-1972 (personnel communication, Sundin) and c) the job-exposure linkage system developed by Hoar et al. (1980). This system was then reviewed and modified by industrial hygiene consultants familiar with formaldehyde exposures in local and national industry from the University of Washington's Department of Environmental Health and from the National Institute for Occupational Safety and Health (NIOSH). All assessments of formaldehyde exposure were made without knowledge of case status.

Overall, subjects reported holding 4244 separate jobs, of which 1748 were unique. Of these, 148 were judged to potentially involve exposure to formaldehyde: 10, 29 and 109 were categorized into high, medium and low exposure levels respectively. The most common jobs (ie. those with the most number of subjects) in each exposure level are listed in Table 2.

For each job reported for a subject, the number of years in that job was calculated and the corresponding formaldehyde exposure code was assigned using the linkage system. Four methods of summarizing a subject's occupational exposure to formaldehyde were then used to explore different risk models. The first determined the maximum exposure category a subject was estimated to have reached in any job. The second calculated the number of years a subject has spent in any job believed to involve formaldehyde exposure. The final two methods involved the calculation of an exposure score. This was a weighted sum of the number of years spent in each job, with the weight being identical to the estimated formaldehyde exposure level of that job (ranging from 0 to 3). The exposure score was also calculated after excluding all jobs within the 15 years immediately before

the reference date (one year before diagnosis for cases, or one year before interview for controls). This latter method assumes an induction period exists - that is, recent exposures are unlikely to be causally related to these cancers.

Estimates of the relative risk associated with formaldehyde exposure were derived from calculation of the exposure odds ratios (OR). To assess the importance of the potential confounding factors and to adjust the risk estimates for their effect, a multiple logistic regression model was used (Breslow and Day, 1980). This model treats the log odds of disease as a linear combination of exposure and other risk factors. The unconditional maximum likelihood procedure was used, with the variables used in the frequency matching (age and sex) examined and included as necessary.

RESULTS

The distribution of the four formaldehyde exposure variables for the cases and controls is described in Table 3. For OHPC and NPC, there were more cases than controls with high exposure scores, but no clear trend with increasingly heavy exposure. There were fewer cases of SNC than controls with potential exposures. Of the 5 SNC cases with exposure scores of 5 or more, 3 were squamous cell carcinomas and none were adenocarcinomas. This was comparable to the overall histology distribution for SNC (51% squamous cell and 11% adenocarcinoma).

In evaluating the potential differences between the cases and controls with respect to occupational formaldehyde exposure, we adjusted for the major confounding factors for each cancer site by including them in an unconditional logistic model. Significant interactions between risk factors were also included when doing so affected the formaldehyde risk

estimates. For the OHPC and SNC sites, the following variables were adjusted for: sex; age (categorized into 20-49, 50-59, and 60-74 years of age); smoking history (calculated as pack-years, grouped into five categories - 0-1, 2-19,, 20-39, 40-59, and 60+ - and entered into the model as a continuous variable with values equal to the median of the category; and recent drinking patterns (calculated as drinks per week, grouped into three categories - 0-6, 7-20, 21+, and entered as a continuous variable with median levels). Smoking and race (white, black, Asian, and other) were the risk factors adjusted for in the analyses of NPC.

The adjusted risk estimates for occupational formaldehyde exposure and OHPC are given in Table 4. While none of the four summary variables was significantly associated with risk of OHPC, the risk estimate for the highest exposure category for three of the variables was elevated. When an exposure score was calculated using all jobs held before the reference date, those with a score of 5 - 19 had an OR of 0.6 (95% Confidence Interval = 0.3 - 1.2) and those with a score of 20 or more had an OR of 1.5 (95% CI = 0.7 - 3.0). Taking into account an induction period increased the OR in the 5 - 19 score category to 0.9 (95% CI = 0.4 - 1.8) while the OR in the highest category decreased slightly to 1.3 (95% CI = 0.6 - 3.1).

For NPC, the risk estimate for the highest exposure category for all four of the variables was also elevated, although not significantly (Table 5). In addition, for three of the variables the OR for the intermediate exposure category (5 - 19) was intermediate in value between the reference category and the highest exposure category, and thus consistent with a dose-response relationship. The risk estimates for increasing exposure score levels with an induction period accounted for were 1.7 (95% CI = 0.5 - 5.7) and 2.1 (95% CI = 0.4 - 10.0).

For SNC cases, there was no evidence for increased risk with any of the four summary variables; in fact almost all odds ratios were below one (Table 6).

To investigate the potential bias associated with the large number of NOK interviews among cases and to quantify its effect, we recalculated the exposure score odds ratios with the NOK interviews excluded (Table 7). The OHPC risk estimates associated with the highest category increased from 1.5 to 2.0 for all years, and from 1.3 to 1.7 when an induction period was taken into account. The OR's associated with the category of 5 - 19 increased from 0.6 to 1.1 and from 0.9 to 1.1 for the two exposure score variables. Increases of similar magnitude occurred for most NPC risk estimates, whereas no such trend was evident for SNC.

DISCUSSION

This study found no association between pharyngeal or sinonasal cancer and occupational formaldehyde exposure beyond that which could be readily attributed to chance. However, several factors combined to limit the ability of the study to find such an association, and must be taken into account in its interpretation.

Most prominent among the limitations is the uncertainty associated with assignment of formaldehyde exposures. Such assignment is a very imprecise and subjective process in a population-based retrospective study. Using a similar method, Hayes et al. (1986) reported approximately a two-fold difference in the number of subjects who were assigned to formaldehyde exposed categories by two independent assessors of exposure. Attempts were made to minimize the effect of subjectivity in this study by seeking a consensus among several consulting industrial hygienists, and by assessing

exposures without knowledge of case status. Therefore, while it is certain that the classification of subjects into formaldehyde exposure categories was imperfect, it is also quite likely that the misclassification was equivalent for cases and controls. The result of such non-selective misclassification would be to bias the results towards the null hypothesis.

It should also be noted that a large proportion of the case interviews were with NOK respondents, whereas all control interviews were with the subjects themselves. It is possible that the NOK respondents would be less likely to remember or report all jobs the subject had held. There is some evidence to support this: controls reported a mean number of jobs of 5.2, live cases reported 5.3 jobs, and NOK cases reported 4.1 jobs. Such under-reporting would reduce the exposure score in those cases for whom the missing job was considered to involve formaldehyde exposure. The effect of such a reduction among cases only would also be to conservatively bias the risk estimates. Re-analysis of this data with NOK interviews excluded suggested that such a bias was indeed operating.

Finally, the small number of cases available for the NPC and SNC analyses limited the power of the study to reliably identify even moderate true elevations in risk for these sites. For OHPC, the minimum detectable relative risks for an exposure score of 20 or more was 2.3 (assuming 5% of controls were in the highest exposure group, 80% power, and a two-sided alpha-level of .05), whereas for the NPC and SNC, the corresponding minimum detectable risk estimates were 5.1 and 3.6 respectively.

We believe that among the measures of formaldehyde exposure available in this study the one that warrants the most attention is the exposure score with an induction period accounted for. This is a cumulative measure which takes into account both the duration of exposure as well as an

estimate of the likelihood and intensity of exposure. Furthermore it recognizes the long periods of time typically found between initiation of exposure to a carcinogen and the clinical recognition of cancer. The relative risk estimates for OHPC and NPC for the highest level of this variable were 1.3 and 2.1 respectively. Possibly more valid point estimates may in fact be given by the analysis of live interviews only, which found risk estimates of 1.7 and 3.1 for OHPC and NPC.

Most mortality studies (Acheson et al., 1984; Walrath and Fraumeni, 1983; Walrath and Fraumeni, 1984) have not reported significant increases in cancer of the buccal cavity and pharynx (usually examined together), although the power to detect such rare outcomes was usually quite limited. Exceptions include positive studies by Liebling et al. (1984), Stayner et al. (1985) and Blair et al. (In Press). In particular, Blair reported 14 deaths from pharyngeal cancer occurring in a cohort of industrial workers, of which 7 were nasopharyngeal cancers. Of these, 6 appeared in the exposed groups, compared with 2.0 expected based on U.S. population death rates, yielding a relative risk of 3.0. However, there was no evidence of a trend in risk with increasing cumulative exposure.

Supporting the hypothesis that formaldehyde exposure is related to NPC are the results of the analysis of residential exposures from this study (Vaughan et al., In Press). Those living in mobile homes for 1-9 years, and for 10 or more years were estimated to have risks of 2.1 (95% CI = 0.7-6.6) and 5.5 (95% CI = 1.6-19.4) respectively. However, there was no corresponding increase in risk for OHPC.

The relative risk estimates for SNC are consistently below one. As such, they agree with the report of Hernberg et al. (1983). The case-control studies by Olsen et al. (1984) and Hayes et al. (1986) remain the

only human studies linking SNC with formaldehyde. In the largest study, Olsen et al. examined computerized occupational histories of cases (with SNC; N=839) and controls (with colorectal, prostate or breast cancer). Using a formaldehyde-occupation linkage system, they found a statistically significant odds ratio of 2.8 for formaldehyde exposure. However, when they examined this risk while controlling for wood exposure (a known risk factor) the risk was reduced to 1.6, which was not significant. Another important risk factor, smoking, was not available for control. Furthermore, the choice of controls may not have been appropriate due to their generally higher socio-economic status, and the consequent decreased likelihood of having jobs with significant formaldehyde exposure.

Hayes et al. examined formaldehyde risk separately for those with high and low wood exposure, with inconsistent results. The cancers in the high wood exposure group were primarily adenocarcinomas, and no formaldehyde association was found. The results in the low wood exposure group (primarily squamous cell carcinomas) differed depending on which formaldehyde exposure assessment system was used: assessor A reported a significant risk of 2.5; whereas assessor B reported a non-significant risk of 1.6.

Taken together, the limitations of the present study probably tend to conservatively bias the results. The lack of statistical significance for the observed OHPC and NPC associations with occupational formaldehyde exposure should be viewed with this in mind and therefore becomes less reassuring, particularly in light of the NPC excess observed by Blair et al., and the NPC risk associated with living in a mobile home. Pharyngeal cancer, particularly NPC, has been inadequately studied with respect to formaldehyde. Additional case-control studies of these and other

respiratory sites are warranted. They must accumulate enough cases to enable detection of moderate risks when analyzed by histologic type. Since assessment of formaldehyde exposure will always be problematical in retrospective studies, standardization of job-exposure matrices, taking into account regional differences, would also be helpful in improving comparability among studies.

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TABLE 1

CHARACTERISTICS OF CASES AND CONTROLS

Variable	Live Cases N	%	NOK Cases N	%	Non-Respondents[1] N	%	Controls N	%
TOTAL:	142	100.0	143	100.0	120	100.0	552	100.0
AGE:								
20 - 49	19	13.4	15	10.5	20	16.7	109	19.7
50 - 59	43	30.3	32	22.4	41	34.2	165	29.9
60 - 74	80	56.3	96	67.1	59	49.2	278	50.4
SEX:								
Male	88	62.0	98	68.5	80	66.7	327	59.2
Female	54	38.0	45	31.5	40	33.3	225	40.8
SITE:								
OHPC	95	66.9	108	75.5	87	72.5		
NPC	15	10.6	12	8.4	11	9.2		
SNC	32	22.5	21	14.7	22	18.3		
HISTOLOGY:								
Squamous Cell	107	75.4	124	86.7	98	81.7		
Adenocarcinoma	7	4.9	4	2.8	4	3.3		
Lymphoma	16	11.3	3	2.1	8	6.7		
Other	12	8.5	12	8.4	10	8.3		

[1]Includes cases lost to follow-up and patient and physician refusals

TABLE 2

MOST COMMON JOBS[1] IN EACH FORMALDEHYDE CLASSIFICATION CATEGORY

Occupation	Industry	Number of Subjects
Formaldehyde Exposure Level		
High (10 Jobs):		
Cementing & Gluing Machine Operators	Wood Product Mfg: Sawmills, Planing & Millwork	3
Dressmakers	Dressmaking Shops	2
Molding & Casting Machine Operators	Iron & Steel Foundries	2
Medium (29 jobs):		
Carpenters	Construction	32
Textile Sewing Machine Operators	Apparel Mfg.	6
Carpenters	Ship & Boat Building & Repairing	4
Textile Sewing Machine Operators	Misc. Textiles Mfg.	4
Assemblers	Furniture & Fixture Mfg.	2
Cabinet Makers	Furniture and Home Furnishings - Retail	2

TABLE 2 (continued)

Low (109 Jobs):

Farm Workers	Agricultural Production	45
Welders & Cutters	Ship & Boat Building & Repairing	14
Plumbers, Pipefitters & Steamfitters	Ship & Boat Building & Repairing	8
Painters, Construction & Maintenance	Construction	8
Machinists	Ship & Boat Building & Repairing	8
Laborers	Pulp, Paper & Paperboard Mills	7
Hairdressers	Beauty Shops	7
Printing Machine Operators	Printing, Publishing & Allied Industries	6
Electricians	Ship & Boat Building & Repairing	6
Roofers	Construction	5
Misc. Machine Operators	Pulp, Paper & Paperboard Mills	5
Laborers	Ship & Boat Building & Repairing	5

[1]Includes all jobs with two or more subjects (high and medium exposure levels) or five or more subjects (low exposure level).

TABLE 3

DISTRIBUTION OF FORMALDEHYDE EXPOSURE VARIABLES AMONG CASES AND CONTROLS

Exposure Variable	Cancer Site OHPC[1] # (%)	NPC[2] # (%)	SNC[3] # (%)	Control # (%)
Maximum Exposure Level:				
Background	147 (71.7)	16 (59.3)	41 (77.4)	381 (69.0)
Low	41 (20.0)	7 (25.9)	9 (17.0)	121 (21.9)
Medium	13 (6.3)	4 (14.8)	3 (5.7)	42 (7.6)
High	4 (2.0)	0 (0.0)	0 (0.0)	8 (1.4)
Number of Years Exposed:				
0	147 (71.7)	16 (59.3)	41 (77.4)	381 (69.0)
1 - 9	32 (15.6)	8 (29.6)	9 (17.0)	127 (23.0)
10+	26 (12.7)	3 (11.1)	3 (5.7)	44 (8.0)
Exposure Score-All Years:				
0 - 4	170 (82.9)	21 (77.8)	48 (90.6)	464 (84.1)
5 - 9	8 (3.9)	3 (11.1)	2 (3.8)	31 (5.6)
10 - 19	6 (2.9)	0 (0.0)	1 (1.9)	28 (5.1)
20+	21 (10.2)	3 (11.1)	2 (3.8)	29 (5.3)
Exposure Score-Induction[4]:				
0 - 4	174 (84.9)	21 (77.8)	48 (90.6)	490 (88.8)
5 - 9	6 (2.9)	3 (11.1)	3 (5.7)	21 (3.8)
10 - 19	10 (4.9)	1 (3.7)	1 (1.9)	19 (3.4)
20+	15 (7.3)	2 (7.4)	1 (1.9)	22 (4.0)

[1]Includes oropharynx, hypopharynx, and other unspecified pharyngeal sites

[2]Nasopharyngeal cancer

[3]Sinonasal cancer

[4]Excludes jobs within 15 years of reference date

TABLE 4

ADJUSTED ODDS RATIOS - OCCUPATIONAL FORMALDEHYDE VARIABLES

OHPC[1]

Variable	Odds Ratio[2] (95% CI)	Likelihood[3] Ratio (d.f.)	P-value
Maximum Exposure Level:		1.18 (3)	.76
Low	0.8 (0.5-1.4)		
Medium	0.8 (0.4-1.7)		
High	0.6 (0.1-2.7)		
Number of Years Exposed:		5.12 (2)	.08
1 - 9	0.6 (0.3-1.0)		
10 +	1.3 (0.7-2.5)		
Exposure Score-All Years:		3.64 (2)	.16
5 - 19	0.6 (0.3-1.2)		
20 +	1.5 (0.7-3.0)		
Exposure Score-Induction[4]:		0.60 (2)	.74
5 - 19	0.9 (0.4-1.8)		
20 +	1.3 (0.6-3.1)		

[1]Includes oropharynx, hypopharynx, and other unspecified pharyngeal sites

[2]Adjusted for age, sex, cigarette smoking and alcohol (22 cases with missing values excluded)

[3]Likelihood ratio statistic (with degrees of freedom) corresponding to addition of formaldehyde variable to model

[4]Excludes jobs within 15 years of reference date

TABLE 5

ADJUSTED ODDS RATIOS - OCCUPATIONAL FORMALDEHYDE VARIABLES

NASOPHARYNGEAL CANCER

Variable	Odds Ratio[1] (95% CI)	Likelihood[2] Ratio (d.f.)	P-value
Maximum Exposure Level:		0.44 (2)	.80
Low	1.2 (0.5-3.3)		
Medium or High	1.4 (0.4-4.7)		
Number of Years Exposed:		0.51 (2)	.77
1 - 9	1.2 (0.5-3.1)		
10 +	1.6 (0.4-5.8)		
Exposure Score-All Years:		1.21 (2)	.55
5 - 19	0.9 (0.2-3.2)		
20 +	2.1 (0.6-7.8)		
Exposure Score-Induction[3]:		1.38 (2)	.50
5 - 19	1.7 (0.5-5.7)		
20 +	2.1(0.4-10.0)		

[1]Adjusted for cigarette smoking and race (1 case with missing values excluded)

[2]Likelihood ratio statistic (with degrees of freedom) corresponding to addition of formaldehyde variable to model

[3]Excludes jobs within 15 years of reference date

TABLE 6

ADJUSTED ODDS RATIOS - OCCUPATIONAL FORMALDEHYDE VARIABLES

SINONASAL CANCER

Variable	Odds Ratio[1] (95% CI)	Likelihood[2] Ratio (d.f.)	P-value
Maximum Exposure Level:		3.61 (2)	.16
Low	0.8 (0.4-1.7)		
Medium or High	0.3 (0.1-1.3)		
Number of Years Exposed:		2.29 (2)	.32
1 - 9	0.7 (0.3-1.4)		
10 +	0.4 (0.1-1.9)		
Exposure Score-All Years:		3.34 (2)	.19
5 - 19	0.5 (0.1-1.6)		
20 +	0.3 (0.0-2.3)		
Exposure Score-Induction[3]:		4.30 (2)	.12
5 - 19	1.0 (0.3-2.9)		
20 +	0.0 (-)		

[1]Adjusted for age, sex, cigarette smoking and alcohol (2 cases with missing values excluded)

[2]Likelihood ratio statistic (with degrees of freedom) corresponding to addition of formaldehyde variable to model

[3]Excludes jobs within 15 years of reference date

TABLE 7

ADJUSTED ODDS RATIOS WITH NOK INTERVIEWS EXCLUDED

Variable	OHPC[1] (N=95)	NPC[2] (N=15)	SNC[3] (N=32)
Exposure Score - All Years:			
5 - 19	1.1 (0.5-2.7)	1.1 (0.2-5.5)	0.5 (0.1-2.4)
20 +	2.0 (0.9-4.6)	2.2(0.4-10.8)	0.0 (-)
Exposure Score - Induction[4]:			
5 - 19	1.1 (0.5-2.7)	1.4 (0.3-7.3)	0.7 (0.2-3.2)
20 +	1.7 (0.6-4.6)	3.1 (0.6-15.4)	0.0 (-)

[1]Includes oropharynx, hypopharynx, and other unspecified pharyngeal sites

[2]Nasopharyngeal cancer

[3]Sinonasal cancer

[4]Excludes jobs within 15 years of reference date

FORMALDEHYDE AND CANCERS OF THE PHARYNX, SINUS AND NASAL CAVITY: II. RESIDENTIAL EXPOSURES

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ABSTRACT

To investigate the possible association between residential formaldehyde exposures and risk of cancer of the oro- and hypopharynx (OHPC, N=205), nasopharynx (NPC, N=27) and sinus and nasal cavity (SNC, N=53), a population-based case-control investigation was carried out in 13 counties of western Washington. Controls (N=552) were selected by random digit dialing. Subjects' residential histories, including type of dwelling, were determined from a structured telephone interview which also collected smoking, alcohol and demographic information. Multiple logistic regression was used to estimate exposure odds ratios (OR) while adjusting for known risk factors.

A strong association was found between a history of having lived in a mobile home and NPC, but not with OHPC or SNC. The NPC risk was found to increase with the number of years lived in a mobile home: for those with 1 to 9 years the OR = 2.1 (95% Confidence Interval = 0.7 - 6.6), and for those with 10 or more years, the OR = 5.5 (95% CI = 1.6 - 19.4). No associations were found between any of the cancers and a history of exposure to new construction containing particle board and plywood, or to urea-formaldehyde foam insulation. The association found with living in a mobile home must be interpreted with caution since it is based on a small number of cases, and may be due to factors other than formaldehyde. This report emphasizes the need for additional studies focusing on potential associations between indoor air pollutants and respiratory cancers.

INTRODUCTION

Since the first reports indicating that formaldehyde was carcinogenic in animals (Swenberg, 1980), there has been concern about a possible increase in cancer risk for those exposed in residential or occupational settings. Although the exposure level in non-occupational environments is usually lower than in the workplace, its potential significance is increased by the large number of people exposed for relatively long periods of time. While a number of studies have examined the cancer risks associated with occupational exposures (Consensus Workshop, 1984; Scott and Margosches, 1985), with inconsistent results, no epidemiologic studies have explored relationships with home exposures.

Formaldehyde is a component in a wide range of products, including cosmetics, textiles and leather goods. However, approximately half of the formaldehyde made goes into the production of resins used in the manufacture of particle-board and plywood. These wood products, in turn, have become important components of many new homes over the last 30 years, particularly mobile homes (Fasick et al., 1972). Urea-formaldehyde foam insulation (UFFI) constitutes an additional source of formaldehyde vapor in the home.

The present report examines associations between potential exposures to formaldehyde in the home and cancers of the pharynx, sinus and nasal cavity using data from a population-based case-control study in thirteen counties in western Washington. A separate report from this study examines associations found with occupational exposures (Vaughan et al., In Press).

METHODS

Cases were identified by the Cancer Surveillance System (CSS) of the Fred Hutchinson Cancer Research Center, a population-based cancer registry operated as part of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. The CSS identifies 98 to 99% of all incident cases of cancer occurring among residents of 13 counties in western Washington. Case identification is accomplished through medical record review in all 58 area hospitals as well as routine surveillance of private radiotherapy and pathology facilities and state death certificates. Attempts were made to identify and interview all incident cases of pharyngeal cancer (diagnosed between 1980 and 1983), and sinonasal cancer (diagnosed between 1979 and 1983) occurring to persons aged 20 to 74 who were resident at the time of diagnosis in the study area.

Controls were identified via random digit dialing (Waksberg, 1976). Phone numbers were randomly generated from a list of working exchanges for the area. Each number generated was called up to nine times at different times of the day and week in order to determine if the number was a residence, and if so, whether an eligible person resided in the household. Controls were selected to be similar in age and sex to the cases. If more than one eligible control resided in a household, only one was randomly selected to be interviewed.

A structured telephone interview sought information on a subject's residential history since 1950 (including type of dwelling, use of UFFI, and occurrence of home renovation or new construction using particle board or plywood) and lifetime occupational history. Information was also collected on potential confounding factors, including lifetime smoking and

recent alcohol histories as well as demographic characteristics. In instances where the cases was deceased, attempts were made to locate and interview the closest next-of-kin (NOK), preferably the spouse.

Overall, 415 cases were identified as potentially eligible for the study. Of these, 59 (14%) could not be located or were deceased with no known next-of-kin, and 61 (15%) were not interviewed due to physician or subject refusal. Of households contacted for control selection, 96% were successfully screened. Of the 690 households in which an eligible household member resided, 573 (83%) completed the interview, yielding an overall control completion rate of 80%. Twenty-one control and 10 case interviews were later excluded on the basis of ineligible age. Available for analysis were 552 controls, 205 oro- and hypopharyngeal cases (OHPC) (including unspecified pharyngeal sites), 27 nasopharyngeal cases (NPC), and 53 sinonasal cases (SNC). NOK interviews were required for half (143) of the cases. Additional description of the cases and controls are given in the report on occupational exposures (Vaughan et al., In Press).

Quality control checks were made by calling back approximately 10% of the subjects and asking a short series of questions, including a history of mobile home residence. In each instance, the call-back interviewer was different than the original interviewer, and unaware of the original answers.

The exposure odds ratio (OR) was used to estimate relative risk in this study. To control for the potential confounding effects of multiple risk factors, a multiple logistic regression model with the unconditional maximum likelihood procedure was used (Breslow and Day, 1980). Variables used in the frequency matching (age and sex) were examined and included as necessary.

RESULTS

Table 1 shows the distribution of residential sources of formaldehyde among cases and controls. Of the 27 NPC cases, 8 (29.6%) reported having lived in a mobile home since 1950 as compared to 82 (14.9%) of the controls. Furthermore, of those having lived in a mobile home, 50% of the NPC cases reported a duration of residence of 10 years or more versus 22% of the controls. In contrast, the OHPC and SNC cases reported similar mobile home histories as the controls.

Twenty-five (47.1%) of the SNC cases reported having resided in a dwelling where inside construction with plywood or particle board had occurred. This compared to 35.7% of the controls, 33.2% of the OHPC cases and 37% of the NPC cases reporting such exposures. Thirteen (2.4%) of the controls reported having lived in a residence with UFFI, whereas only 2 (0.7%) of the cases did (one SNC and one OHPC); therefore no further analyses of this variable are presented.

We adjusted for the major confounding factors for each cancer site by including them in an unconditional logistic model. Significant interactions between variables were also included when doing so affected the formaldehyde risk estimates. For the OHPC and SNC sites, the following risk factors were adjusted for in the analyses: sex; age (categorized into 20-49, 50-59, and 60-74 years of age); smoking history (calculated as pack-years, grouped into five categories - 0-1, 2-19,, 20-39, 40-59, and 60+ - and entered into the model as a continuous variable with values equal to the median of the category; and recent drinking patterns (calculated as drinks per week, grouped into three categories - 0-6, 7-20, 21+, and entered as a continuous variable with median levels). For the NPC

analyses, we controlled for the confounding effects of smoking and race (white, black, Asian, and other).

The adjusted risk estimates for mobile home and particle board/plywood exposures are given in Table 2. There is a strong and significant association between living in a mobile home for 10 or more years and risk of nasopharyngeal cancer (OR = 5.5, 95% Confidence Interval = 1.6 - 19.4). For those who have lived in a mobile home from 1 to 9 years, the risk estimate is 2.1 (95% CI = 0.7 - 6.6). A test for trend was accomplished by replacing the three-level factored variable for mobile home history with a continuous variable, coded 1 to 3. The p-value (Wald test) associated with the addition of this variable to the model with smoking and race included was .006. There was no evidence for a positive association between SNC or OHPC and mobile home history.

No associations nor any indication of a trend was found between any of the cancer sites and reported exposures to particle board and plywood. Risk estimates were highest for SNC: 1.8 (95% CI = 0.9 - 3.8) for an exposure history of one to nine years, and 1.5 (95% CI = 0.7 - 3.2) for 10 or more years.

We also investigated whether the NPC risk associated with living in a mobile home was modified by potential occupational formaldehyde exposures (Table 3). The occupational exposures were derived from a job-exposure matrix developed for this study (Vaughan et al., In Press). An exposure score was calculated as a weighted sum of years spent in formaldehyde-associated jobs (excluding 15 years before diagnosis), with the weight taking into account estimates of both the likelihood and intensity of exposure. For this analysis, subjects with exposure scores of 5 or more were considered occupationally exposed. Compared to those subjects with

neither occupational nor mobile home exposures, the adjusted risk estimates were: 1.7 (95% CI = 0.5 - 5.7) for occupational exposures only, 2.8 (95% CI = 1.0 - 7.9) for residential exposures only, and 6.7 (95% CI = 1.2 - 38.9) for both occupational and residential exposures.

To investigate whether living in a mobile home in the distant past was more likely to be associated with NPC risk than recent exposures, the number of years in mobile homes was recalculated with exposures occurring in the previous 15 years excluded (Table 4). The risk estimate with such an induction period (OR = 3.0, 95% CI = 0.8 - 11.2) was unchanged from that calculated from all years (OR = 3.0, 95% CI = 1.2 - 7.5). To determine whether the large number of NOK interviews may have biased the results, the mobile home analysis was repeated with all NOK interviews excluded, again with very little change in the risk estimate (95% OR = 2.8, CI = 0.9 - 8.8).

A total of 59 subjects (including NOK) were called back as part of the interview validation check. One of the questions asked was whether the subject had ever lived in a mobile home. Fifty-eight of the 59 answers (98.3%) on the call-back agreed with the original questionnaire response.

DISCUSSION

Our results show a strong association between a history of having lived in a mobile home and nasopharyngeal cancer, but not with other cancers of the pharynx, or sinonasal cancer. To our knowledge, this is the first report examining this question.

There are several factors which lend credence to the possibility that the association is a causal one. First, it is well-established that

elevated formaldehyde concentrations do in fact occur in residences, particularly mobile homes. Indoor air measurements in homes in a variety of areas in the U.S. and Scandinavia have revealed levels of formaldehyde which approach those found in the workplace (Niemela and Vainio, 1981; Dally et al., 1981; Garry et al., 1980; Anderson et al., 1975; Breysse, 1977; Hanrahan et al. 1984).

Secondly, the finding with respect to NPC and mobile home exposure is consistent with results from two recent reports. The occupational formaldehyde analysis from this study (Vaughan et al., In Press) found risk estimates consistently but not significantly above one for NPC. Similarly, in Blair et al.'s (In Press) mortality study of industrially exposed workers, a significant excess of NPC deaths were reported (6 observed among the exposed group and 2.0 expected).

Additional support comes from the evidence of increasing NPC risk associated with increasing number of years in a mobile home. Furthermore, there is limited evidence (based on two exposed cases) that occupational and residential formaldehyde exposures may act multiplicatively in increasing the risk of NPC cancer.

One potential limitation of the study is the large number of next-of-kin interviews which were conducted among the cases, but not the controls. In assessing certain exposures, this incomparability between cases and controls, together with the possibility of differential recall usually present in a case-control study might bias the results. In is unlikely, however, for this to be a serious problem for the present study since a history of living in a mobile home is a fairly objective one which is unlikely to be preferentially answered positively by cases or their NOK. In fact, it might be more likely that NOK would tend to be uncertain or

forget about a mobile home residence in the more distant past. If this occurred, it would conservatively bias the results. Results from analysis with NOK interviews excluded support the assumption that this was not an important limitation in the study.

It should be noted that the association found with living in a mobile home may not be due to formaldehyde. While this study has adjusted for or ruled out the confounding effects of cigarettes, alcohol, age, sex and race, there may be other factors which are associated with living in a mobile home and the risk of NPC.

It has been estimated that as many as 11 million people experience elevated formaldehyde concentrations in the home. Many more come into contact with formaldehyde vapor in polluted air and in cigarette smoke. If formaldehyde does act as a respiratory tract carcinogen at relatively lov concentrations, the impact could be quite large. The present finding is based on a small sample of cases, and until this relationship has been verified by other studies, it should be interpreted with extreme caution. Additional studies of this important issue examining not only nasopharyngeal cancer but additional respiratory sites are clearly necessary. More detailed assessment of factors affecting the concentration of formaldehyde as well as other indoor air pollutants should be an integral part of these studies.

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TABLE 1

DISTRIBUTION OF RESIDENTIAL SOURCES OF FORMALDEHYDE

AMONG CASES AND CONTROLS

	Subject Type							
	OHPC[1]		NPC[2]		SNC[3]		Control	
Exposure Variable	#	(%)	#	(%)	#	(%)	#	(%)
Mobile Home:								
Number of Years								
0	177	(86.3)	19	(70.4)	48	(90.6)	469	(85.1)
1 - 9	21	(10.2)	4	(14.8)	5	(9.4)	64	(11.6)
10 +	7	(3.4)	4	(14.8)	0	(0.0)	18	(3.3)
Particle Board/Plywood:								
Number of Years								
0	137	(66.8)	17	(63.0)	28	(52.8)	352	(64.1)
1 - 9	40	(19.5)	6	(22.2)	13	(24.5)	100	(18.2)
10 +	28	(13.7)	4	(14.8)	12	(22.6)	97	(17.7)

[1]Includes oropharynx, hypopharynx and unspecified pharyngeal sites

[2]Nasopharyngeal cancer

[3]Sinonasal cancer

TABLE 2

ADJUSTED ODDS RATIOS

RESIDENTIAL FORMALDEHYDE SOURCES

	Exposure Variable			
	Mobile Home		Particle Board	
Site	1 - 9 yrs	10 + yrs	1 - 9 yrs	10 + yrs
OHPC[1]				
Odds Ratio	0.9	0.8	1.1	0.8
(95% CI)	(0.5 - 1.8)	(0.2 - 2.7)	(0.7 - 1.9)	(0.5 - 1.4)
NPC[2]				
Odds Ratio	2.1	5.5	1.4	0.6
(95% CI)	(0.7 - 6.6)	(1.6 - 19.4)	(0.5 - 3.4)	(0.2 - 2.3)
SNC[3]				
Odds Ratio	0.6[4]		1.8	1.5
(95% CI)	(0.2 - 1.7)		(0.9 - 3.8)	(0.7 - 3.2)

[1]Includes oropharynx, hypopharynx and unspecified pharyngeal sites - adjusted for cigarette smoking, alcohol, sex and age (22 cases with missing values excluded)

[2]Nasopharyngeal cancer - adjusted for cigarette smoking and race (1 case excluded)

[3]Sinonasal cancer - adjusted for cigarette smoking, alcohol, sex and age (2 cases excluded)

[4]There were no cases exposed for 10 or more years; the exposure categories were collapsed into one.

TABLE 3

ADJUSTED ODDS RATIOS BY FORMALDEHYDE SOURCE

Exposure source	NPC[1]	Control	Adjusted[2] Odds Ratio	95% CI
None	15	414	reference	
Occupation only[3]	4	55	1.7	(0.5 - 5.7)
Mobile home only	6	75	2.8	(1.0 - 7.9)
Both	2	7	6.7	(1.2 - 38.9)

[1]Nasopharyngeal cancer

[2]Adjusted for race and cigarette smoking

[3]Occupational exposures described in Vaughan et al. (In Press)

TABLE 4

EFFECT OF INDUCTION PERIOD AND NEXT-OF-KIN INTERVIEWS ON ODDS RATIOS

Mobile Home Status[1]	NPC[2]	Control	Adjusted[3] Odds Ratio	95% CI
ALL SUBJECTS:				
+	8	82	3.0	(1.2 - 7.5)
-	19	469		
INDUCTION PERIOD[4]:				
+	3	24	3.0	(0.8 - 11.2)
-	24	527		
LIVE INTERVIEWS ONLY:				
+	5	82	2.8	(0.9 - 8.8)
-	10	469		

[1] + indicates one or more years in a mobile home

[2] Nasopharyngeal cancer

[3] Adjusted for race and cigarette smoking

[4] Excluding mobile home residences within previous 15 years