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Formaldehyde exposure and respiratory and related cancers

A case-referent study among Finnish woodworkers

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PARTANEN T, KAUPPINEN T, NURMINEN M, NICKELS J, HERNBERG S, HAKULINEN T, PUKKALA E, SAVONEN E. Formaldehyde exposure and respiratory and related cancers: A case-referent study among Finnish woodworkers. *Scand J Work Environ Health* 11 (1985) 409—415. A case-referent study was undertaken to investigate the associations between formaldehyde exposure and respiratory and related cancers. Fifty-seven such cancers from a retrospective cohort of male woodworkers formed the case group. They were matched by year of birth with 171 referents. Exposure to formaldehyde was assessed with job-exposure matrices. The median of the time-weighted average concentration was about 1 ppm, and the mean duration of exposure was 10 years among the exposed. Odds ratios (ÔR) were calculated for formaldehyde exposure (1.44), peak exposure to formaldehyde (1.26), and exposure to formaldehyde-containing wood dust (1.22). None of the values exceeded unity with statistical significance. Allowance was also made for a 10-year period from the onset of exposure. Birth year, cigarette smoking and exposure to wood dust, chlorophenols, pesticides, and terpenes were controlled by stratification. The adjusted ÔRs did not change appreciably. The highest ÔR was 1.95 for formaldehyde exposure without allowance for minimum latency, adjusted for exposure to terpenes. No exposure-response relation was observed for the level, duration, or dose (ppm-years) of formaldehyde exposure. The result is nonpositive and may be explained by absence of effect, by too short a follow-up, or by insufficient power for detecting a mild excess risk.

Key terms: epidemiology, wood industry.

Formaldehyde inhalation has been shown to induce squamous cell carcinomas of the nasal cavity in rats and mice (3, 14). The epidemiologic studies published on cancer risk among workers exposed to formaldehyde have been inconclusive so far (1, 2, 4, 6, 8, 9, 10, 11, 12, 15, 16, 18, 19, 21, 22, 23).

In the wood industry, the major source of exposure to formaldehyde is the glue used in particleboard and plywood manufacturing. The estimated total number of workers occupationally exposed to formaldehyde is about 20 000 in Finland (about 1 % of the employed labor force). This group was considered suitable for providing additional data on the risk of respiratory cancer among workers exposed to formaldehyde.

Subjects and methods

The *nested case-referent design* was adopted. The cases and the referents were selected from a *retrospective cohort base* of an average 25-year retrospective follow-up of male production workers in the wood industry and in formaldehyde glue manufacturing.

Nineteen Finnish particleboard, plywood, and formaldehyde glue factories and sawmills[3] were identified with complete retrospective personnel registers since 1944. From these registers, a list of all male workers who were born after 1904 and who had entered jobs in one of the factories in 1944—1966 was prepared. A minimum of one year of employment in one or several of the 19 factories was required. The eligible workers, 3 805 in number, formed the cohort of the study (table 1). Twenty-eight percent of the cohort was estimated to have been occupationally exposed to formaldehyde. The birth and entry year distributions of the cohort are illustrated in figure 1.

From the cohort, 151 primary malignant tumors were notified as incident cancers to the Finnish Cancer Registry from January 1957 through December 1980. The case coverage of the Finnish Cancer Register is judged to have been complete during this period (20). Of interest were those cancers originating in sites which are in relatively direct contact with formaldehyde. They were labeled "respiratory" cancers for convenience and refer to the following sites, as defined by the International Classification of Diseases (ICD 7 Codes): tongue, ICD 141 (N = 1); mouth, other, ICD 143—144 (N = 0); pharynx, ICD 145—148 (N = 1); nose,

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[3] Sawmills were included for the purpose of securing a sufficient number of workers *not* occupationally exposed to formaldehyde in the case-referent comparison.

Table 1. Characterization of the cohort by industry.

	Particle-board	Plywood	Sawmill	Formal-dehyde glue	All
Number of factories	3	7	8	1	19
Number of entries into cohort	619	1 780	1 394	12	3 805
Rough estimate of prevalence (%) of formaldehyde-exposed (> 0.1 ppm) workers in cohort	80	30	0	80	28

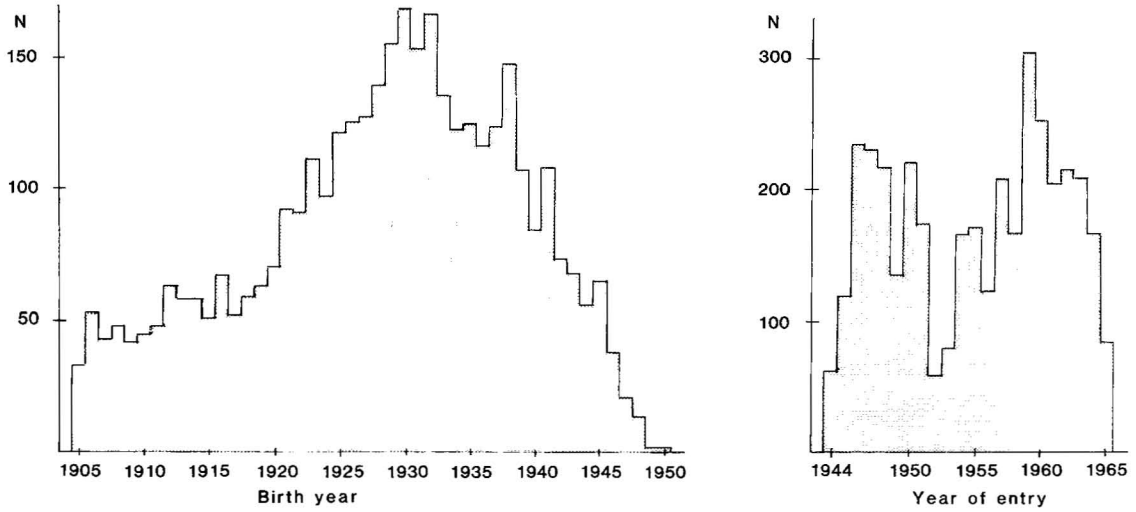

Figure 1. Distributions of year of birth and year of entry into the cohort (N = 3 805).

sinuses, ICD 160 (N = 0); larynx, epiglottis, ICD 161 (N = 4); and lung, trachea ICD 162.0—1 (N = 54) (total N = 60).

A request for histological or cytological specimens was addressed to the appropriate hospitals and laboratories for all of the 60 cases. Specimens were available for 49; these were reevaluated by a pathologist (JN). Autopsy and hospital protocols were studied for the 11 cases lacking histological or cytological samples. Two cases were rejected because of a false preliminary cancer diagnosis, and one because of a diagnosis of chronic lymphocytic leukemia. The final size of the *case group* was thus reduced to 57.

For each case, three *referents* were selected from the cohort, in all 171 men. The referents had not contracted respiratory cancer — according to the notifications to the Finnish Cancer Registry — during the follow-up. They were individually matched to each case by year of birth, which ranged from 1905 to 1933 for both the cases and the referents (median 1915). In addition, each referent had to be alive at the time of diagnosis of the corresponding case. The selection of the referents was strictly random within these constraints. The exposure histories (see the following section) were compiled for each case until the time of diagnosis; for the referents, it was done until the month of diagnosis of the matched case.

The minimum odds ratio to be detected in a fourfold table (unstratified, unmatched) with the power 0.80 at alpha = 0.05 (one-sided) turned out to be 2.25 with this study size, on the assumption that the proportion of the exposed in the reference series equals 0.25.

Evaluation of exposures

The most common exposures in Finnish particleboard, plywood, and formaldehyde glue factories and sawmills comprise formaldehyde, wood dust, chlorophenols, pesticides, phenol, components in casein-albumin glues, those in melamine glues, terpenes, solvents, exhaust gases, molds and bacteria, and possibly bis(chloromethyl)ether — the particular combination of exposing agents depending on the industry, job, and period. All these exposures were evaluated for both the cases and the referents. Of them, formaldehyde, wood dust, pesticides (eg, lindane, aldrin, dieldrine), chlorophenols, exhaust gases (may contain, eg, polycyclic aromatic hydrocarbons and formalde-

hyde), and bis(chloromethyl)ether may be carcinogenic. A major nonoccupational determinant was tobacco smoking.

Job-exposure matrices were used in the determination of exposures in the target factories. They were constructed for every factory, for all the prevalent exposing agents (see the preceding list), and for every calendar year of the follow-up period by an industrial hygienist (TK) using the hygienic data of the plant, general hygienic data on exposures, and information on ventilation, work procedures, and other relevant factors at the plants. Each factory was visited, and supervisors or workers with long experience were interviewed. In two plywood factories, one particleboard factory, and one sawmill, measurements were made of some air contaminants for which quantitative data were lacking. The matrices were constructed systematically on the basis of preset exposure criteria and without any knowledge of the case-referent status of the individual workers.

The work histories of the cases and referents in the target factories were assessed independently of the construction of the job-exposure matrices and by a different person (ES) for the purpose of minimizing information bias in the evaluation of the exposures. Work histories were based on factory registers, on interviews of factory personnel, and on questionnaire responses of the cases, referents, or their relatives. They were coded into the occupational categories included in the matrices. The matrices included a total of 73 occupational categories internally homogeneous as to exposures.

The work history data and the job-exposure matrices were linked by a computer program which calculated several exposure indices for every case and referent. The basic indicators of formaldehyde exposure were the estimated mean level (ppm) and cumulative dose [product of level and exposure time, summed up over all exposure periods (ppm-years)]. In order to minimize the misclassification of exposure, the lower limit for occupational formaldehyde exposure was set at 0.1 ppm, which corresponds to about the same or higher formaldehyde dose as nonoccupational exposure through inhalation of domestic indoor air. An additional criterion of a minimum of 3 ppm-months was introduced in order to exclude persons with low-level exposures of short duration. The hygienic data on formaldehyde allowed a three-category classification of the exposure level: low (0.1—1 ppm), moderate (1—2 ppm), and heavy (> 2 ppm). As repeated, high peak exposures (> 2 ppm) and exposure to formaldehyde-containing wood dust might be particularly risky, they were evaluated and coded separately.

The exposures other than formaldehyde were evaluated according to the same principles. The results concerning them will be reported in another paper (13).

Formaldehyde exposure in worksites other than those in the target factories was roughly estimated from questionnaire responses on job histories on a no-yes scale. This procedure was possible for 41 cases and 131 referents for whom an "ever exposed" variable (no/yes) was constructed from the combination of the information from the target factories with questionnaire data on exposures elsewhere.

The smoking histories of the cases and referents were collected by means of a postal questionnaire, completed with a phone interview when necessary. The questionnaire was addressed to the next-of-kin if the subject himself was deceased by the time of the data collection.

The number of subjects with missing data varied by exposure. Data on formaldehyde exposure was not obtained for two cases and two referents, and information on exposure to formaldehyde-containing wood dust remained missing for one case and one referent. Smoking history was lacking for 18 cases and 41 referents. In all the analyses involving smoking, subjects with missing data on smoking were excluded.

Statistical methods

Odds ratio (OR) estimates were calculated by the maximum likelihood method introduced by Gart (7), and their confidence limits by Cornfield's procedure (5). More complete work histories were obtained for subjects who were alive at the time of the data collection than for those deceased by that time. In order to correct for this information bias, all the estimates were adjusted through stratification by survival status (alive/dead) in 1983. Year of birth (cutoff 1915), duration of cigarette smoking ($\leq$ 35/> 35 years), and some industrial exposures (coded no-yes) were treated as potential confounders by further stratification. The cutoff point for years of cigarette smoking (35 years) was certainly not optimal, considering the aim of controlling the possible confounding effect of smoking. This division was however necessary for securing a sufficient number of exposed subjects in all strata, as the subjects had long smoking histories.

The odds ratio estimates were calculated for the following indicators of formaldehyde exposure (all coded no-yes): (i) formaldehyde exposure with a minimum dose of 3 ppm-months and no allowance for latency; (ii) formaldehyde exposure with a minimum dose of 3 ppm-months and an allowance for a minimum latency of 10 years; (iii) peak exposure over 2 ppm with no allowance for latency; (iv) peak exposure over 2 ppm with an allowance for a minimum latency of 10 years; (v) exposure to formaldehyde-containing wood dust for a minimum of one month with no allowance for latency; (vi) exposure to formaldehyde-containing wood dust for a minimum of one month with an allowance for a latency of 10 years; and (vii) "ever exposed" (combined data on job-exposure matrix and questionnaire responses).

Mantel's extension (17) of the Mantel-Haenszel test was applied in the analysis of the exposure-response

relations. No confounding by year of birth was present (correlation coefficients between year of birth and formaldehyde exposure indicators ranging between —0.01 and 0.04 in the reference group). Conditional multiple logistic analysis was attempted, but difficulties in interpretation arose, mainly because of correlations in the data between some exposure variables. As survival status was not one of the matching factors, stratified tabular analyses were carried out throughout with the matching broken up. In some analyses, allowance for "latency" periods was made by excluding exposures during the 10 years immediately preceding the diagnosis of the cases. For the referents, correspondingly, exposures during 10 years before the diagnosis of the respective cases were excluded in these analyses. The critical significance level adopted was one-sided alpha = 0.05, corresponding to the calculated 90 % confidence limits of the odds ratios.

Results

The distributions of the level and duration of formaldehyde exposure among the cases and the referents are shown in table 2. The differences between the cases and the referents were minor with regard to both level and duration of exposure. The average level of exposure was a time-weighted average of 1 ppm, and the mean duration of exposure was 10 years among the exposed subjects.

Table 2. Levels and durations of formaldehyde exposure of the cases and referents, by survival status in 1983.

	Living		Deceased	
	Cases	Referents	Cases	Referents
Average level of exposure (ppm)				
<0.1	1	80	41	44
0.3	2	19	8	8
1.5	—	12	3	1
3.0	—	4	—	1
All	3	115	52	54
Duration of exposure of the exposed, ≥ 3 ppm-months (years)				
Minimum	10.3	1.0	1.3	0.8
Median	11.3	11.7	3.9	5.1
Maximum	12.2	26.7	26.5	17.8
Number of exposed	2	35	11	10

The period from the time of entrance into formaldehyde exposure to the time of diagnosis ranged from 4 to 26 years (median 14 years) among the cases exposed to formaldehyde.

Table 3 shows the estimated odds ratios for the different indicators of formaldehyde exposure, adjusted for survival status. They ranged from 0.82 to 1.44, and none differed significantly from unity. Adjustment for cigarette smoking did not change the overall result (table 3).

The estimated odds ratio for the "ever exposed" variable (formaldehyde exposure in target factories or other worksites) was 1.52 (90 % confidence interval 0.75—3.10).

There was some overlap between formaldehyde and other occupational exposures. Thus, 87 % of the referents exposed to formaldehyde were also exposed to wood dust, whereas 54 % of the referents not exposed to formaldehyde were exposed to wood dust. For chlorophenol exposure the corresponding percentages were 0 and 13, respectively. For pesticides, they were 40 and 4 %, respectively, and for terpenes, 2 and 17 %, respectively. As a control of such possible confounding, formaldehyde exposure was stratified according to exposure to these four factors, and the odds ratio estimates were adjusted accordingly (table 4). None of the adjusted estimates differed significantly from unity. The highest value was 1.95, adjusted for exposure to terpenes but without allowance for latency.

The exposure-response relation between formaldehyde exposure and respiratory cancer was analyzed through the classification of the exposed persons into levels of exposure (time-weighted average in parts per million). The odds ratio estimates were then calculated for both levels against the unexposed category. The same was done for cumulative dose (ppm-years) and duration of exposure (years). Adjustment for survival status was retained. Only the duration of exposure to

Table 3. Odds ratio estimates and 90 % confidence intervals for respiratory cancer and formaldehyde exposure (without allowance for a minimum latency period and with allowance for a minimum of 10 years' latency). Adjusted by stratification for survival status (1983) and years of cigarette smoking.

Exposure	Number of exposed cases	Odds ratio estimate with the 90 % confidence interval (in parentheses) adjusted for survival status	Odds ratio estimate adjusted for survival status and cigarette smoking
Formaldehyde			
No allowance for minimum latency	13	1.44 (0.69–3.00)	1.33
Allowance for a minimum latency of 10 years	8	1.27 (0.54–3.03)	1.60
Formaldehyde, peak exposure			
No allowance for minimum latency	5	1.26 (0.44–3.62)	0.92
Allowance for a minimum latency of 10 years	4	1.05 (0.34–3.25)	0.65
Formaldehyde-containing wood dust			
No allowance for minimum latency	10	1.22 (0.55–2.71)	1.24
Allowance for a minimum latency of 10 years	5	0.82 (0.31–2.19)	1.14

formaldehyde-containing wood dust suggested a positive exposure-response relationship, which, however, was not statistically significant (table 5).

Discussion

In some epidemiologic studies (table 6), increased risk of cancer has been observed in jobs involving exposure to formaldehyde. Among embalmers in New York State, elevated mortality (proportionate mortality ratio) was reported for cancers of the skin, colon, kidney, and brain (22). An excess of lymphatic and hematopoietic neoplasms was found among British male pathologists (9). This finding however disappeared in a later follow-up; instead, deaths from brain tumor were in excess (8). Elevated risks of cancers of different sites have been reported among chemical workers with exposure to formaldehyde (1, 16, 18, 23). In particular, an increased risk of cancers related to the respiratory tract was observed in two studies: a controversial finding of excess lung cancers among formaldehyde-exposed workers in the chemical and plastics industries in the United Kingdom (1, 2), and a suggestion of an increased risk of nasal cancers among workers in formaldehyde-related jobs and industries in Denmark (19). An excess of buccal and pharyngeal cancers has been reported among workers exposed to formaldehyde in a chemical plant in the United States (16). A significant elevation in proportionate mortality has also been observed for malignant neoplasms of the buccal cavity among workers exposed to formaldehyde in the garment industry (21); the finding was based on three cases.

The preceding findings do not strongly incriminate formaldehyde as an etiologic factor for cancer. A major reason for the uncertainty is a suspected or manifest confounding with a variety of concomitant occupational exposures. (See table 6.) Most authors also consider cancer caused by formaldehyde exposure to be unlikely in sites other than those in direct contact with the agent, ie, in those other than the respiratory tract.

In addition to these uncertain findings, there are several epidemiologic studies which have failed to demonstrate associations between formaldehyde exposure and cancer risk. Thus, in a case-referent study of lung cancer among Danish physicians, no association was observed between formaldehyde exposure and employment in pathology, forensic medicine, or anatomy (12). A standardized mortality ratio study of Ontario undertakers (15) provided no indications of elevated cancer mortality. In the case-referent study of lung cancer among formaldehyde-exposed employees of Du Pont chemical plants in the United States, no association with formaldehyde exposure was found (6).

Table 4. Odds ratio estimates for respiratory cancer and formaldehyde exposure, adjusted by stratification for some possible confounders. All estimates adjusted also for survival status (1983); 90 % confidence intervals in parentheses.

Adjustment factor	Formaldehyde exposure (no/yes)	
	No allowance for minimum latency	Allowance for a minimum latency of 10 years
Wood dust (no/yes)	1.60 (0.72—3.55)	1.35 (0.55—3.32)
Chlorophenols (no/yes)	1.52 (0.70—3.33)	1.15 (0.48—2.74)
Pesticides (no/yes)	1.13 (0.49—2.60)	0.67 (0.23—1.94)
Terpenes (no/yes)	1.95 (0.84—4.53)	1.39 (0.52—3.73)

Table 5. Odds ratio estimates and 90 % confidence intervals for respiratory cancer by level, dose, and duration of formaldehyde exposure — Adjusted for survival status.

Formaldehyde exposure	Allowance for minimum latency	Number of exposed cases	Odds ratio estimate with the 90 % confidence interval in parentheses
Level	None		
0.1—1 ppm		10	1.51 (0.66—3.42)
>1 ppm		3	1.35 (0.35—5.26)
Level	10 years		
0.1—1 ppm		6	1.94 (0.68—5.60)
>1 ppm		2	0.63 (0.16—2.60)
Dose	None		
0.25—5 ppm-years		9	1.93 (0.78—4.74)
>5 ppm-years		4	0.96 (0.31—2.96)
Dose	10 years		
0.25—5 ppm-years		6	2.01 (0.69—5.86)
>5 ppm-years		2	0.63 (0.16—2.58)
Total duration of peak exposure	None		
1 month—5 years		3	6.26 (0.92—45.4)
>5 years		2	0.56 (0.15—2.18)
Duration of exposure to formaldehyde-containing wood dust	None		
1 month—5 years		4	0.78 (0.26—2.35)
>5 years		6	1.82 (0.64—5.18)

Table 6. General review of epidemiologic studies of formaldehyde exposure and cancer. (SMR = standardized mortality ratio, PMR = proportionate mortality ratio, PCMR = proportionate cancer mortality ratio; TWA = time-weighted average)

Study	Base	Type	Increased risk observed	Reference	Possible confounders	Control of smoking	Formaldehyde exposure	Latency periods
Jensen (11), Jensen & Andersen (12)	Danish physicians 1943—1976	Case-referent 84 lung cancer, 242 referents	None	Physicians	..	No	Not documented	..
Walrath & Fraumeni (22)	1 673 embalmers (New York) 1902—1980	PMR, PCMR 1 263 deaths (all causes)	Colon, skin, kidney & brain cancer	National rates	Chemical exposures	No	Not documented	..
Harrington & Shannon (9)	2 079 pathologists (United Kingdom) 1955—1973	SMR 156 deaths (all causes)	Lymphoma, leukemia	National rates	Social class	No	Not documented	Short latencies included
Harrington & Oakes (8)	2 720 pathologists (United Kingdom) 1974—1980	SMR 126 deaths (all causes)	Brain cancer	National rates	Social class, smoking, organic solvents, tuberculosis	No	Not documented	Short latencies included
Levine et al (15)	1 413 undertakers (Ontario) 1928—1977	SMR 319 deaths (all causes)	None	Ontario rates	Social class, phenol	No	40-h week TWA roughly 0.02 ppm	Average period of observation 25 years
Wong (23)	2 026 chemical workers (United States) 1940—1977	SMR 146 deaths (all causes)	Prostate cancer	Rates in the United States	Other oxygenated hydrocarbons, benzene, asbestos, pigments	No	Not documented	Allowance for latency of ≥10 years
Fayerweather et al (6)	Employees in Du Pont plants (United States) 1957—1979	Case-referent 481 cancer deaths, 481 referents	None	Co-workers	A number of chemicals	Yes	Up to over 2 ppm but levels <0.1 ppm included in many analyses	Variable from 0 to over 25 years
Marsh (18)	2 490 workers in chemical plant (United States) 1950—1976	PMR, PCMR 592 deaths (all causes)	Digestive cancer	National & local rates	For example: vinyl chloride, polyvinyl chloride, styrene, phenol, asbestos	No	Low, brief	Average 18 years
Liebling et al (16)	As in Marsh (18) but 1976—1980	PMR, PCMR 24 deaths (all causes)	Buccal & pharyngeal, colon, and rectal cancer	National & local rates	As in Marsh (18)	No	Average 1 ppm	19—33 years
Acheson et al (1, 2)	7 680 workers in chemical and plastics industry (United Kingdom) 1941—1981	SMR 1 619 deaths (all causes)	Lung cancer, rectal, bone & thyroid cancer at one plant	National & local rates	Asbestos	No	From <0.1 to over 2 ppm	Short latencies included
Olsen et al (19)	Danish employees	Case-referent 839 nasal cancers, 2 465 referents	Cancer of nasal cavity & sinuses	Cancer, some other sites	Wood dust	No	Certain/ probable/ no, based on industry or occupation	Allowance for latency of ≥10 years
Stayner et al (21)	Garment factory workers (United States)	PMR, PCMR 256 deaths (all causes)	Cancer of buccal cavity, biliary passages & liver, lymphatic & hematopoietic	National rates	None suggested	No	From 0.1 to 1 ppm or higher	Maximum 24 years

Considering nasal cancers in particular, little epidemiologic evidence has been advanced so far indicating that formaldehyde is an etiologic factor for humans (4, 10, 11). However, in a recent study in Denmark, an association between formaldehyde exposure and carcinoma of the nasal cavity and sinuses was indicated, although confounding by wood dust exposure could not be excluded (19).

Many of the "negative" studies concerning formaldehyde and cancer risk suffer from deficiencies such as undocumented or low levels and durations of formaldehyde exposure, low power, or short follow-up. In addition, there is some suspicion of overmatching in one study (6) — the cases and the referents having been matched not only for age, but also for factory, pay class, and service period.

The result of our study is nonpositive. Hence, despite the lack of a statistically significant association, only very strong excess risks can be ruled out. We were able to assess formaldehyde exposure by time and to some degree by intensity. We could also roughly control for possible confounding due to cigarette smoking, wood dust, chlorophenols, pesticides, and terpenes. If formaldehyde is indeed carcinogenic for humans, this effect may have gone unnoticed because of the low power of detection of excess risk corresponding to odds ratios lower than two. In addition, the follow-up after onset of exposure may have been too short (median 14 years), at least for part of the subjects. This occurrence would have had the additional effect of lowering the power of the study. It is also possible that the intensities and/or periods of exposure were insuffi-

cient. The reverse appearing exposure-response relations (table 5) remain unexplained. They may reflect no real association or chance. In addition, allowance for "latency" periods made little, if any, change in the odds ratio estimates, while an increase would have been expected on the hypothesis of an effect. It should, however, be pointed out that we were able to allow only for latencies of 10 years or longer; the 10-year limit is probably too low, considering the cancers of interest. The power of the study was also lowered, when the latency periods are taken into account, as the number of exposed cases decreased.

For nasal cancers in particular, the power was grossly insufficient. No cases of nasal or sinonasal malignancy appeared in the cohort during the follow-up. According to national rates, the expected number was less than one.

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