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Formaldehyde exposure and respiratory cancer among woodworkers — an update

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PARTANEN T, KAUPPINEN T, HERNBERG S, NICKELS J, LUUKKONEN R, HAKULINEN T, PUKKALA E. Formaldehyde exposure and respiratory cancer among woodworkers — an update. *Scand J Work Environ Health* 1990;16:394–400. Respiratory cancer was examined in relation to occupational formaldehyde exposure in a case-referent study (136 cases, 408 referents) nested in a woodworker cohort. Plant- and time-specific job-exposure matrices were constructed for formaldehyde exposure. Over 3 ppm-months of formaldehyde exposure was associated with an odds ratio of 1.4 [90 % confidence interval (90 % CI) 0.5–4.1]. The odds ratios for lung cancer were near unity, the excess risk concentrating on the upper respiratory tract. That for combined exposure to formaldehyde-phenol exposure (all respiratory cancers) was 1.6 (90 % CI 0.6–4.4) but 1.0 for formaldehyde only. No consistent exposure-response patterns emerged for the level, duration, or cumulative exposure. The results are hardly more than debatable support for the hypothesis concerning formaldehyde as a carcinogen in humans, the possible risk seemingly concentrating on the upper respiratory tract rather than the lung.

Key terms: case-referent study, larynx cancer, lung cancer, phenol.

Concern about the carcinogenicity of formaldehyde in humans was intensified by the positive findings of animal experiments, particularly those done on the rat (1–3). These experiments were soon followed by a number of epidemiologic studies. Indications for an increased risk of nasal and sinonasal tumors (4–6), and also nasopharyngeal tumors (6–10), were found for persons with previous occupational or residential exposure to formaldehyde. Elevated risks of lung cancer were also reported for exposed workers (9, 11–15). In spite of all the effort, the body of epidemiologic evidence on the carcinogenicity of formaldehyde is not quite compelling. Very few strong excess relative risks have been observed for exposed persons, and “non-positive” results have been reported frequently (eg, in references 16 and 17). Convincing exposure-response relationships have not been established. Customary epidemiologic sources of uncertainty and bias — suboptimal exposure contrasts, misclassification of exposures, interconfounding exposures, insufficient follow-up periods, and low power — have operated to various degrees in these studies. These common shortcomings tend to become pronounced whenever the relative risks are close to unity — a situation characteristic of the current state of the epidemiology of formaldehyde and cancer of the lung. Having combined the “limited” human evidence and the “sufficient” animal evidence, a working group of the Inter-

national Agency for Research on Cancer recently reached the conclusion that formaldehyde “is probably carcinogenic to humans [p 42]” (18).

We have earlier reported a statistically nonsignificant rate ratio of 1.4 for respiratory cancer among Finnish woodworkers exposed to formaldehyde, as contrasted to woodworkers occupationally unexposed to formaldehyde (19). The data derived from a case-referent study nested within a woodworker cohort. We subsequently expanded the cohort to roughly double. This report is based on case-referent data obtained from the expanded cohort. The results concerning other agents used in woodworking will be reported in another paper.

Subjects and methods

A retrospective cohort of 7307 woodworkers was formed from the personnel files of 35 Finnish factories claiming complete rolls of all persons employed since 1944. The follow-up of all male production workers who entered and were employed for at least a year in these plants between 1 January 1944 and 31 December 1965 formed the “entry” cohort base from which the case-referent study was built. The numbers of cohort members from the various woodworking facilities were 630 from particle board plants, 1775 from plywood plants, 876 from construction carpentry plants, 1483 from furniture manufacturing plants, 2531 from sawmills, and 12 from a glue manufacturing plant. This was the final combined cohort base embracing the experience of the original cohort (N=3805; 57 cases during 1957–1980), the results of which

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have been published earlier (19); the extended follow-up of the same cohort (16 additional cases during 1981–1982); and the follow-up of the augmented cohort, mainly from construction carpentry and furniture industries ($N = 3502$; 63 cases during 1957–1982).

By design, some 25 % of the cohort members were estimated to have been occupationally exposed to formaldehyde. The unexposed workers came from various woodworks, particularly sawmills.

In all, 136 cases of newly diagnosed respiratory cancers were notified to the Finnish Cancer Registry from among the cohort members between 1957 and 1982. The respiratory cancers were defined, for the purposes of the study, as primary malignant neoplasms of sites [according to the seventh revision of the International Classification of Diseases (ICD 7)] with which inhaled gaseous formaldehyde was thought to come into direct epithelial contact: the tongue (ICD 7 141, 3 cases), mouth, other (ICD 7 143–144, 1 case), pharynx (ICD 145–148, 1 case), nose, sinuses (ICD 7 169, 1 case), larynx, epiglottis (ICD 7 161, 12 cases), and lung, trachea (ICD 7 162.0–1, 118 cases). The coverage of the Registry has been, and is, practically complete across the nation; the case coverage in this study was therefore very high, if not complete. Histological, cytological, autopsy, and/or hospital data were reevaluated for about half of the cases by the pathologist of our team (JN).

Three referents (408 in all) were individually matched to each case according to year of birth (but not according to vital status at the time of the data collection). They were drawn at random, within the constraints of individual matching, from among those cohort members who had not contracted respiratory cancer and who were alive at the time of the diagnosis of the case. The referents for the cases from the original and the augmented subcohorts were drawn from their particular subcohorts. The vital status of the subjects was obtained from the update acquired from the Population Register Centre.

The study size was determined beforehand with the intent that an odds ratio of at least 2 would be detected for respiratory cancer and formaldehyde exposure at an alpha of 0.05 (one-sided) and a power of 0.8.

Plant- and time-specific job-exposure matrices (see reference 20) were constructed for 12 chemicals, among them, formaldehyde. The matrices were programmed so as to translate the job histories of the cases and the referents into indicators of exposure denoting the rough exposure levels (dichotomous or trichotomous, plus “unknown” category) for each study subject. For this purpose, job titles and work areas were identified in the personnel files of the companies. The facilities were visited, and interviews were conducted on work tasks and past exposures of the cases and the referents. Data on hygiene, ventilation, and work procedures were scrutinized. All the assessments were made blindly as to the case-referent status of the subjects. To minimize false positive misclassifications of ex-

posure, uncertain and unknown exposures were coded as missing, and they were rejected from the analyses.

A questionnaire was sent to the cases and the referents or their next-of-kin for a further check of the job history and also for smoking history. The postal addresses were obtained from central and local population registers.

Several indicators of exposure to formaldehyde were derived on the basis of the reconstructed job histories and the job-exposure matrices. The basic indicator was the simple exposed-unexposed dichotomy. To avoid misclassification between occupational exposure of low level or short duration with nonoccupational exposure, we required a minimum level of 0.1 ppm and a minimum cumulative exposure of 3 ppm-months before the subjects could be assigned to the exposed category. The estimated mean level (parts per million) and cumulative exposure (parts per million-years) were calculated for each subject for the analysis of the exposure-response relationship. Because repeated peak exposures (over 2 ppm) and exposure to formaldehyde carried to the lungs on wood dust might be predictors of risk, we constructed separate indicators for these conditions so that we could address their possible effect.

Odds ratio (OR) estimates were calculated for the different indicators of occupational formaldehyde exposure by conditional logistic regression (21), adapted for a variable number (here, 1, 2, or 3) of referents. The 90 % confidence intervals (90 % CI) were calculated under the assumption of a Gaussian distribution of the estimates of the coefficients in the logit model. Indicators of vital status (alive versus deceased) and smoking-years (<35 versus ≥ 35 years) were included in the analyses in order to correct for the information bias induced by survival status (which was not matched for) and possible confounding due to smoking. The cutoff point for smoking-years (35 years) equaled roughly the median smoking-years in the data. No interactions among the exposure indicators were considered except when simultaneous exposures to formaldehyde and phenol were being dealt with. Persons with missing smoking data were discarded from the analyses in which the indicator of smoking history was involved. As the proportion of persons with an unknown smoking history was fairly high (35 %) on the whole, control of smoking had to be neglected in analyses of few data.

We searched for exposure-response relationships by estimating the odds ratios separately for the contrasts between medium and no occupational exposure and between high and no occupational exposure. The cutoff points for the “medium” and “high” categories are given in table 5 of the Results section. The conditional logistic regression was used, but the data allowed for adjustment for vital status only. The levels, durations, and cumulative “doses” of formaldehyde exposure were treated in this fashion.

Results for occupational formaldehyde exposure, peak exposures to formaldehyde, and formaldehyde

Table 1. Distribution of the cases of respiratory cancer and referents according to the indicators of formaldehyde exposure.

	Cases			Referents		
	N	%	Number with missing data	N	%	Number with missing data
Duration of exposure, no minimum induction period						
<0.1 years	97	83	·	287	83	·
0.1–5.0 years	10	9	·	14	4	·
>5.0 years	10	9	·	45	13	·
Total	117	100	19	346	100	62
Duration of exposure, minimum induction period of 10 years						
<0.1 years	105	88	·	302	86	·
0.1–5.0 years	8	7	·	17	5	·
>5.0 years	6	5	·	33	9	·
Total	119	100	17	352	100	56
Level of exposure, ^a no minimum induction period						
<0.1 ppm	97	83	·	287	83	·
0.1–1.0 ppm	16	14	·	38	11	·
>1.0 ppm	4	3	·	21	6	·
Total	117	100	19	346	100	62
Level of exposure, ^a minimum induction period of 10 years						
<0.1 ppm	105	88	·	302	86	·
0.1–1.0 ppm	11	9	·	30	8	·
>1.0 ppm	3	3	·	20	6	·
Total	119	100	17	352	100	56
Cumulative exposure, no minimum induction period						
<0.25 ppm-years	97	83	·	287	83	·
0.25–5 ppm-years	15	13	·	29	8	·
5–60 ppm-years	5	4	·	30	9	·
Total	117	100	19	346	100	62
Cumulative exposure, minimum induction period of 10 years						
<0.25 ppm-years	105	88	·	303	86	·
0.25–5 ppm-years	11	9	·	27	8	·
5–60 ppm-years	3	3	·	22	6	·
Total	119	100	17	352	100	56
Repeated peak exposures of >2 ppm, no minimum induction period						
<1 month	125	95	·	373	94	·
1–60 months	4	3	·	4	1	·
>60 months	3	2	·	22	5	·
Total	132	100	4	399	100	9
Formaldehyde in wood dust, no minimum induction period						
<1 month	114	89	·	335	89	·
1–60 months	6	5	·	14	4	·
>60 months	8	6	·	29	7	·
Total	128	100	8	378	100	30

^a Estimated 8-h time-weighted average during exposure.

attached to wood dust are reported. The analyses were done both without a minimum induction period and with an induction period of at least 10 years preceding the date of the diagnosis of each individual case. The allowance for the latency period was accomplished by suspending any industrial exposure to formaldehyde during the 10-year period in question for the cases and

their matched referents. In addition to the analyses of all respiratory cancers pooled, odds ratios for formaldehyde exposure were calculated separately for lung cancer and cancers of the upper respiratory tract. For the assessment of exposure-response relationships, however, the number of exposed subjects was insufficient in these cancer subgroups.

Results

The subjects' occupational exposure to formaldehyde ranged from less than 0.1 to 3 ppm. The distributions of the different indicators of formaldehyde exposure were fairly similar between the cases and the referents (table 1). Direct comparison of the distributions was however impeded by the bias introduced by the imbalanced proportion of decedents among the cases (90 %) and the referents (33 %). The number of job titles recorded was lower for the decedents than for the living, a higher proportion of missed (false negative) exposures therefore being suggested for the decedents. The subsequent analyses were therefore conditional on the vital status of the subjects at the time of the data collection.

The odds ratios for formaldehyde exposure (≥ 3 ppm-months versus < 3 ppm-months) are given in table 2. Perhaps the most relevant figure is the odds ratio adjusted for both vital status and smoking, with provision for a latency period of at least 10 years. This

odds ratio was 1.4, which did not differ from unity to a statistically significant degree. The odds ratios for lung cancer were near unity, and the excess risk concentrated into the category of upper respiratory cancers (OR 2.4, based on two exposed cases).

The number of cases exposed to repeated peak exposures to formaldehyde was small, and no excess risk was observed (table 3).

The odds ratios for exposure to dustborne formaldehyde (table 4) were close to those for over 3 ppm-years of exposure to formaldehyde, as given in table 2. An exception was the odds ratio of 0.9 for dustborne formaldehyde after adjustment for vital status and provision for a minimum induction period of 10 years. The odds ratios for lung cancer were slightly lower than for all respiratory cancers. For the cancers of the upper respiratory tract, the odds ratio was 3.2 when adjusted for vital status. This figure was based on two exposed cases (no provision for minimum latency period).

Table 2. Odds ratio (OR) estimates and 90 % confidence intervals (90 % CI) from the conditional logistic regression for respiratory cancer and formaldehyde exposure (≥ 3 ppm-months versus < 3 ppm-months), adjusted for vital status (alive versus deceased) or for vital status and smoking (< 35 years versus ≥ 35 years), according to length of minimum induction period.

	All respiratory cancer			Lung cancer			Upper respiratory cancer		
	Exposed cases (N)	OR	95 % CI	Exposed cases (N)	OR	90 % CI	Exposed cases (N)	OR	90 % CI
No minimum induction period									
Adjusted for vital status	20	1.40	0.72—2.74	18	1.25	0.60—2.60	2	2.38	0.43—13.2
Adjusted for vital status and smoking	11	1.11	0.40—3.11	9	0.69	0.21—2.24	2	^a	^a
Minimum induction period of 10 years									
Adjusted for vital status	14	1.27	0.59—2.73	12	1.06	0.45—2.50	2	2.40	0.31—18.6
Adjusted for vital status and smoking	9	1.39	0.4—4.10	7	0.89	0.26—3.00	2	^a	^a

^a Parameter estimate did not converge.

Table 3. Odds ratio (OR) estimates and 90 % confidence intervals (90 % CI) from the conditional logistic regression for respiratory cancer and peak exposure of formaldehyde (repeated peaks > 2 ppm versus none), adjusted for vital status (alive versus deceased) or for vital status and smoking (< 35 years versus ≥ 35 years), according to length of minimum induction period.

	All respiratory cancer			Lung cancer		
	Exposed cases (N)	OR	90 % CI	Exposed cases (N)	OR	90 % CI
No minimum induction period						
Adjusted for vital status	7	0.95	0.30—3.05	7	1.10	0.31—3.85
Adjusted for vital status and smoking	4	0.22	0.03—1.48	4	0.17	0.02—1.95
Minimum induction period of 10 years						
Adjusted for vital status	6	0.93	0.28—3.14	6	1.08	0.29—4.00
Adjusted for vital status and smoking	3	0.17	0.02—1.39	3	0.14	0.01—1.90

Table 4. Odds ratio (OR) estimates and 90 % confidence intervals (90 % CI) from the conditional logistic regression for respiratory cancer and exposure to dustborne formaldehyde (yes versus no), adjusted for vital status (alive versus deceased) or for vital status and smoking (<35 years versus ≥35 years), according to length of minimum induction period.

	All respiratory cancer			Lung cancer			Upper respiratory cancer		
	Exposed cases (N)	OR	95 % CI	Exposed cases (N)	OR	90 % CI	Exposed cases (N)	OR	90 % CI
No minimum induction period									
Adjusted for vital status	14	1.37	0.66–2.82	12	1.13	0.51–2.52	2	3.17	0.50–20.0
Adjusted for vital status and smoking	9	1.33	0.49–3.62	7	0.89	0.29–2.70	2	1.00	0.12–8.09
Minimum induction period of 10 years									
Adjusted for vital status	9	0.90	0.37–2.17	8	0.85	0.32–2.27	1	a	a
Adjusted for vital status and smoking	7	1.42	0.41–4.91	6	1.19	0.31–4.56	1	a	a

a Parameter estimate did not converge.

No significant exposure-response relation was observed (table 5). A statistically significant elevation of risk was observed for the intermediate category between no and high cumulative exposures. Because of the many missing data for the smoking variate, smoking was left uncontrolled in the trend analyses, which by definition involved a finer than binary stratification of the exposure indicators.

Phenol exposure (coded as >1 month versus none) correlated with formaldehyde exposure in the data. This correlation was due to the fact that glue formulations common in Finland in the manufacturing of plywood since the 1960s contained both formaldehyde and phenol. When the 10-year latency period was used, 405 subjects (cases or referents) had neither formaldehyde nor phenol exposure; 30 were exposed to formaldehyde only; 30 were exposed to both formaldehyde and phenol; and none were exposed to phenol only. A conditional logistic analysis adjusted for vital status and a minimum induction period of 10 years for both exposures resulted in an odds ratio of 1.0 for the subjects with formaldehyde exposure only (number of exposed cases 5) and an odds ratio of 1.6 (90 % CI 0.6–4.4) for those exposed to both formaldehyde and phenol (number of exposed cases 8), the reference being those with neither exposure. The subjects with both exposures had experienced lower levels (estimated mean 0.8 ppm) but longer periods (mean 10.4 years) of exposure to formaldehyde than those exposed to formaldehyde only (1.1 ppm and 4.6 years, respectively). The numbers of exposed subjects were too small for the calculation of exposure-response relationships for those exposed to formaldehyde only. Small numbers precluded analyses of the phenol-formaldehyde combinations in relation with lung cancer or cancers of the upper respiratory tract separately.

Discussion

The results of this study suggest a slightly elevated relative risk for a combined category of cancers of the respiratory organs among workers occupationally exposed to formaldehyde. At first this finding seems compatible with the results on lung cancer in the extensive cohort study of mortality among industrial workers exposed to formaldehyde in the United States (10). There were limitations, however, in our data, namely, low power, inconsistencies between the original and the supplementary data, lack of exposure-response, possible misclassification of early exposures, confounding by phenol, and pooling of the different "respiratory" cancers.

As to the first of the aforementioned limitations, the power of the study remained insufficient for the statistical demonstration of odds ratios lower than two for respiratory cancers. Hence no significant elevations in the risk of respiratory cancer could be demonstrated. Furthermore, the excess risk seemed to concentrate on the rare cancers of the upper respiratory tract, the majority of which were cancers of the larynx, but the numbers of these cancers were indeed too small for sufficient statistical power.

As a check of the consistency of the general result between the original cohort and the subsequently added data, we recalculated the odds ratios for formaldehyde exposure in both data sets by the conditional logistic model. The odds ratio for all respiratory cancers as adjusted for vital status was 1.8 for the original data, but only 0.9 for the augmented data (pooled OR 1.3). An explanation for this discrepancy might be the fact that the exposed subjects in the first set of data had higher cumulative exposures (particle board and plywood factories, the median cumulative exposure being

28 ppm-months), while those from the second set originated predominantly from construction carpentry and furniture industries and had lower cumulative exposures (median 6 ppm-months).

Rates of exposure misclassification — which may introduce substantial biases in the effect estimates — were, in all likelihood, low in our study, except for early exposures, part of which were probably missed. The company files often did not record changes in jobs within the plant. In addition, the recall of the persons interviewed at the various workplaces was weaker for the subjects' early jobs than for their late ones. This situation was reflected in the lack of detail in the early job histories, which was more pronounced for the decedents, who were not available to provide job information themselves. We partially remedied this problem by adjusting the analyses for vital status, though initial matching of the cases and the referents with respect to vital status would have been more effective, as the number of subjects alive and deceased would have been balanced. Other biases might however have been introduced, as some competing causes of death might have been connected with formaldehyde exposure. Even if vital status would have been one of the matching factors, misclassification of early exposures might still have influenced the exposure-response relations obtained because possible effects of high exposure levels, long periods of exposure, and high cumulative exposures would have been underestimated. In this study, misclassification of exposure was likely to be nondifferential between the cases and the referents because the industrial exposure data, the industrial hygiene evaluations, and the job-exposure matrices were independent of the case-referent status of the study subjects. Smoking may have been an exception. The data on smoking were ascertained through the use of a questionnaire and may have been more accurate for the cases, as the cases and their next-of-kin may have paid more attention to former smoking because of the contraction of a respiratory cancer. The management of the possible confounding due to smoking was probably incomplete both for this reason and because of the rough binary indicator of history of smoking which was utilized in the analyses. However, selected runs on the logistic model showed that there were very small differences in the results between a model with the binary smoking indicator and an alternative model in which a (skewed) "smoking-years" variate (with an accuracy of one year) was used instead.

The lack of exposure-response may have been real or may have been due to a misclassification of early exposures, as has already been explained. There might have even been no true effect at all in the exposures encountered by the workers. If, on the other hand, there is an effective level, dose, or duration of exposure, it may imply the existence of a threshold effect. This possibility might be arguable if the carcinogenic effect of formaldehyde is mediated through epithelial irritation rather than through mutagenic ac-

Table 5. Odds ratio (OR) estimates and 90 % confidence intervals (90 % CI) from the conditional logistic regression for all respiratory cancer by level, duration, and cumulative formaldehyde exposure, as adjusted for survival status.

Formaldehyde exposure	Exposed cases (N)	OR	90 % CI
Level, no minimum induction period			
0.1–1 ppm	16	1.54	0.75–3.16
>1 ppm	4	0.97	0.16–5.85
Level, minimum induction period of 10 years			
0.1–1 ppm	11	1.56	0.66–3.69
>1 ppm	3	0.51	0.09–2.81
Duration, no minimum induction period			
1 month–5 years	10	1.31	0.46–3.73
>5 years	10	1.53	0.63–3.67
Duration, minimum induction period of 10 years			
1 month–5 years	8	1.62	0.52–5.08
>5 years	6	1.04	0.38–2.84
Cumulative, no minimum induction period			
0.25–5 ppm-years	15	2.26	1.01–5.02
>5 ppm-years	5	0.45	0.11–1.88
Cumulative, minimum induction period of 10 years			
0.25–5 ppm-years	11	2.32	0.91–5.93
>5 ppm-years	3	0.35	0.08–1.62
Total duration of repeated exposures to peak (>2 ppm) levels, no minimum induction period			
1 month–5 years	4	4.64	0.38–57.2
>5 years	3	0.55	0.12–2.48
Total duration of exposure to dust-borne formaldehyde, no minimum induction period			
1 month–5 years	6	1.51	0.51–4.48
>5 years	8	1.37	0.52–3.61

tivity. Another explanation for the lack of an exposure-response relationship may be that exposure-response was scrutinized in a pooled group of cancers, of which the bulk (ie, cancers of the lung) may be irrelevant if the excess risk is associated with cancers of the upper respiratory organs.

A further uncertainty in the interpretation arises from the fact that the odds ratio for formaldehyde dropped to 1.0 when not connected with concomitant exposure to phenol, while the phenol-formaldehyde combination yielded an odds ratio of 1.6.

In respect to the issue of site-specificity of the possible effect, the pooling of the different respiratory cancers in the design turned out, a posteriori, to be a dubitable operation. If the possible carcinogenic effect really is site-specific for the different respiratory tissues, then the study design and data analysis should

have addressed site-specific cancers. We did however make an attempt to break the data down by subsites (lung and the upper respiratory organs). The analyses suggested that, if exposure conditions similar to those encountered by the study subjects have any effect, it will be on the upper respiratory organs. It might indeed be reasonable to assume that the most likely target tissues would be the epithelial linings of the nose, mouth, pharynx, and larynx, as these tissues are likely to receive higher doses of inhaled formaldehyde vapor than are the bronchi.

In view of the positive results of relevant animal experiments (1–3), cancers of the nasal cavity and sinuses may bear particular significance in spite of the differences between rodents and humans in the structure and functioning of the breathing apparatus. This study was not designed to provide information about formaldehyde and nasal cancer. Among the cohort members, a single case of nasal cancer — a nodular lymphoma in the left sinus — was diagnosed in 1982, the expected number of nasal cancers being roughly of the same order. The worker was employed as a barrelmaker between 1946 and 1950. The barrels were manufactured out of plywood, and his job history did not indicate exposure to formaldehyde.

The results of this study may be chance findings in the face of a true absence of effect at the exposure intensities encountered, but they are equally compatible with weak true effects which might be more pronounced with higher intensities or doses of exposure, or longer latency or exposure periods — the latter having been less than 20 years on the average among the subjects of this study. With its limitations, this study at best yields only a weak positive contribution to the credibility of formaldehyde being a human carcinogen, the most likely target being not the lung but rather the upper respiratory organs.

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