Int Arch Occup Environ Health (1993) 64:593–596

International Archives of
Occupational and Environmental Health

Malignant lymphomas and leukemias, and exposures in the wood industry: an industry-based case-referent study

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Received October 26, 1992 / Accepted February 6, 1993

Summary. Jobs and exposures in woodwork may entail an elevated risk of lymphomas and leukemias. Exposures occurring in woodwork were scrutinized in a small industry-based case-referent study of four cases of Hodgkin's disease, eight cases of non-Hodgkin's lymphoma, 12 cases of leukemia, and 152 matched referents, all from the Finnish wood industry. Past exposures to wood dust, chlorophenols, terpenes, and engine exhaust, individually reconstructed through plant- and period-specific job exposure matrices, were unrelated to lymphoma/leukemia risk. Exposures to various solvents were associated with an odds ratio (OR) of 5.6 (95% confidence interval 1.0–32.0). The OR for formaldehyde was 2.5 (nonsignificant). The results are interpreted as providing limited evidence of the role of exposure to some as yet unidentified organic solvents in increasing the risk of malignant lymphomas. Formaldehyde may be another woodwork-related risk factor for some lymphomas, but the power of the study was too low for empirical confirmation of this possibility. Leukemias did not seem to be associated with any of the exposures studied.

Key words: Leukemia – Lymphoma – Formaldehyde – Solvents – Chlorophenols

Introduction

Epidemiologic studies have given rise to some concern over the possibility of an elevated risk, in various categories of woodworkers, of Hodgkin's disease [1, 9, 10, 12, 13, 23, 24, 32], non-Hodgkin's lymphoma [24, 30], and leukemia [7, 8, 16, 17, 20, 22, 24, 25, 27, 28, 34]. The wood industry presumably entails exposures to chemical risk factors for leukemias and lymphomatous malignancies. Benzene may have been present, at least in lacquer production [26]. Additional compounds, agents, and mixtures related to woodwork and suspected of being associated with risk of leukemia include fresh wood [8], formaldehyde [33], organic solvents [21, 28], e.g., acetone and hexane [6], and engine exhaust [4, 8]. As regards Hodgkin's and/or non-Hodgkin's lymphomas, organic solvents [5, 14, 21, 29, 31], diesel exhaust [4], creosote [31], and other wood preservatives, notably chlorophenols and chlorophenates [12, 14], have been pinpointed as possibly hazardous factors present in the wood industry. An enhanced lymphoma hazard was observed for men in Swedish silvicultural occupations [35], but no specific chemical agents could be identified as responsible.

This is a report of a small case-referent study intended to explore whether selected exposures in the wood industry increase the risk of contracting malignant lymphoma or leukemia.

Materials and methods

The case of malignant lymphoma (ICD-7 codes 200–202) and leukemia (204) in a retrospective all-male cohort of 7307 Finnish production workers in the wood industry were traced through the data base of the Finnish Cancer Registry. This cohort was initially employed in a case-referent study on respiratory cancer and formaldehyde exposure [30]. It was an entry cohort of workers first employed between 1945 and 1963 in particle board, plywood, construction carpentry, furniture, sawmilling, and formaldehyde adhesive manufacturing industries. At least a year of employment in the factories was required for eligibility. Only plants that claimed to have complete retrospective employee files since 1944 were considered. The number of plants was 35.

Between 1957 and 1982, eight non-Hodgkin's lymphomas, four cases of Hodgkin's disease, and 12 leukemias were diagnosed and notified to the Finnish Cancer Registry from among the cohort members, the combined case series totalling 24. One to eight matched referents were selected for each case from among the cohort members who had not contracted cancer during the retrospective follow-up. The matching was effected with reference to year of birth and survival/nonsurvival in 1983. The total number of qualified referents was 152 (52 for the cases of non-Hodgkin's lymphoma, 21 for the cases of Hodgkin's disease, and 79 for the cases of leukemia).

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Individual exposures to formaldehyde, wood dust, pesticides, chlorophenols, phenol, terpenes, solvents, and engine exhaust were reconstructed using a plant/period-specific job exposure matrix [18, 19, 30]. The job histories of the cases were extracted from the company records and completed by interviews of selected persons at the plants and by questionnaires sent to the cases or to their next-of-kin in 1982–1983. The job histories of the referents were based on the company records only, because no additional data collection was feasible in 1990, when the referents were selected. This asymmetry in exposure data between cases and referents introduces a potential source of bias (see Discussion).

The exposure reconstruction resulted in binary categorization (yes/no) of each exposure, the cutoff points corresponding roughly to the concentrations in the nonoccupational environment. A minimum of 1 month of exposure was required for positive exposure. The minimum criterion of formaldehyde exposure was set at an estimated cumulative exposure of 3 ppm-months. When there was doubt regarding the presence or absence of exposure in any individual assessment, the value of the exposure indicator was declared missing, and the person was excluded from the statistical analysis if the exposure indicator was included in the model.

To allow for equal exposure opportunity between the cases and the referents and for a latency period of some length, the exposures in each set of cases and referents were lagged by 10 years, i.e., exposures that had occurred during the 10-year period prior to the diagnosis of the case were ignored.

Bi- and multivariate logistic regression models, conditional on the matched sets, were fitted to the data. Odds ratios (OR) were estimated, and 95% confidence intervals (95% CI) were calculated on the assumption of Gaussian sampling distribution of the coefficients of the models. The numbers of cases exposed to pesticides and phenol were too small for statistical analysis.

Table 1. Odds ratios (OR) and their 95% confidence intervals (95% CI) for the exposures under study. Leukemias and lymphomas pooled. Conditional logistic regression

Exposure	N[a]	OR	95% CI
Formaldehyde	7	2.49	0.81– 7.59
Wood dust	15	1.06	0.38– 2.93
Chlorophenols	2	0.91	0.18– 4.51
Terpenes	2	0.82	0.17– 3.93
Solvents	4	5.62	0.99–32.0
Engine exhaust	2	0.81	0.15– 4.21

[a] Number of exposed cases

Results

The mixed category of solvents was associated with the highest OR (5.6) of leukemias and lymphomas combined (Table 1); this value bordered on statistical significance. The OR for formaldehyde was 2.5, the lower confidence limit remaining well below unity. Wood dust, chlorophenols, terpenes, and engine exhaust were not associated with an excess risk.

Concurrent exposures within individuals in the study base may have been a confounding factor. This was scrutinized among the referents for formaldehyde and solvents (i.e., the exposures possibly associated with an elevated risk) and wood dust (i.e., the most prevalent exposure). The most obvious potential confounding occurred due to the association of wood dust with formaldehyde: only three referents exposed to formaldehyde were unexposed to wood dust. The three exposures were therefore added to the regression models, according to their conjectured potential to confound each other. In an alternative model, subjects with two interrelated exposures were omitted from the data, and bivariate regression was carried out for one of the exposures at a time.

Table 2 shows that the elevated risk of lymphomas and leukemias (pooled) associated with solvent and formaldehyde exposure remained roughly at the levels observed in the crude analysis after control for confounding effects (Table 1), while the borderline statistical significance observed for solvents in the crude analysis was lost. The ORs for wood dust remained near or below unity after controlling for potential confounding effects.

The different types of cancer were then separated to reveal whether any particular exposures were associated with specific cancers. Table 3 shows that formaldehyde

Table 2. Odds ratios (OR) and their 95% confidence intervals (95% CI) for formaldehyde, wood dust, and solvents, adjusted for confounding effects of each other. Multivariate conditional logistic regression on complete data and bivariate conditional logistic regression on data subsets

Complete data			
Exposure	Factor adjusted for	OR	95% CI
Formaldehyde	Solvents	2.27	0.64– 7.98
Formaldehyde	Wood dust	2.73	0.79– 7.98
Solvents	Formaldehyde	5.07	0.40–63.5
Wood dust	Solvents	1.04	0.36– 3.06
Wood dust	Formaldehyde	0.67	0.24– 2.17
Wood dust	Solvents, formaldehyde	0.69	0.21– 2.29
Restricted data			
Exposure	Data	OR	95% CI
Formaldehyde (FA)	Unexposed to SOL	2.01	0.56– 7.27
Solvents (SOL)	Unexposed to FA	3.36	0.45–25.0
Wood dust	Unexposed to FA	1.32	0.37– 4.71
Wood dust	Unexposed to SOL	1.11	0.33– 3.67
Wood dust	Unexposed to FA and SOL	1.25	0.30– 5.14

Table 3. Odds ratios (OR) and their 95% confidence intervals (95% CI) for the selected exposures. Conditional logistic regression

Exposure	Leukemias			All lymphomas			Hodgkin's disease			Non-Hodgkin's lymphomas		
	N^a	OR	95% CI	N^a	OR	95% CI	N^a	OR	95% CI	N^a	OR	95% CI
Formaldehyde	2	1.40	0.25–7.91	5	4.02	0.87–18.6	1	–[b]		4	4.24	0.68–26.6
Wood dust	6	0.56	0.15–2.18	8	2.14	0.43–10.6	3	2.14	0.21–21.6	5	2.13	0.23–19.7
Solvents	2	–[b]		2	3.06	0.41–22.7	–	–[b]		2	–[b]	

[a] Number of exposed cases
[b] Not calculable

exposure might be related to non-Hodgkin's lymphomas, wood dust to all types of lymphoma, and solvents to some or all types of lymphoma. The numbers, however, dwindled rapidly after diagnostic stratification, and the ORs are very unstable.

Discussion

The precision of this study suffers from low power deriving from the small number of cases. Inaccuracy may arise from possible misclassification of diagnoses and exposures. We have every reason to believe, however, that the accuracy of cancer diagnoses has been high, as all were rechecked at the Finnish Cancer Registry.

The specificity of the exposure assessment – which is crucial when exposures are rare – was in all likelihood sufficiently high. Every effort was directed toward avoiding false-positive exposures. In case of doubt, individual exposure indicators were handled as missing values and omitted from the analysis.

The most serious potential source of bias concerns the reconstruction of exposures, which was probably effected with higher accuracy for the cases than for the referents. This is reflected in the fact that 71% of the cases but only 36% of the referents were designated as holders of more than one job title in the data from the time of entry into the cohort until 10 years before the diagnosis of the case. For more than two job titles, the figure was 8% among both the cases and the referents. The asymmetry of information was unavoidable, as the particular conditions at the time of data collection did not allow for the acquisition of more symmetric information from the cases and the referents. Any misclassification of exposures originating at this source is likely to have induced uniform effect amplification in the OR estimates across the different exposures. While full recognition should be accorded to the seriousness of the bias potentially induced, it appears that the ORs were not uniform between exposures. For this reason, we believe that some significance can be assigned to the elevated risk associated with exposure to solvents and possibly formaldehyde. It is of some interest that no indication of elevated risk was discernible for either chlorophenols or wood dust. The predominant species of wood that had been processed were pine, spruce, and birch.

Smoking may have been a potential confounding variable if smoking indeed has a role in the development of lymphomas and leukemias. Smoking data were not available for the referents, and control for any possible confounding effect from this source was therefore impossible. It is conceivable, however, that smoking was fairly evenly distributed in the study base as all were industrial workers subject to presumably similar restrictions on smoking on the working premises. Nevertheless, the small numbers may have invited chance confounding, assuming that these cancers have a smoking-related etiology, which in itself is by no means obvious.

The main result of this small study concerns solvent exposure in the various woodworking industries. The number of solvents to which exposure occurs is substantial; they include constituents of stains, lacquers, and varnishes such as aromatic hydrocarbons (toluene, xylenes; less often benzene and styrene), esters (butyl acetate, ethyl acetate), alcohols (butanol, isopropanol, ethanol), aliphatic hydrocarbons (solvent naphtha, white spirits), ketones, and glycol ethers. The different compounds vary between countries, time periods, manufacturing categories, facilities, and job titles. Surface coating of furniture and wooden structures probably carries the highest burden of organic solvent exposure, which in individual workers typically consists of multiple compounds.

The statistically unstable indication that formaldehyde exposure is associated with an elevated risk seems to relate more to lymphomas and particularly non-Hodgkin's lymphomas than to leukemias. To our knowledge, few such findings have been reported in epidemiologic studies. One reason might be that the issue has seldom been seriously addressed. As possibly relevant findings one might cite a highly unstable indication of elevated mortality from hematologic neoplasms among formaldehyde-exposed workers producing resins [2], a statistically nonsignificant O/E ratio of 14:10 for Hodgkin's disease among workers exposed to formaldehyde in formaldehyde-producing or -using facilities [3]; and an increased SMR (O/E = 8:3.3; $P < 0.01$) for lymphoma and hematoma but not Hodgkin's disease among British pathologists and medical laboratory technicians presumably exposed to formaldehyde [15]. In contrast to these results, no association was found between either Hodgkin's disease or non-Hodgkin's lymphomas and formaldehyde exposure in a multisite case-control study in Montreal [11].

In conclusion, the data are supportive, though to a limited degree only, of the role of exposure to some unidentified organic solvents in increasing the risk of malignant lymphomas. Formaldehyde may be another wood-

work-related risk factor for some lymphomas, but the power of the study was too low for empirical confirmation of this possibility. Leukemia did not show any clear association with any of the exposures studied.

Acknowledgements. This study has been supported by grants from the Academy of Finland and the Finnish Work Environment Fund. We thank Professor Sven Hernberg for commenting on the manuscript.

References

1. Abramson JH, Pridan H, Sacks MI, Avitzour M, Peritz E (1978) A case-control study of Hodgkin's disease in Israel. J Natl Cancer Inst 61:307–314
2. Bertazzi PA, Pesatori AC, Radice L, Zocchetti C, Vai T (1986) Exosure to formaldehyde and cancer mortality in a cohort producing resins. Scand J Work Environ Health 12: 461–468
3. Blair A, Stewart P, O'Berg M, Galley W, Walrath J, Ward J, Bales R, Kaplan S, Cubit D (1986) Mortality among industrial workers exposed to formaldehyde. J Natl Cancer Inst 76:1971–1984
4. Boffetta P, Stellman SD, Garfinkel L (1988) Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med 14:403–415
5. Capurro PU, Eldridge JE (1978) Solvent exposures and cancer. Lancet 324:942
6. Checkoway H, Wilcosky T, Wolf P, Tyroler H (1984) An evaluation of the associations of leukemia and rubber industry solvent exposures. Am J Med 5:239–249
7. Dubrow R, Wegman D (1984) Cancer and occupation in Massachusetts – a death certificate study. Am J Ind Med 6:207–230
8. Flodin U, Fredriksson M, Persson B, Axelson O (1988) Chronic lymphatic leukemia and engine exhausts, fresh wood, and DDT: a case-referent study. Br J Ind Med 45:33–38
9. Fonte R, Grigis L, Grigis P, Franco G (1982) Chemicals and Hodgkin's disease. Lancet 328:50
10. Franco G, Fonte R (1983) Malignant lymphomas and occupational risk in woodworkes. IRCS Med Sci 11:216–217
11. Gerin M, Siemiatycki J, Nadon L, Dewar R, Krewski D (1989) Cancer risk due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montreal. Int J Cancer 44:53–58
12. Greene MH, Brinton LA, Fraumeni JF, D'Amico R (1978) Familial and sporadic Hodgkin's disease associated with occupational wood exposure. Lancet 324:626–627
13. Grufferman S, Duong T, Cole P (1976) Occupation and Hodgkin's disease. J Natl Cancer Inst 57:1193–1195
14. Hardell L, Eriksson M, Lenner P, Lundgren E (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 43:169–176
15. Harrington JM, Shannon HS (1975) Mortality study of pathologists and medical laboratory technicians. Br Med J 4:329–332
16. Ishimaru T, Okada H, Tomiyasu T, Tsuchimoto T, Hoshino T, Ichimaru M (1971) Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Am J Epidemiol 93:157–165
17. Jäppinen P, Pukkala E, Tola S (1989) Cancer incidence of workers in a Finnish sawmill. Scand J Work Environ Health 15:18–23
18. Kauppinen TP, Partanen TJ, Nurminen MM, Nickels JI, Hernberg SG, Hakulinen TR, Pukkala EI, Savonen ET (1986) Respiratory cancers and chemical exposures in the wood industry: a nested case-control study. Br J Ind Med 43:84–90
19. Kauppinen T, Partanen T (1988) Use of plant- and period-specific job-exposure matrices in studies on occupational cancer. Scand J Work Environ Health 14:161–167
20. Kawachi I, Pearce N, Fraser J (1989) A New Zealand Cancer Registry-based study of cancer in wood workers. Cancer 64: 2609–2613
21. Lindquist R, Nilsson B, Eklund G, Gahrton G (1987) Increased risk of developing acute leukemia after employment as a painter. Cancer 60:1378–1384
22. Linet MS, Malker HSR, McLaughlin JK, Weiner JA, Stone BJ, Blot WJ, Ericsson JLE, Fraumeni JF (1988) Leukemias and occupation in Sweden: a registry-based analysis. Am J Ind Med 14:319–330
23. Milham S Jr (1974) A study of the mortality experience of the AFL-CIO United Brotherhood of Carpenters and Joiners of America, 1969–1970. DHEW Publ. No (NIOSH) 74–129. National Technical Information Service, Springfield, VA
24. Milham S Jr, Hesser JE (1967) Hodgkin's disease in woodworkers. Lancet 317:136–137
25. Miller BA, Blair AE, Raynor HL, Stewart PA, Hoar Zahm S, Fraumeni JF Jr (1989) Cancer and other mortality patterns among United States furniture workers. Br J Ind Med 46:508–515
26. Morgan RW, Claxton KW, Kaplan SD, Parsons JM, Wong O (1985) Mortality of paint and coating industry workers. J Occup Med 27:377–378
27. Morton W, Marjanovic D (1984) Leukemia incidence by occupation in the Portland-Vancouver metropolitan area. Am J Ind Med 6:185–205
28. Oleske D, Golomb HM, Farber MD, Levy PS (1985) A case-control inquiry into the etiology of hairy cell leukemia. Am J Epidemiol 121:675–683
29. Olsson H, Brandt L (1988) Risk of non-Hodgkin lymphoma among men occupationally exposed to organic solvents. Scand J Work Environ Health 14:246–251
30. Partanen T, Kauppinen T, Hernberg S, Nickels J, Luukkonen R, Hakulinen T, Pukkala E (1990) Formaldehyde exposure and respiratory cancer among woodworkers – an update. Scand J Work Environ Health 16:394–400
31. Persson B, Dahlander AM, Fredriksson M, Noorlind Brage H, Ohlson CG, Axelson O (1989) Malignant lymphomas and occupational exposures. Br J Ind Med 46:516–520
32. Petersen GR, Milham S (1974) Hodgkin's disease mortality and occupational exposure to wood. J Natl Cancer Inst 53: 957–958
33. Stayner LT, Elliott L, Blade L, Keenlyside R, Halperin W (1988) Formaldehyde in the garment industry. Am J Ind Med 13:667–681
34. Stellman S, Garfinkel L (1984) Cancer mortality among woodworkers. Am J Ind Med 5:343–357
35. Wiklund K, Lindfors BM, Holm LE (1988) Risk of malignant lymphoma in Swedish agricultural and forestry workers. Br J Ind Med 45:19–24