

## ORIGINAL ARTICLE

## Occupation and malignant lymphoma: a population based case control study in Germany

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**Aims:** To identify occupations suspected to be associated with malignant lymphoma and to generate new hypotheses about occupational risks in a multicentre, population based case control study.

**Methods:** Male and female patients with malignant lymphoma (n = 710) aged 18–80 years of age were prospectively recruited in six study regions in Germany. For each newly recruited lymphoma case, a sex, region, and age matched control was drawn from the population registers. Odds ratios and 95% confidence intervals for major occupations and industries were calculated using conditional logistic regression analysis, adjusted for smoking (in pack-years) and alcohol consumption. Patients with specific lymphoma subentities were additionally compared with the entire control group using unconditional logistic regression analysis.

**Results:** The following economic/industrial sectors were positively associated with lymphoma: food products, beverages, tobacco; paper products, publishing and printing; and metals. Chemicals; real estate, renting, and business activities were negatively associated with lymphoma diagnosis. The authors observed an increased overall lymphoma risk among architects; maids; farmers; glass formers; and construction workers. Shoemaking and leather goods making was negatively associated with the lymphoma diagnosis (although based on small numbers). In the occupational group analysis of lymphoma subentities, Hodgkin's lymphoma was significantly associated only with rubber and plastic products making; diffuse large B cell lymphoma risk was considerably increased among metal processors; follicular lymphoma showed highly significant risk increases for several occupational groups (medical, dental, and veterinary workers; sales workers; machinery fitters; and electrical fitters); and multiple myeloma showed a particularly pronounced risk increase for farmers as well as for agriculture and animal husbandry workers.

**Conclusions:** The results partly confirm previously defined occupational risks. Occupational risk factors for follicular lymphomas might differ from the overall risk factors for malignant lymphoma.

During the past few decades, the incidence of non-Hodgkin's lymphoma (NHL) increased in most Western countries.<sup>1–4</sup> Only recent data indicate a leveling off of this trend. In Germany, NHL made up an estimated 3% of the male and 3.4% of the female incident cancer cases in 2000.<sup>5</sup>

The aetiology of malignant lymphoma is still largely unknown. Strong evidence exists for the association between NHL and congenital or acquired immunosuppression, especially AIDS.<sup>6–10</sup> Immune factors also seem to play a role in the aetiology of Hodgkin's lymphoma:<sup>7</sup> an excess has been found after transplantations<sup>11,12</sup> as well as among HIV infected patients.<sup>13,14</sup>

The known risk factors explain only a small proportion of malignant lymphoma. Several studies point to a potential aetiological role of occupational factors to malignant lymphoma. Hodgkin lymphomas have been found in excess among farmers or carpenters,<sup>15,16</sup> welding workers,<sup>17</sup> wood workers,<sup>18,19</sup> workers in the paper industry,<sup>20</sup> painters,<sup>21</sup> workers in the chemical industry exposed to solvents, and teachers.<sup>22</sup> Increased NHL risks have been found among painters;<sup>23</sup> farmers;<sup>15,24</sup> female physicians, machine fitters, metal workers, cowmen;<sup>25</sup> shoe makers, cobblers, wood workers;<sup>20</sup> furniture makers, dairy workers;<sup>26</sup> printers and workers in the porcelain industry;<sup>27</sup> leather manufacturing;<sup>28</sup> textile;<sup>29,30</sup> or chemical industry.<sup>16</sup>

The aim of the present multicentre, population based case control study is to identify occupations suspected to be associated with lymphoma risk and to generate new hypotheses about occupational risks. The diagnosis is based on the new WHO classification<sup>31,32</sup> which is believed to be

more appropriate for aetiological research than earlier classifications.

## MATERIALS AND METHODS

### Study population

The study design has been described in detail in previous publications.<sup>33,34</sup> Briefly, the study was conducted under the leadership of the German Cancer Research Center (DKFZ) in six defined regions in Germany: Ludwigshafen/Upper Palatinate, Heidelberg/Rhine-Neckar-County, Würzburg/Lower Frankonia, Hamburg, Bielefeld/Guetersloh, and Munich. In the mentioned study areas, all hospital and ambulatory physicians involved in the diagnosis and therapy of malignant lymphoma were asked to identify prospectively all patients aged 18–80 years with newly diagnosed lymphoma (NHL and Hodgkin's lymphoma). Lymphoma patients were required to be resident in the study area and to be familiar with the German language.

All cases were classified according to the new WHO classification.<sup>31,32</sup> The WHO classification of lymphoma defines subentities which are based, to a larger extent than previous classifications, on their natural history and biological features. Of 710 participating lymphoma patients (participation rate, 87.4%), 115 suffered from Hodgkin lymphoma, 554 suffered from B-non-Hodgkin's lymphoma, 35 from T-non-Hodgkin's lymphoma, one suffered from combined B-non-Hodgkin's lymphoma and Hodgkin's lymphoma, and

**Abbreviations:** CLL, chronic lymphocytic leukaemia; JEM, job exposure matrix; NHL, non-Hodgkin's lymphoma; SLL, small lymphocytic lymphoma

five from other lymphoma. According to the WHO classification, B-non-Hodgkin's lymphoma were further subdivided into the following subentities (only subentities with  $n > 30$  cases are mentioned): diffuse large B-cell lymphoma ( $n = 158$ ); follicular lymphoma ( $n = 92$ ); chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) ( $n = 104$ ); plasma cell myeloma (plasmacytoma) ( $n = 76$ ); and marginal zone B-cell lymphoma ( $n = 38$ ).

For each newly recruited lymphoma case, a sex, region, and age matched (plus or minus 1 year of birth) population control was drawn from the population registration office. Control subjects that were not familiar with the German language were excluded from the study. For each participant who had to be excluded from the study or rejected participation, the recruitment procedure was repeated. Among population controls the participation rate was 44.3%. Of the non-participants, 24.9% could not be traced, 51% refused to participate due to lack of interest, and 11.5% due to health problems. The remaining 12.4% mentioned other reasons for non-participation. A total of 710 case control pairs were included in the analysis.

### Data collection

In a face to face interview, intensively trained interviewers elicited detailed information about the medical history (including medication), lifestyle (including smoking, alcohol consumption, and leisure time activities), and occupation. Three cases could not be interviewed and four additional cases lacked the information regarding the occupational history. All residual subjects were personally interviewed. The interviewers documented a complete occupational history, including every occupational period that lasted at least one year. For every job held, information was elicited about the start and the end of the job phase, job title, industry, and specific job tasks. Study subjects having held potentially hazardous jobs were additionally asked to reply to job task-specific supplementary questions. For this purpose, a set of 14 job task-specific supplementary questionnaires had been developed following Bolm-Audorff *et al.*<sup>35</sup>

### Exposure assessment

Job titles and branches of industry were coded blind to the case control status by two experienced coders in the Frankfurt Institute for Occupational Medicine, according to the International Standard Classification of Occupations (ISCO-68) and the Statistical Classification of Economic Activities in the European Community (NACE Rev 1). These classifications, based on five and four digits, respectively, increase the specificity of each occupation/industry with increasing number of digits (for example, ISCO code 92: printers and related workers, and ISCO 92155: photo-type-setting machine operator).

### Characteristics of cases and control subjects

The characteristics of the cases with lymphoma and control subjects are available online (see <http://www.occnvmed.com/supplemental>). The mean (standard deviation) age of cases with any lymphoma ( $n = 710$ ) was 56.1 (SD 16.3) years; of cases having Hodgkin's lymphoma ( $n = 116$ ), 38.8 (SD 15.9) years, of cases having B-non-Hodgkin's lymphoma ( $n = 554$ ) 60.2 (SD 13.6) years; and of cases having T non-Hodgkin's lymphoma ( $n = 35$ ) 50.6 (SD 17.0) years. Of the 710 case control pairs, 55% were male and 45% were female. The average number of different occupations (held for at least one year) was 2.4 for lymphoma cases as well as for control subjects. The average count of different industries was 2.9 for lymphoma cases as well as for control subjects.

### Data analysis

Major occupations and industries were a priori formed on the basis of the two digit job title codes and the three digit industry codes, respectively. Risk by job duration was calculated for major occupations and industries using two categories of duration (1–10 years, more than 10 years). Those who were never employed in the particular occupation or industry were included in the reference category. In the analysis of occupational groups, only subjects having worked in non-exposed white collar works as main occupation were included in the reference category. Missing values were analysed as a separate category (results not shown here).

At first, we analysed the relation between industrial as well as occupational groups and lymphomas as a whole ( $n = 710$ ). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression analysis, adjusted for smoking (in pack-years) and alcohol consumption. Lymphomas comprise a multitude of pathogenetically different subentities with little information to what extent they are also aetiologically different or share common environmental factors. Secondly, we calculated odds ratios for the more frequent lymphoma subentities (with  $n > 30$  cases; please see under Study population). To increase the statistical power, patients with these lymphoma subentities were compared separately with the entire control group ( $n = 710$ ) using unconditional logistic regression analysis. Covariates included in this unmatched analysis were age (as a continuous variable), sex, region, smoking (in pack-years), and alcohol consumption. To exclude potentially "non-causal" occupational exposures from analysis, in an additional latency analysis, only exposures up to 10 years before the lymphoma diagnosis were considered.

### RESULTS

Table 1 presents odds ratios and 95% confidence intervals (CI) for the association between economic or industrial sectors and the entire case group ( $n = 710$  lymphoma patients); only the results for industrial groups with at least five lymphoma cases are reported. Significantly increased risks can be seen for the sectors food products, beverages, tobacco (NACE 150-160) and pulp paper, paper products, publishing and printing (NACE 210-223). In the subentity analysis, for the sector "food products, beverages, tobacco (NACE 150-160) particularly strongly increased odds ratios can be seen for follicular lymphomas and CLL (table 2), while for other subentities the numbers were too small to provide conclusive results. For pulp papers, paper products, publishing and printing (NACE 210-223) the odds ratios were significantly increased for multiple myeloma as well as T cell and NK cell NHL.

For the sector basic metals and fabricated metal products (NACE 270-287) an overall null result covers a strongly increased odds ratio among long term exposed subjects; however, based on small numbers. In the subentity analysis significant increases are found for Hodgkin's lymphoma.

Significantly decreased odds ratios occur for the sectors chemicals, chemical products, and man-made fibres (NACE 240-247) and real estate, renting, business activities (NACE 700-748) with consistent but non-significant decreases for short term and long term exposures. In the subentity analysis, the negative association with these industrial sectors loses its statistical significance.

The top level evaluation (all lymphoma combined) might mask associations between specific factors and individual subentities. Therefore, in table 2 all significant associations between industrial sectors and lymphoma subentities are reported (except for B-NHL in total, which mainly reflect the risks of all lymphomas combined). Several associations with economic sectors are found which are statistically significant

**Table 1** Odds ratios and 95% confidence limits for economic/industrial sectors in relation to lymphomas (n=710 matched pairs; only sectors with at least five exposed cases are presented)

NACE Rev 1	Industry	1–10 years				>10 years				All	
		Cases	Controls	Adj OR*	95% CI	Cases	Controls	Adj OR*	95% CI	Adj OR*	95% CI
010–020	Agriculture, hunting, forestry	59	63	1.0	0.6–1.4	26	18	1.5	0.8–2.8	1.1	0.8–1.6
100–145	Mining and quarrying	5	5	0.9	0.2–3.8	–	1	–	–	0.7	0.2–2.7
150–160	Food products, beverages, tobacco	44	30	1.5	0.9–2.5	27	15	1.9	1.0–3.8	1.7†	1.1–2.5
170–183	Textiles, textile products	37	39	0.9	0.6–1.6	15	19	0.8	0.4–1.7	0.9	0.6–1.4
190–193	Leather, leather products	7	18	0.4†	0.1–0.9	7	2	3.4	0.7–16.9	0.7	0.3–1.4
200–205	Wood, wood products	10	11	0.7	0.3–1.8	3	4	0.7	0.1–3.1	0.7	0.3–1.6
210–223	Pulp paper, paper products, publishing and printing	24	14	1.7	0.9–3.4	19	12	1.7	0.8–3.6	1.7†	1.0–2.8
230–233	Coke, refined petroleum products, nuclear fuel	3	2	1.3	0.2–7.9	3	1	3.5	0.4–34.6	2.0	0.5–8.1
240–247	Chemicals, chemical products, and man-made fibres	26	35	0.6	0.3–1.1	34	47	0.7	0.4–1.1	0.6†	0.4–0.9
250–252	Rubber, plastic products	14	10	1.4	0.6–3.2	5	6	0.9	0.2–3.2	1.2	0.6–2.5
260–268	Other non-metallic mineral products	13	13	0.9	0.4–2.1	6	9	0.8	0.2–2.3	0.9	0.5–1.7
270–287	Basic metals and fabricated metal products	35	37	0.8	0.5–1.4	22	9	3.3‡	1.4–7.9	1.2	0.8–1.8
290–297	Machinery and equipment NEC	45	50	0.9	0.6–1.4	33	34	0.9	0.5–1.6	0.9	0.7–1.3
300–335	Electrical and optical equipment	26	31	0.8	0.5–1.4	16	21	0.9	0.4–1.7	0.8	0.5–1.3
340–355	Transport equipment	22	30	0.7	0.4–1.2	16	11	1.5	0.7–3.4	0.9	0.6–1.4
360–372	Manufacturing NEC	23	20	1.0	0.5–1.9	5	14	0.4	0.1–1.1	0.8	0.5–1.3
400–410	Electricity, gas, water supply	10	6	1.7	0.6–4.8	6	7	0.8	0.3–2.5	1.2	0.6–2.6
450–455	Construction	63	53	1.1	0.7–1.6	52	40	1.3	0.8–2.1	1.2	0.8–1.6
500–527	Wholesale retail trade, repair of motor vehicles etc	108	108	1.1	0.8–1.5	101	82	1.2	0.9–1.7	1.1	0.9–1.5
550–555	Hotels, restaurants	49	23	1.9†	1.1–3.2	15	21	0.7	0.4–1.5	1.4	0.9–2.1
600–642	Transport, storage, communication	32	36	0.9	0.5–1.4	39	41	0.9	0.6–1.5	0.9	0.6–1.3
650–672	Financial intermediation	17	27	0.7	0.4–1.3	26	30	0.9	0.5–1.5	0.8	0.5–1.2
700–748	Real estate, renting, business activities	53	66	0.8	0.5–1.2	30	51	0.6†	0.4–1.0	0.7†	0.5–1.0
750–753	Public administration defence, compulsory social security	125	141	0.8	0.6–1.2	42	48	0.8	0.5–1.3	0.8	0.6–1.1
800–804	Education	191	191	1.0	0.8–1.3	31	44	0.7	0.4–1.2	1.0	0.7–1.2
850–853	Health, social work	49	50	1.0	0.6–1.5	36	33	1.1	0.7–1.9	1.0	0.7–1.5
900–930	Other community, social, personal service activities	30	32	0.9	0.5–1.6	29	26	1.1	0.6–1.9	1.0	0.7–1.5
950–950	Private households with employed persons	50	47	1.1	0.7–1.7	8	5	3.3	0.8–13.6	1.2	0.8–1.9

Reference group: having worked 0 years in the specific industry.

\*Odds ratio (OR) adjusted for smoking (pack-years) and alcohol consumption.

†p&lt;0.05; ‡p&lt;0.01.

NEC, not elsewhere classified.

only for one or few lymphoma subgroups. Importantly, most of them are not based on small numbers. Partially, the involved sectors provide increased odds ratios for several lymphoma subgroups—for example, construction (NACE 450-455) to Hodgkin's lymphoma and CLL/SLL, "wholesale retail trade, repair of motor vehicles etc" (NACE 500-527) to CLL/SLL and marginal zone B cell lymphoma.

Tables 3 and 4 present the odds ratios for the association between occupational groups and lymphoma. In table 3, all lymphomas are combined; in table 4, statistically significant subentity specific odds ratios are presented. Increased odds ratios can be seen for the five occupational groups architects, engineers, and related technicians (ISCO 02-03), maids (ISCO 54), farmers (ISCO 60-61), glass formers, potters (ISCO 89) and bricklayers, carpenters, and other construction workers (ISCO 95). A decreased odds ratio can be seen for shoemakers and leather goods makers (ISCO 80). The separation of data into short term and long term exposures indicates that the altered risks seem not to be confined to the subgroup of long term exposed subjects. However, in a further occupational group, plumbers, welders, sheet metal and structural metal preparers and erectors (ISCO 87), an overall unaltered odds ratio masks an increased odds ratio among the short term exposed individuals.

For the mentioned occupational groups, the subentity analysis reveals risk patterns which do not substantially differ from the risks for all lymphoma combined, with one exception: the increased odds ratio for multiple myeloma among farmers (OR=9.2; 95% CI 2.6 to 33.1; table 4) exceeds by far the odds ratio for all lymphomas combined (OR=2.4; 95% CI 1.1 to 5.4) and is despite the small numbers highly significant for short term exposures as well as for long term exposures.

The subentity analysis reveals increased risks among some occupational groups that are not statistically associated with all lymphomas combined: rubber and plastic product makers (ISCO 90) constitute the only occupational group to be significantly associated with Hodgkin's lymphoma. For diffuse large B cell lymphoma, the odds ratio is considerably and highly significantly increased for metal processors (ISCO 72); however, numbers are small. Several occupational groups are highly significantly associated with follicular lymphoma: medical, dental, and veterinary workers (ISCO 06-07); sales workers (ISCO 41-45); machinery fitters, machine assemblers, and precision instrument makers (ISCO 84); and electrical fitters and related electrical and electronics workers (ISCO 85). The multiple myeloma risk for material handlers, dockers, and freight handlers (ISCO 97) is consistently increased over the short term and long term exposure categories; long term agriculture and animal husbandry workers (ISCO 62) show a considerably increased multiple myeloma risk.

In a latency analysis (data not shown; detailed results are available from the authors), only exposures up to 10 years before lymphoma diagnosis or (in controls) to lymphoma diagnosis of the matched case were included. The exclusion of recent occupational exposures did not substantially change the results for all lymphomas combined. The latency analysis of lymphoma subentities led to few changes in the results: having worked in the industrial sector basic metals and fabricated metal products was no longer significantly associated with Hodgkin's lymphoma. In the latency analysis, electrical fitters lost their significant association with diffuse large B cell lymphoma, but were significantly associated with chronic lymphocytic leukaemia. Having worked more than 10 years as a transport equipment operator was significantly

**Table 2** Odds ratios and 95% confidence limits for significant associations of economic/industrial sectors with specific lymphoma subentities

NACE Rev 1	Industry	1–10 years				>10 years				All	
		Cases	Controls	Adj OR†	95% CI	Cases	Controls	Adj OR†	95% CI	Adj OR†	95% CI
<b>Hodgkin's lymphoma (n=116)</b>											
270–287	Basic metals and fabricated metal products	9	37	2.1	0.9–5.0	3	9	4.3†	1.0–18.4	2.4†	1.1–5.3
450–455	Construction	14	53	2.3†	1.1–4.8	8	40	1.7	0.7–4.3	2.0†	1.1–3.8
<b>B cell non-Hodgkin's lymphoma (total) (n=554)</b>											
<i>Diffuse large B cell lymphoma (n=158)</i>											
270–287	Basic metals and fabricated metal products	8	37	1.0	0.5–2.3	6	9	4.3‡	1.4–12.8	1.5	0.8–3.0
550–555	Hotels, restaurants	11	23	2.2†	1.0–4.6	10	21	2.2†	1.0–5.0	2.2†	1.3–3.9
<i>Follicular lymphoma (n=92)</i>											
150–160	Food products, beverages, tobacco	9	30	2.4†	1.1–5.4	5	15	3.3†	1.1–9.7	2.7‡	1.4–5.2
190–193	Leather, leather products	4	18	1.5	0.5–4.9	3	2	13.9‡	2.2–89.7	2.6†	1.0–6.7
340–355	Transport equipment	2	30	0.5	0.1–2.4	4	11	3.5†	1.0–11.6	1.3	0.5–3.2
850–853	Health, social work	8	50	1.2	0.5–2.8	13	33	3.4‡	1.7–7.1	2.1†	1.2–3.6
<i>Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) (n=104)</i>											
150–160	Food products, beverages, tobacco	7	30	1.8	0.7–4.3	11	15	5.0‡	2.2–11.6	3.0‡	1.6–5.5
450–455	Construction	13	53	1.5	0.7–3.0	15	40	2.1†	1.1–4.1	1.8†	1.0–3.0
500–527	Wholesale retail trade, repair of motor vehicles etc	14	108	1.3	0.7–2.4	21	82	1.9†	1.1–3.4	1.6†	1.0–2.5
<i>Plasma cell myeloma (plasmacytoma) (n=76)</i>											
010–020	Agriculture, hunting, forestry	7	63	1.0	0.4–2.3	8	18	4.1‡	1.7–10.5	1.7	0.9–3.2
210–223	Pulp paper, paper products, publishing and printing	5	14	3.5†	1.1–11.5	4	12	3.3	1.0–10.8	3.4‡	1.4–8.0
750–753	Public administration, defence, compulsory social security	5	141	0.2‡	0.1–0.6	6	48	0.9	0.4–2.3	0.4†	0.2–0.8
<i>Marginal zone B cell lymphoma (n=38)</i>											
500–527	Wholesale retail trade, repair of motor vehicles etc	12	108	3.2‡	1.4–7.1	9	82	2.8†	1.2–6.6	3.0‡	1.5–5.9
750–753	Public administration defence, compulsory social security	7	141	1.4	0.5–3.6	7	48	3.6†	1.4–9.4	2.0	0.9–4.4
<b>T cell and NK cell non-Hodgkin's lymphoma (n=35)</b>											
210–223	Pulp paper, paper products, publishing and printing	4	14	8.8‡	2.5–30.7	1	12	2.2	0.3–18.2	5.5‡	1.9–16.0

All lymphoma subentities with n>30 are included in the analysis; odds ratios for B-NHL in total are not shown.

†Odds ratio (OR) adjusted for age, sex, region, smoking (pack-years), and alcohol consumption.

‡p<0.05; †p<0.01.

associated with follicular lymphoma (ISCO 98). According to the latency analysis, sales workers (ISCO 41-45) showed—in addition to the increased follicular lymphoma risk—a significantly increased CLL and marginal zone B cell lymphoma risk. Having worked more than 10 years as an agriculture and animal husbandry worker (ISCO 62) was associated with diffuse large B cell lymphoma. Finally, cabinet makers (ISCO 51) had a significantly increased CLL risk (<10 years exposure) and plasmacytoma risk in the latency analysis.

## DISCUSSION

In this study, several economical/industrial sectors and occupational groups show an increased and some a decreased lymphoma risk. Due to the broad definition of the respective categories, these findings are not directly conclusive for a causal relation. However, they provide indications to potentially hazardous exposures which may be worth considering in more detail in subsequent analyses. These include solvents, electromagnetic fields, mineral dusts, pesticides, viruses, and others.

## Solvents

Exposure to solvents can occur in the economical/industrial sectors (a) pulp paper, paper products, publishing and printing, (b) chemicals, chemical products, and man-made fibres, (c) basic metals and fabricated metal products, and in the occupational groups (d) shoemakers and leather goods makers, (e) printers, (f) rubber and plastic product makers, and to some extent among (g) bricklayers, carpenters, and other construction workers, (h) maids on the level of household application, (i) plumbers, welders, sheet metal and structural metal preparers, and erectors, (j) metal processors, (k) machinery fitters, and (l) cabinet makers. For the mentioned industries and occupations, increased odds ratios were observed with the exception of (b); shoemakers and leather goods makers (d) are significantly negatively associated with all lymphomas combined, but (non-significantly) positively associated with follicular lymphoma. Increased risks among cabinet makers (l) were found solely in the latency analysis. The mentioned increased risks are concordant with several previous studies which pointed to a potential relation between solvent exposure and lymphoma.<sup>36–43</sup> Due to small sample sizes, we could not conclusively determine whether the found increased risks are



**Table 3** Odds ratios and 95% confidence limits for occupational groups in relation to lymphomas (n = 710 matched pairs; only sectors with at least five cases are presented)

ISCO-68	Occupational group	1–10 years				>10 years				All	
		Cases	Controls	Adj OR*	95% CI	Cases	Controls	Adj OR*	95% CI	Adj OR*	95% CI
01; 05	Physical scientists; life scientists	7	7	1.3	0.4–3.9	7	10	0.8	0.3–2.3	1.0	0.5–2.2
02–03	Architects, engineers, and related technicians	21	16	2.0	1.0–4.2	34	32	1.5	0.9–2.7	1.7†	1.0–2.7
06–07	Medical, dental, veterinary, and related workers	21	27	0.9	0.5–1.6	17	18	1.3	0.6–2.6	1.0	0.6–1.7
11; 14; 17–18	Other professional and technical workers	5	6	1.0	0.3–3.3	8	4	2.3	0.7–7.9	1.5	0.6–3.6
13	Teachers	15	26	0.7	0.3–1.4	18	27	0.9	0.5–1.8	0.8	0.5–1.3
31; 35–38	Other clerical workers	25	15	2.2†	1.1–4.7	21	27	1.0	0.5–2.0	1.5	0.9–2.4
41–45	Sales workers	58	55	1.3	0.8–2.0	74	70	1.2	0.8–1.9	1.3	0.9–1.8
51	Working proprietors (catering and lodging services)	8	2	3.7	0.8–17.7	1	2	0.6	0.1–7.2	2.3	0.7–7.5
53	Cooks, waiters, bartenders	15	13	1.4	0.6–3.1	12	13	1.2	0.5–2.7	1.3	0.7–2.4
54	Maids	78	61	1.6†	1.1–2.9	15	8	2.8†	1.1–7.0	1.7‡	1.2–2.6
55	Building caretakers, charworkers, cleaners	17	15	1.3	0.6–2.7	8	12	0.7	0.3–1.9	1.1	0.6–1.9
56	Laundrers, dry cleaners, and pressers	6	9	0.8	0.3–2.5	5	2	3.4	0.6–18.5	1.3	0.5–3.2
57	Hairdressers, barbers, beauticians	5	5	1.1	0.3–3.9	3	7	0.5	0.1–2.0	0.7	0.3–1.9
58	Protective service workers	6	7	1.2	0.4–3.7	7	6	1.3	0.4–4.1	1.3	0.6–2.8
52; 59	Other service workers	14	12	1.4	0.6–3.2	5	5	1.3	0.4–4.8	1.4	0.7–2.8
60–61	Farmers	8	4	2.8	0.8–9.7	10	6	2.1	0.7–6.1	2.4†	1.1–5.4
62	Agriculture and animal husbandry workers	39	53	0.8	0.5–1.4	18	12	1.9	0.9–4.1	1.0	0.7–1.6
70	Production supervisors and general foremen	9	9	1.3	0.5–3.4	10	17	0.7	0.3–1.6	0.9	0.5–1.7
72	Metal processors	6	5	1.4	0.4–5.1	4	1	5.2	0.6–48.8	2.1	0.7–6.3
74	Chemical processors and related workers	12	11	1.1	0.5–2.7	9	3	3.4	0.9–13.0	1.6	0.8–3.3
75	Spinners, weavers, knitters, dyers	10	10	1.3	0.5–3.3	1	5	0.3	0.03–2.5	1.0	0.4–2.2
77	Food and beverage processors	16	14	1.4	0.6–3.0	11	5	2.8	0.9–8.5	1.7	0.9–3.3
79	Tailors, dressmakers, sewers, upholsterers	25	26	1.2	0.6–2.3	15	14	1.3	0.6–2.8	1.3	0.7–2.2
80	Shoemakers and leather goods makers	5	14	0.4	0.1–1.1	1	4	0.3	0.04–3.0	0.4†	0.1–1.0
81	Cabinet makers	17	10	1.7	0.7–4.0	8	15	0.6	0.3–1.5	1.1	0.6–1.9
83	Blacksmiths, toolmakers, and machine tool operators	21	32	0.8	0.4–1.4	14	14	1.2	0.5–2.5	0.9	0.5–1.5
84	Machinery fitters, machine assemblers, and precision instrument makers (except electrical)	48	49	1.1	0.7–1.8	38	32	1.4	0.8–2.4	1.2	0.8–1.8
85	Electrical fitters and related electrical and electronics workers	24	31	0.9	0.5–1.6	19	10	2.2	1.0–5.1	1.2	0.7–2.0
87	Plumbers, welders, sheet metal and structural metal preparers, and erectors	31	19	1.9†	1.0–3.5	8	20	0.5	0.2–1.2	1.2	0.7–2.1
89	Glass formers, potters	4	1	5.4	0.6–49.4	4	1	6.4	0.7–58.8	5.9†	1.2–28.4
90	Rubber and plastics product makers	11	9	1.7	0.7–4.4	2	2	1.4	0.2–10.6	1.7	0.7–3.9
92	Printers	7	11	0.9	0.3–2.4	11	6	2.4	0.9–6.8	1.4	0.7–2.9
93	Painters	4	5	0.9	0.2–3.6	6	5	1.1	0.3–3.9	1.0	0.4–2.6
94	Production and related workers	7	6	1.2	0.4–3.6	–	3	–	–	0.9	0.3–2.7
95	Bricklayers, carpenters, and other construction workers	32	30	1.3	0.7–2.4	25	10	2.9†	1.3–6.9	1.7†	1.0–2.8
97	Material handling and related equipment operators, dockers, and freight handlers	25	20	1.3	0.7–2.5	12	6	2.0	0.7–5.6	1.5	0.9–2.6
98	Transport equipment operators	27	25	1.3	0.7–2.3	29	25	1.4	0.7–2.6	1.3	0.8–2.1
76; 78; 86; 91; 96; 99	Other production workers and labourers	32	24	1.4	0.8–2.6	14	12	1.3	0.6–2.9	1.4	0.8–2.3

Reference group: 0 years and non-exposed white collar works as main occupation: ISCO-68 groups 08, 09, 12, 15, 19, 20–21, 30, 32–34, 39, 40, 50 (statisticians, mathematicians, system analysts, economists, jurists, authors, journalists, other professional or technical workers; legislative officials and government administrators, managers, clerical supervisors; stenographers, typists, and card and tape punching machine operators, bookkeepers, cashiers, computing machine operators, other clerical related workers).

\*Odds ratio (OR) adjusted for smoking (pack-years) and alcohol consumption; probands with blue collar work as main occupation were analysed in a separate category (not shown).

†p<0.05; ‡p<0.01.

confined to specific target subentities. Some particularly strongly increased odds ratios indicate that such specific targets might exist (for example, multiple myeloma in the pulp paper, paper products, publishing and printing sector), but they might not necessarily be caused by solvents. Furthermore, in our study several occupations which can be expected to be prone to solvent exposure (for example, dry cleaners, painters) are not associated with lymphoma diagnosis. Larger study sizes to overcome the limitation of

too small sample sizes for a proper subentity analysis and the application of job exposure matrices (JEM) to focus on exposure to specific agents are the next steps required to prosecute these indications.

The decreased odds ratio just for the industrial sector chemicals, chemical products, and man-made fibres (b) points to a fundamental problem of analysing occupational cancer studies along industrial sectors: the grouping of employees by such sectors may lead to conglomerates of

**Table 4** Odds ratios and 95% confidence limits for significant associations of occupational groups with specific lymphoma subentities

ISCO-68	Occupational group	1-10 years				>10 years				All			
		Cases	Controls	Adj OR†	95% CI	Cases	Controls	Adj OR†	95% CI	Adj OR†	95% CI		
Hodgkin's lymphoma (n = 116)													
90	Rubber and plastics product makers	5	9	4.6†	1.2-17.0	-	2	-	-	3.9†	1.1-14.0		
B cell non-Hodgkin's lymphoma (total) (n = 554)													
Diffuse large B cell lymphoma (n = 158)													
02-03	Architects, engineers, and related technicians	6	16	3.3†	1.1-9.4	6	32	1.1	0.4-3.0	1.7	0.8-3.7		
53	Cooks waiters bartenders	3	13	1.5	0.4-5.5	6	13	3.1†	1.1-8.9	2.3	1.0-5.3		
54	Maids	24	61	†2.2	1.1-4.2	5	8	3.4†	1.0-11.7	2.3†	1.2-4.3		
72	Metal processors	3	5	4.1	0.9-19.7	3	1	-	-	7.3†	2.1-26.0		
85	Electrical fitters and related electrical and electronics workers	4	31	0.6	1.2-2.1	5	10	3.2†	1.0-10.5	1.2	0.5-2.9		
Follicular lymphoma (n = 92)													
02-03	Architects, engineers, and related technicians	2	16	3.1	0.6-15.6	6	32	3.0	1.0-9.2	3.0†	1.1-8.2		
06-07	Medical, dental, veterinary, and related workers	7	27	2.5	0.9-6.7	6	18	4.0†	1.4-11.7	3.1†	1.4-6.8		
41-45	Sales workers	12	55	3.2†	1.3-7.7	11	70	2.5†	1.0-6.0	2.8†	1.3-5.9		
74	Chemical processors and related workers	3	11	3.0	0.7-12.8	2	3	10.8†	1.6-73.4	4.3†	1.3-14.7		
77	Food and beverage processors	3	14	2.8	0.7-10.9	3	5	6.4†	1.3-31.2	3.8†	1.3-11.1		
84	Machinery fitters, machine assemblers, and precision instrument makers (except electrical)	6	49	2.3	0.8-6.5	9	32	5.3†	2.0-14.1	3.4†	1.5-7.8		
85	Electrical fitters and related electrical and electronics workers	5	31	2.1	0.7-6.4	5	10	9.3†	2.7-32.4	3.5†	1.5-8.4		
92	Printers	2	11	2.2	0.4-11.3	3	6	6.3†	1.3-29.8	3.6†	1.2-11.4		
Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) (n = 104)													
54	Maids	12	61	2.5†	1.1-5.9	1	8	1.6	0.2-14.6	2.4†	1.0-5.6		
58	Protective service workers	3	7	3.3	0.7-14.5	2	6	3.7	0.6-21.2	3.4†	1.0-11.3		
77	Food and beverage processors	2	14	1.1	0.2-5.3	5	5	8.4†	2.1-32.8	2.9†	1.1-8.0		
95	Bricklayers, carpenters and other construction workers	6	30	1.3	0.5-3.7	6	10	4.3†	1.3-13.7	2.0	0.9-4.7		
97	Material handling and related equipment operators, dockers and freight handlers	5	20	1.9	0.6-5.8	3	6	5.2†	1.1-23.3	2.5	1.0-6.5		
Plasma cell myeloma (plasmacytoma) (n = 76)													
31; 35-38	Other clerical workers	3	15	3.5	0.9-14.6	4	27	2.5	0.7-8.9	2.9†	1.0-8.2		
54	Maids	8	61	2.4	0.9-6.7	3	8	5.9†	1.3-27.2	2.9†	1.1-7.4		
55	Building caretakers, charworkers, cleaners	1	15	1.3	0.2-11.0	4	12	5.1†	1.3-19.7	3.1	1.0-10.1		
60-61	Farmers	2	4	10.4†	1.5-69.8	3	6	8.6†	1.8-40.0	9.2†	2.6-33.1		
62	Agriculture and animal husbandry workers	4	53	0.9	0.3-3.0	6	12	7.2†	2.2-24.2	1.9	0.8-4.9		
95	Bricklayers, carpenters, and other construction workers	6	30	3.6†	1.1-11.3	3	10	4.7†	1.0-21.4	3.9†	1.4-10.9		
97	Material handling and related equipment operators, dockers, and freight handlers	5	20	3.9†	1.2-12.5	3	6	8.1†	1.6-41.3	4.8†	1.7-13.2		

All lymphoma subentities with n > 30 are included in the analysis; odds ratios for B-NHL in total are not shown.

†Odds ratio (OR) adjusted for age, sex, region, smoking (pack-years), and alcohol consumption.

†p < 0.05; ††p < 0.01.

rather different workplaces and factual exposures with unpredictable overall risks. When employees in the chemical sector with non-exposed white collar work as main occupation (nine cases, 17 control subjects) were excluded from the analysis, the negative association between working in the chemical sector and lymphoma diagnosis lost its statistical significance.

In accordance with Persson *et al.*,<sup>17</sup> our data suggest an association between rubber and plastics work and Hodgkin's lymphoma, but not NHL (except marginal zone B cell lymphoma). In a later publication, the mentioned study group also revealed an increased NHL risk for workers exposed to plastic and rubber chemicals.<sup>44</sup> Rubber and plastics workers might be occupationally exposed to solvents (particularly benzene), aromatic amines, nitrosamines, and polycyclic aromatic hydrocarbons. In 1982 an International Agency for Research on Cancer (IARC) working group<sup>45</sup> concluded that there was sufficient evidence for excess mortality from leukaemia among workers employed in the rubber industry. A recently published cohort study<sup>46</sup> revealed an increased mortality from leukaemia, but not from NHL among rubber hydrochloride workers. Similarly, in a large German cohort study, mortality from leukaemia (ICD-9 204-208), but not from lymphoma (ICD-9 200-203) was significantly increased among rubber workers in the areas "preparation of materials" and "technical rubber goods".<sup>47</sup> In our study, chronic lymphocytic leukaemia risk was not significantly increased among rubber workers; however, numbers were small. Although there is nevertheless sufficient evidence for an association between rubber work and leukaemia, the evidence to date for an association between rubber work and lymphoma is weak. However, one has to point out that according to the ICD classification some NHL (lymphatic leukaemia) are classified as leukaemia, not as lymphoma. Therefore most epidemiological studies on leukaemia have included some NHL cases in their case definition.

### Electromagnetic fields

In our study, the occupational groups plumbers and welders as well as electrical workers showed an increased odds ratio. As a potentially underlying commonality, the exposure to electromagnetic fields has to be taken into account, though the so far available literature appears inconsistent. For orientation, we took a first look on exposure assessment by a Finnish job exposure matrix (FINJEM)<sup>48</sup> and found that only follicular lymphoma were significantly positively associated with magnetic field exposure. Several studies point to a potential relation between electromagnetic fields and NHL;<sup>26 42 49-55</sup> other studies fail to demonstrate an excess risk in NHL among people exposed to electromagnetic fields.<sup>28 56-59</sup> Though several potential modes of action of electromagnetic fields on calcium ion homeostasis,<sup>60</sup> protein kinases,<sup>61</sup> ornithine decarboxylase,<sup>62</sup> and immune response of cells<sup>63</sup> have been proposed, convincing mechanistic pathways from electromagnetic fields to lymphoma are still lacking.

### Mineral dusts

The two mentioned occupational groups (plumbers and welders as well as electrical workers), together with chemical processors and construction workers, might also have been exposed to mineral dusts including asbestos. Several epidemiological studies point to a potential aetiological relevance of asbestos exposure to lymphoma;<sup>64-66</sup> (for an overview see Becker *et al.*<sup>67</sup>) other studies do not support this relation.<sup>23 26 68-71</sup> Dodson *et al.*<sup>72</sup> detected asbestos fibres in the thoracic lymph nodes of exposed subjects. Therefore, lymph nodes as part of the drainage system of the gastrointestinal organs might get directly in contact with asbestos fibres. As an alternative

pathophysiological explanation, lymph nodes might be indirectly involved in the inflammatory process related to the interaction between the fibres inhaled or ingested and the respective tissues.<sup>67 73</sup> When the exposure to asbestos was assessed by the FINJEM, low asbestos exposure was found to be significantly associated with B cell NHL in total, follicular lymphoma, and marginal cell lymphoma. In accordance with these results, Blair *et al.* revealed a significant association between asbestos exposure and follicular lymphoma.<sup>27</sup>

### Pesticides

The increased odds ratio of farmers and agriculture workers points to several potentially carcinogenic exposures including pesticides. Additionally, extensive insecticide use in the household may even be a cofactor of the increased odds ratio among maids. Many previous studies indicated an increased lymphoma risk—especially an increased multiple myeloma risk—by pesticide exposure.<sup>74-83</sup> The carcinogenic effects of pesticides may be associated with their genotoxicity and immunotoxicity,<sup>84-86</sup> increased cell proliferation,<sup>87</sup> and association with chromosomal aberrations.<sup>88</sup> Again, in our study the definition of agricultural workers is too crude to draw definite conclusions about an aetiological role of pesticides: Pesticides constitute a heterogeneous group of chemical substances; not all agricultural workers apply pesticides; even among those who do, exposure frequency varies considerably. Nevertheless, some studies point to a specific aetiological role of pesticides at least for multiple myeloma: although Demers *et al.* found only a small excess risk among all agricultural workers combined,<sup>81</sup> the risk of multiple myeloma was strongly increased among agricultural workers who reported having been highly exposed to pesticides. Furthermore, a recently published study reveals an increased mortality from multiple myeloma among phenoxy herbicide producers and sprayers.<sup>89</sup> Precise exposure assessment and application of JEM should help to address the relation between specific pesticides and specific lymphoma subentities more conclusively. According to a preliminary FINJEM analysis, B cell NHL in total, follicular lymphoma, and multiple myeloma, but not Hodgkin's lymphoma, are significantly associated with pesticides.

### Viruses and others

A further potential exposure of farmers, agriculture, and husbandry workers is that to cattle and thus to zoonotic infectious agents. According with this hypothesis, the case control study of Nanni *et al.* reveals associations between NHL as well as CLL with farming and animal breeding, but not with farming alone.<sup>75</sup> The exposure to zoonotic infectious agents must also be taken into account when considering the increased odds ratio in the industrial sector food products which comprises processing of meat and meat products, and potentially even regarding the increased risk of maids who may have close contact with pet excrement while cleaning the cages. Additionally, our study<sup>33</sup> as well as several other studies<sup>90-93</sup> revealed a significant association between contact to cattle and lymphoma risk. Not only zoonotic, but also human to human transmission of infectious agents might play a potential aetiological role for lymphoma. In our study, the increased lymphoma risks of maids, sales workers, and medical personnel might be related to human-to-human transmission of infectious agents. However, other occupations with frequent public contact (for example, teachers) are not associated with lymphoma diagnosis in our study.

Our finding of an increased lymphoma risk among architects, engineers, and other technicians has not been previously reported. However, these occupations may be involved in working processes of the construction or

industrial production area and could be subsumed under the respective exposures.

### Latency period analysis

The average latency time from start of occupational exposure until the diagnosis of acute leukaemia might be about 10–11 years.<sup>34</sup> It is not clear if this latency period is valid also for lymphomas. To exclude potentially “non-causal” occupational exposures from analysis, in an additional analysis we considered only exposures up to 10 years before the lymphoma diagnosis. On the whole, the exclusion of recent occupational exposures led to slightly increasing lymphoma risks. The results of the latency analysis are to a large extent compatible with a potential role of solvents, electromagnetic fields, mineral dusts, pesticides, and viruses in the aetiology of lymphomas.

### Limitations

Exposure assessment based on job and industry titles always implies misclassification of exposure to known and unknown carcinogens. Several potentially hazardous substances (for example, solvents) are used in many different occupations and industries; therefore, the risk estimates might be diluted when each occupation or industry category is examined separately. Moreover, subjects included in the reference group might have actually had exposures from other occupational or industrial categories similar to the subjects in an exposed group. Due to small numbers, particularly for rare lymphoma subentities, the power of the study to detect risk factors is limited. On the other hand, several tests were performed, introducing a problem of multiple comparisons.

Furthermore, the low response rate among control subjects might have introduced selection bias. However, when only the two study regions with the highest response rate (Heidelberg and Bielefeld: response rate, 50%) are included in the analysis, the results do not substantially change. Moreover, it is worth mentioning that we used a conservative approach to calculate participation rates. If we had excluded individuals from the denominator—as done in some studies—who could not be reached or did not participate due to illnesses, the participation increased to 56% for men and 50% for women. The main difference of calculation is related to failure of getting contact to the randomly selected control subjects (for example, no reply to several mail contact attempts and no telephone number identifiable) who are counted as non-participants in our study, but left out of consideration in many other studies.

### CONCLUSIONS

To further clarify the association between specific occupational exposures and cancer subentities, there is a need for multinational epidemiological studies applying a common study protocol and questionnaire. For this purpose, our study will be evaluated as a multinational epidemiological case control study of lymphoma (EPILYMPH) in eight countries, coordinated by the International Agency for Research on Cancer.

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### Main messages

- In a population based case control study applying the new WHO classification, occupations with potential exposure to pesticides, solvents, electromagnetic fields, mineral dusts, and viruses were found to be associated with lymphoma risk.
- According to our study, risk factors might differ between specific lymphoma subentities. A particularly strong association was found between multiple myeloma and agriculture work including farming and animal husbandry.

### Policy implications

- To further clarify the association between specific occupational exposures and cancer subentities, there is a need for multinational epidemiological studies applying a common study protocol and questionnaire. For this purpose, our study will be evaluated as a multinational epidemiological case control study of lymphoma (EPILYMPH) in eight countries, coordinated by the International Agency for Research on Cancer (IARC).

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The authors declare that they do not have any competing interests.

The study protocol has been approved by the ethics committees of Ruprecht-Karls University Heidelberg, Landesärztekammer Rheinland-Pfalz, Würzburg University, Ärztekammer Hamburg, and Bielefeld University.

### REFERENCES

- 1 **Baris D**, Zahm SH. Epidemiology of lymphomas. *Curr Opin Oncol* 2000;**12**:383–94.
- 2 **Devesa SS**, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res* 1992;**52**(Suppl):5432s–40s.
- 3 **Hartge P**, Devesa SS. Quantification of the impact of known factors on time trends in Non-Hodgkin's lymphoma incidence. *Cancer Res* 1992;**52**(suppl):5566–9.
- 4 **Holford TR**, Zheng T, Mayne ST, et al. Time trends of non-Hodgkin's lymphoma: are they real? What do they mean? *Cancer Res* 1992;**52**(suppl):5443s–5446s.
- 5 **Arbeitsgemeinschaft Bevölkerungsbezogener Krebsregister in Deutschland**. Krebs in Deutschland. 4th ed. Saarbrücken 2004.
- 6 **Bernstein L**, Ross RK. Prior medication use and health history as risk for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. *Cancer Res* 1992;**52**(Suppl):5510–15.
- 7 **Filipovich AH**, Mathur A, Kamat D, et al. Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res* 1992;**52**(suppl):5465–5466.
- 8 **Kinlen L**. Immunosuppressive therapy and acquired immunological disorders. *Cancer Res* 1992;**52**(suppl):5474–6.
- 9 **Fabbro-Peray P**, Daures J-P, Rossi J-F. Environmental risk factors for Non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes Control* 2001;**12**:201–12.
- 10 **Armenian HK**, Hoover DR, Rubb S, et al. Risk factors for non-Hodgkin's lymphoma in acquired immunodeficiency syndrome (AIDS). *Am J Epidemiol* 1996;**143**:374–9.
- 11 **Birkeland SA**, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic Countries, 1964–1986. *Int J Cancer* 1995;**60**:183–9.



- 12 **Rowlings PA**, Curtis RE, Passweg JR, *et al*. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *J Clin Oncol* 1999;17:3122-7.
- 13 **Grulich AE**. AIDS-associated Non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 1999;21:S31-3.
- 14 **Petruckevitch A**, Del Amo J, Phillips AN, *et al*. Risk of cancer in patients with HIV disease. *Int J STD AIDS* 1999;10:38-42.
- 15 **Brownson RC**, Reif JS. A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukaemia. *Int J Epidemiol* 1988;17:27-32.
- 16 **LaVecchia C**, Negri E, D'Avanzo B, *et al*. Occupation and lymphoid non-Hodgkin lymphoma. *Br J Cancer* 1989;60:385-8.
- 17 **Persson B**, Dahlander AM, Fredriksson M, *et al*. Malignant lymphomas and occupational exposures. *Br J Ind Med* 1989;46:516-20.
- 18 **McCunney RJ**. Hodgkin's disease, work, and the environment. *J Occup Environ Med* 1999;41:36-46.
- 19 **Briggs NC**, Levine RS, Hall HL, *et al*. Occupational risk factors for selected cancers among African American and white men in the United States. *Am J Public Health* 2003;93:1748-52.
- 20 **Persson B**, Fredriksson M, Olsen K, *et al*. Some occupational exposures for malignant lymphomas. *Cancer* 1993;72:1773-8.
- 21 **Seniori Costantini A**, Miligi L, Kriebel D, *et al*. A multicenter case-control study in Italy on hematolymphopoietic non-Hodgkin lymphoma and occupation. *Epidemiology* 2001;12:78-87.
- 22 **Grufferman S**, Delzell E. Epidemiology of Hodgkin's disease. *Epidemiol Rev* 1984;76-106.
- 23 **Schumacher MC**, Delzell E. A death-certificate case-control study of non-Hodgkin's lymphoma and occupation in men in North Carolina. *Am J Ind Med* 1988;13:317-30.
- 24 **Kelleher C**, Newell J, MacDonagh-White C, *et al*. Incidence and occupational pattern of leukaemias, lymphomas, and testicular tumours in western Ireland over an 11 years period. *J Epidemiol Community Health* 1998;52:651-6.
- 25 **Skov T**, Lyng E. Non-Hodgkin's lymphoma and occupation in Denmark. *Scand J Soc Med* 1991;19:162-9.
- 26 **Linét MS**, Malker HS, McLaughlin JK, *et al*. Non-Hodgkin's lymphoma and occupation in Sweden: a registry based analysis. *Br J Ind Med* 1993;50:79-84.
- 27 **Blair A**, Linos A, Stewart PA, *et al*. Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case-control study. *Am J Ind Med* 1993;23:301-12.
- 28 **Scherr PA**, Hutchison GB, Neiman S. Non-Hodgkin's lymphoma and occupational exposure. *Cancer Res* 1992;52(suppl):5503-9.
- 29 **Fritschi L**, Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. *Int J Cancer* 1996;67:498-503.
- 30 **Miligi L**, Seniori Costantini AS, Crosignani P, *et al*. Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. *Am J Ind Med* 1999;36:60-9.
- 31 **Harris NL**, Jaffe ES, Stein H, *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361-92.
- 32 **Jaffe ES**, Harris NL, Stein H, *et al*. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. *International Agency for Research on Cancer*. Lyon: IARC Press 2001.
- 33 **Becker N**, Deeg E, Nieters A. Population-based study of lymphoma in Germany: rationale, study design and first results. *Leuk Res* 2004;28:713-24.
- 34 **Becker N**, Deeg E, Rüdiger T, *et al*. Medical history and risk for lymphoma: results of a population-based case-control study in Germany. *Eur J Cancer* 2005;41:133-42.
- 35 **Bolm-Audorff U**, Ahrens W, Jöckel K-H, *et al*. Experience with supplementary questionnaires in a lung cancer case reference study. In: Hemon D, Goldberg M, eds. *Proceedings of the workshop on methodology of assessment of occupational exposures in the context of epidemiology detection of cancer risks*. Paris, 18-19 February 1988. Luxembourg: Office for the Official Publications of the European Communities 1989:117-68.
- 36 **Aksoy M**, Erdem S, Dincol K, *et al*. Chronic exposure to benzene as a possible contributory etiologic factor in Hodgkin's disease. *Blut* 1974;28:293-8.
- 37 **Vianna NJ**, Polan A. Lymphomas and occupational benzene exposure. *Lancet* 1979;1:1394-5.
- 38 **Olsson H**, Brandt L. Occupational exposure to organic solvents and Hodgkin's disease in men. *Scand J Work Environ Health* 1980;6:302-5.
- 39 **Raaschou-Nielsen O**, Hansen J, McLaughlin JK, *et al*. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. *Am J Epidemiol* 2003;158:1182-92.
- 40 **Rego MAV**. Non-Hodgkin's lymphoma risk derived from exposure to organic solvents: a review of epidemiologic studies. *Cad Saude Publica* 1998;14:41-66.
- 41 **O'Connor SR**, Farmer PB, Lauder I. Benzene and non-Hodgkin's lymphoma. *J Pathol* 1999;189:448-53.
- 42 **Dryver E**, Brandt L, Kauppinen T, *et al*. Occupational exposures and non-Hodgkin's lymphoma in Southern Sweden. *Int J Occup Environ Health* 2004;10:13-21.
- 43 **Persson B**, Fredriksson M. Some risk factors for non-Hodgkin's lymphoma. *Int J Occup Environ Health* 1999;12:135-42.
- 44 **Rego MAV**, Sousa CSC, Kato M, *et al*. Non-Hodgkin's lymphomas and organic solvents. *J Occup Environ Med* 2002;44:874-81.
- 45 **International Agency for Research on Cancer**. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 28. *The rubber industry*. Lyon: IARC 1982.
- 46 **Rinsky RA**, Hornung RW, Silver SR, *et al*. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. *Am J Ind Med* 2002;42:474-80.
- 47 **Straif K**, Weiland SK, Werner B, *et al*. Workplace risk factors for cancer in the German rubber industry: part 2. Mortality from non-respiratory cancers. *Occup Environ Med* 1998;55:325-32.
- 48 **Kauppinen T**, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose information systems: a new job-exposure matrix. *Am J Ind Med* 1998;33:409-17.
- 49 **Dubrow R**, Wegman DH. Cancer and occupation in Massachusetts: a death certificate study. *Am J Ind Med* 1984;6:207-30.
- 50 **Figgs LW**, Dosemeci M, Blair A. United States non-Hodgkin's lymphoma surveillance by occupation 1984-9: a twenty four state death certificate study. *Am J Ind Med* 1995;27:817-35.
- 51 **Schroeder JC**, Savitz DA. Lymphoma and multiple myeloma mortality in relation to magnetic field exposure among electric utility workers. *Am J Ind Med* 1997;32:392-402.
- 52 **Miller AB**, To T, Agnew DA, *et al*. Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers. *Am J Epidemiol* 1996;144:150-60.
- 53 **Sahl JD**, Kelsh MA, Greenland S. Cohort and nested case-control studies of hematopoietic cancers and brain cancer among electric utility workers. *Epidemiology* 1993;4:104-14.
- 54 **Theriault G**, Goldberg M, Miller AB, *et al*. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970-89 [Erratum in comments *Am J Epidemiol* 1994;139:1053]. *Am J Epidemiol* 1994;139:550-60.
- 55 **Band PR**, Le ND, Fang R, *et al*. Identification of occupational cancer risks in British Columbia: a population-based case-control study of 769 cases of non-Hodgkin's lymphoma analysed by histopathology subtypes. *J Occup Environ Med* 2004;46:479-89.
- 56 **Floderus B**, Törnqvist S, Stenlund C. Incidence of selected cancers in Swedish railway workers, 1961-1979. *Cancer Causes Control* 1994;5:189-94.
- 57 **Tynes T**, Reitan JB, Andersen A. Incidence of cancer among workers in Norwegian hydroelectric power companies. *Scand J Work Environ Health* 1994;20:339-44.
- 58 **Youngson JH**, Clayden AD, Myers A, *et al*. A case-control study of adult haematological malignancies in relation to overhead powerlines. *Br J Cancer* 1991;63:977-85.
- 59 **Verkasalo PK**, Pukkala E, Kaprio J, *et al*. Magnetic fields of high voltage power lines and risk of cancer in Finnish adults: nationwide cohort study. *BMJ* 1996;313:1047-51.
- 60 **Loscher W**, Liburdy RP. Animal and cellular studies on carcinogenic effects of low frequency (50/60-Hz) magnetic fields. *Mutat Res* 1998;410:185-220.
- 61 **Hardell L**, Holmberg B, Malker H, *et al*. Exposure to extremely low frequency electromagnetic fields and the risk of malignant diseases: an evaluation of epidemiological and experimental findings. *Eur J Cancer Prev* 1995;4(suppl 1):3-107.
- 62 **Litovitz TA**, Krause D, Mullins JM. Effect of coherence time of the applied magnetic field on ornithine decarboxylase activity. *Biochem Biophys Res Commun* 1991;178:862-5.
- 63 **Phillips JL**, Rutledge L, Winters WD. Transferrin binding to two human colon carcinoma cell lines: characterization and effect of 60-Hz electromagnetic fields. *Cancer Res* 1986;46:239-44.
- 64 **Cantor KP**, Sontag JM, Heid MF. Patterns of mortality among plumbers and pipefitters. *Am J Ind Med* 1986;10:73-89.
- 65 **Michaels D**, Zoloth S. Asbestos disease in sheet metal workers: proportional mortality update. *Am J Ind Med* 1988;13:731-4.
- 66 **Ross R**, Nichols P, Wright W, *et al*. Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. *Lancet* 1982;2:1118-20.
- 67 **Becker N**, Berger J, Bolm-Audorff U. Asbestos exposure and malignant lymphomas—a review of the epidemiological literature. *Int Arch Occup Environ Health* 2001;74:459-69.
- 68 **Selikoff IJ**, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann N Y Acad Sci* 1979;330:91-116.
- 69 **Raffn E**, Lyng E, Juel K, *et al*. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br J Ind Med* 1989;46:90-6.
- 70 **Bengtsson NO**, Hardell L, Eriksson M. Asbestos exposure and malignant lymphoma [letter to the editor]. *Lancet* 1982;2:1463.
- 71 **Siemiatycki J**, ed. *Risk factors for cancer in the workplace*. CRC Press, Boca Raton, FL, USA 1991.
- 72 **Dodson RF**, Huang J, Bruce JR. Asbestos content in the lymph nodes of nonoccupationally exposed individuals. *Am J Ind Med* 2000;37:169-74.
- 73 **Rosenthal GJ**, Simeonova P, Corsini E. Asbestos toxicity: an immunologic perspective. *Rev Environ Health* 1999;14:11-20.
- 74 **Zahm SH**, Weisenburger DD, Babbitt PA, *et al*. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1990;1:349-56.
- 75 **Nanni O**, Amadori D, Lugaresi C, *et al*. Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population-based case-control study based on a priori exposure matrices. *Occup Environ Med* 1996;53:652-7.
- 76 **McDuffie HH**, Pahwa P, McLaughlin JR. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomark Prev* 2001;10:1155-63.
- 77 **DeRoos AJ**, Zahm SH, Cantor KP, *et al*. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 2003;60:e11.
- 78 **Miligi L**, Seniori Costantini A, Bolejack V, *et al*. Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study. *Am J Ind Med* 2003;44:627-36.

- 79 **Baris D**, Silverman DT, Brown LM, *et al.* Occupation, pesticide exposure and risk of multiple myeloma. *Scand J Work Environ Health* 2004;**30**:215–22.
- 80 **Eriksson M**, Karlsson M. Occupation and other environmental factors and multiple myeloma: a population based case-control study. *Br J Ind Med* 1992;**49**:95–103.
- 81 **Demers PA**, Vaughan TL, Koepsell, *et al.* A case-control study of multiple myeloma and occupation. *Am J Ind Med* 1993;**23**:629–39.
- 82 **Khuder SA**, Mutgi AB. Meta-analyses of multiple myeloma and farming. *Am J Ind Med* 1997;**32**:510–16.
- 83 **Nanni O**, Falcini F, Buiatti E. Multiple myeloma and work in agriculture: results of a case-control study in Forlì, Italy. *Cancer Causes Control* 2001;**9**:277–83.
- 84 **Zahn SH**, Blair A. Pesticides and non-Hodgkin's lymphoma. *Cancer Res* 1992;**52**:5485s–5488s.
- 85 **Zahn SH**, Ward MH, Blair A. Pesticides and cancer. *Occup Med* 1997;**12**:269–89.
- 86 **Faustini A**, Settini L, Pacific R, *et al.* Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations. *Occup Environ Med* 1996;**53**:583–5.
- 87 **Figgs LW**, Holland NT, Rothman N, *et al.* Increased lymphocyte replicative index following 2,4-dichlorophenoxyacetic acid herbicide exposure. *Cancer Causes Control* 2000;**11**:373–80.
- 88 **Schroeder JC**, Olshan AF, Baric R, *et al.* Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology* 2001;**12**:701–9.
- 89 **T'Mannetje A**, McLean D, Cheng S, *et al.* Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. *Occup Environ Med* 2005;**62**:34–40.
- 90 **Blair A**, Thomas TL. Leukemia among Nebraska farmers: a death certificate study. *Am J Epidemiol* 1979;**110**:264–73.
- 91 **Clavel J**, Mandereau L, Cordier S, *et al.* Hairy cell leukaemia, occupation, and smoking. *Br J Haematol* 1995;**91**:154–61.
- 92 **Cano MI**, Pollan M. Non-Hodgkin's lymphomas and occupation in Sweden. *Int Arch Occup Environ Health* 2001;**74**:443–9.
- 93 **Fritschi L**, Johnson KC, Kliever EV, *et al.* The Canadian Cancer Registries Epidemiology Research Group. Animal-related occupations and the risk of leukaemia, myeloma, and non-Hodgkin's lymphoma in Canada. *Cancer Causes Control* 2002;**13**:563–71.
- 94 **Brandt L**. Exposure to organic solvents and risk of haematological malignancies. *Leukemia Research* 1992;**16**:67–70.

## ECHO

### Chemical fire drill survives reality check ...this time



Please visit the *Occupational and Environmental Medicine* website [www.occenvmed.com] for a link to the full text of this article.

A chemical incident at a plastics factory has put to the test official UK guidance on how to deal with nearby residents. A partial evacuation during a fire lasting 48 hours in a plastics factory adjoining a large residential area in southwest England afforded researchers the chance to compare for the first time health outcomes between evacuees in the first six hours and residents sheltering at home during the emergency.

In this incident the results of the cross sectional study upheld the guidance, which is for residents to shelter at home. Health outcomes were better for those who stayed indoors: they had significantly fewer mean symptom scores, though the difference lessened with time. The main risk factors contributing to becoming a case (having  $\geq 4$  symptoms) were evacuation (odds ratio (OR) 2.5) and direct exposure to smoke for more than two hours at the time (OR 2.0).

Health outcomes were assessed by a postal questionnaire based on existing models in London and Wales, which was sent to all residents in the vicinity—472 evacuees and 1278 who remained indoors. Response rate was 63% overall: 27% (299) for evacuees and 73% (797) for sheltering residents.

Official guidance relies on mathematical models of likely scenarios after incidents at storage sites or in the plant releasing a chemical cloud for 30 minutes, but the consequences of exposure to low cumulative amounts of irritant gases in people with health compromised by, for example, asthma and chronic lung disease need to be studied.

However, staying indoors may not be best if toxic irritant gases are inhaled in large amounts over longer time, contends one public health expert. Toxic pneumonitis and even death can result, and even short exposure may trigger airways dysfunction syndrome. In the incident described, complications of asthma and other respiratory diseases were few, and environmental sampling 12 hours after the fire started detected only 1 ppm hydrogen chloride 100 m downwind within the smoke plume; other irritant gases were undetectable.

Temporary evacuation may be called for depending on management of the fire, materials involved, wind and weather forecasts, and local topography. It should always be considered, ideally with advice from the public health response team, in chemical fires, which can last for days. More epidemiological studies and good information on exposure are essential to test the validity of the guidance in such circumstances

▲ Kinra S, *et al.* *BMJ* 2005; **330**:1471–1474.

▲ Baxter PJ, *et al.* *BMJ* 2005;**330**:1474–1475.