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Risk of Leukemia and Multiple Myeloma Associated With Exposure to Benzene and Other Organic Solvents: Evidence From the Italian Multicenter Case–Control Study

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Background *While there is a general consensus about the ability of benzene to induce acute myeloid leukemia (AML), its effects on chronic lymphoid leukemia and multiple myeloma (MM) are still under debate. We conducted a population-based case–control study to evaluate the association between exposure to organic solvents and risk of myeloid and lymphoid leukemia and MM.*

Methods *Five hundred eighty-six cases of leukemia (and 1,278 population controls), 263 cases of MM (and 1,100 population controls) were collected. Experts assessed exposure at individual level to a range of chemicals.*

Results *We found no association between exposure to any solvent and AML. There were elevated point estimates for the associations between medium/high benzene exposure and chronic lymphatic leukemia (OR = 1.8, 95% CI = 0.9–3.9) and MM (OR = 1.9, 95% CI = 0.9–3.9). Risks of chronic lymphatic leukemia were somewhat elevated, albeit with wide confidence intervals, from medium/high exposure to xylene and toluene as well.*

Conclusions *We did not confirm the known association between benzene and AML, though this is likely explained by the strict regulation of benzene in Italy nearly three decades prior to study initiation. Our results support the association between benzene,*

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xylene, and toluene and chronic lymphatic leukemia and between benzene and MM with longer latencies than have been observed for AML in other studies. Am. J. Ind. Med. 51:803–811, 2008. © *2008 Wiley-Liss, Inc.*

KEY WORDS: leukemia; multiple myeloma; benzene; solvents; case–control study

INTRODUCTION

The association between leukemia and benzene has been described among workers exposed to benzene in several productive sectors. The International Agency of Research on Cancer classified benzene as carcinogenic to humans on the basis of case series reported in workers exposed to high levels of benzene in shoe manufacturing and printing in Italy, France, and Turkey as well as some epidemiologic studies of workers in shoe production and the rubber industry [Aksoy et al., 1974; Infante et al., 1977; Rinsky et al., 1981; IARC, 1982]. Subsequently, new data from cohort studies have confirmed a strong association between leukemia and benzene exposure [Rinsky et al., 1987; Crump, 1994, 1996; Paxton et al., 1994a,b; Seniori Costantini et al., 2003].

The risk was particularly elevated for acute myeloid leukemia (AML)—for which a strong dose/response relationship was evidenced [Wong, 1995; Wong and Raabe, 1996]. Findings from studies conducted in China [Yin et al., 1996; Hayes et al., 1996, 1997, 2000] showed an association between benzene exposure in different industries and AML at levels lower than those described in the European or US studies. Recently two nested case–control studies in gas and electric utility workers and petroleum workers also found elevated risks of AML for people exposed to low levels of benzene [Guenel et al., 2002; Glass et al., 2003].

While there is a general consensus about the ability of benzene to induce AML, its effects on chronic lymphoid leukemia (CLL) and multiple myeloma (MM) are still under debate. Few studies have reported a risk of CLL with benzene exposure. In the two cited nested case–control studies, the risk of CLL was raised, but only for the highest exposure category [Guenel et al., 2002; Glass et al., 2003]. An increased risk of MM was reported in the same rubber industry in which an excess of leukemia was seen [Rinsky et al., 1987; Wong, 1995], as well as in the Chinese cohort [Yin et al., 1996] and in the US chemical industry [Collins et al., 2003]. In other studies of chemical and petroleum industries in US, and United Kingdom, no increased risks of MM were observed [Bond et al., 1986; Wong, 1987a,b; Wong and Raabe, 1995, 1997, 2000]. Case–control studies on MM conducted in US and Europe also did not uncover evidence of an increased risk of MM [Morris et al., 1986; Flodin et al., 1987; Linet et al., 1987; Eriksson and Karlosson, 1992; Heinemann et al., 1992; Pottern et al., 1992]. In a recent meta-analysis of seven benzene cohort studies in which heavy exposures to benzene occurred, a significant excess of MM in relation to benzene exposure was reported [Infante, 2006].

In contrast to this rather extensive literature on hematolymphopoietic cancers and benzene, there is much less information on the risk from exposure to other organic solvents. An association between solvent exposure and mortality from hematolymphopoietic malignancies, and in particular lymphatic leukemia, was been reported for rubber workers [McMichael et al., 1975]. Increased risks were reported in two case–control studies on AML and exposure to mixtures of organic solvents [Albin et al., 2000; Lazarov et al., 2000].

Exposure to benzene is not confined to work environments. The major route of non occupational exposure is through air pollution; for smokers, the overwhelming source of benzene is mainstream cigarette smoke and suggestions of an increased risk of leukemia, and in particular AML have been reported for smokers in some recent case–control studies [Kasim et al., 2005; Pogoda and Preston-Martin, 2006].

In the present article, we present results concerning the association between solvent exposure and occurrence of leukemia and MM from the Italian Multicenter Case–control Study on Hematolymphopoietic Malignancies and Exposure to Solvents and Pesticides.

MATERIALS AND METHODS

Case and Control Recruitment

We conducted a population-based case–control study in 11 areas in Italy, in which all cases of hematolymphopoietic malignancies, incident in males and females aged 20–74 years in the period 1991–1993 were identified. A total of 2,737 cases of hematolymphopoietic malignancies were interviewed. The control group was formed from 1,779 subjects randomly selected through the demographic files of the municipalities in each of the areas under study, stratified by sex and 5-year age groups. Details on case ascertainment and recruitment and control sampling procedures have been described previously [Seniori Costantini et al., 2001].

Here we present results concerning 586 cases of leukemia collected in 7 out off the 11 areas (Torino, Verona, Imperia, Forlì, Firenze, Ragusa, Latina), and 1,278 controls sampled in the same areas. We also report results for

263 cases of MM collected in 6 areas (Torino, Imperia, Forlì, Firenze, Ragusa, Latina), and 1,100 controls sampled in the same areas. Restrictions were necessary in order to limit the study to all subjects for whom a detailed assessment of exposure to solvents had been performed, as described below. Results concerning CLL cases (and their controls) are reported from eight areas (the seven just indicated plus the province of Varese, where NHL, that include CLL, but not MM and leukemias were collected).

Data Collection and Exposure Assessment

All cases and controls received a letter asking if they agree to participate to the study and accept to be interviewed by trained personnel through a specific questionnaire. We conducted person-to-person interviews primarily at the interviewee's home. Individuals affected by acute leukemia were interviewed mostly in the hospital.

We obtained information on education, relevant life style factors such as tobacco smoking and beverage consumption, a detailed occupational history (including a collection of detailed data on specific jobs through the use of a job specific questionnaire for occupation [JSQ]), extra-occupational exposure to solvents and pesticides, hair dye use, lifelong residential history, previous diseases, use of diagnostic or therapeutic X-rays, specific medications, family medical history, and reproductive history.

The exposure assessment approach used in this study utilized job or industry-specific questionnaires and subsequent expert ratings in order to assign a level of exposure to a definitive list of agents. Industrial hygiene experts from each geographic area were selected to examine questionnaires and assess a level of probability and intensity of exposure to classes of solvents as well as substances at the individual level for each case and control. The assessment was blind with respect to case/control status. The following categories of solvents were considered: solvents in general; aromatic hydrocarbons; chlorinated hydrocarbons; technical hydrocarbons; aliphatic hydrocarbons; and oxygenated derivative hydrocarbons. Evaluation was also made for exposure to these specific chemicals: benzene; chloroform; dichloromethane; 1,4-dioxane; styrene; tetrachloroethylene; trichloroethylene; 1,1,1-trichloroethane; toluene; and xylene.

Exposures were rated on two scales: ''probability'' represented the certainty/uncertainty of exposure based on knowledge of the materials used and technologies applied in the particular activity/production process reported in a given calendar period. It was classified into three levels: low, medium, high. The second scale was ''intensity,'' which represented the estimated concentration of the agent in the work environment and was measured on a 4-point scale: very low, low, medium, and high. The first class of intensity, ''very low,'' was used for subjects judged to have occupational exposure intensities comparable to the upper end of the normal range of exposures for the general population. ''Low level'' intensity was assigned when workplace exposure was judged to be low because of control measures, but nevertheless higher than in the general population. Medium exposure was assigned to subjects who worked where only moderate or poor control measures were judged to exist. The highest category was used for subjects who worked in workplaces with no control measures. To ensure a standardized approach, the assessors were centrally trained prior, and periodically during their independent evaluation of questionnaires. Furthermore, in order to reduce the exposure assessment variability of the different experts, a job exposure matrix was developed collecting the minimum overall consensus for the most frequent job titles/sectors in the study areas and it was used as baseline for the individual exposure assessment.

Data Analysis

Data analyses were performed with SAS statistical software [SAS, 1999]. Point estimates of odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were calculated. We computed ORs separately for leukemia and MM. All the analyses were performed using multiple logistic regression models, taking into account relevant potential confounders (age, gender, education, and area). Subjects who never used any of the listed chemicals were used as the referent population. Subjects assigned with a low probability of exposure were excluded. Two collapsed classes of exposure were considered: (I) very low and low versus (II) medium/high. Analyses for duration of exposure considered two levels: less than 15, and 15 or more years, and these were each compared to the never exposed referent group. Tests for trend were conducted across these three categories. The linear test for trend used the mid-points of the duration categories (0, 7.5, and 35 years).

RESULTS

The main characteristics of the interviewed subjects are reported in Table I.

ORs for leukemia and MM and exposure to chemical classes of solvents and individual agents are presented in Table II. There was essentially no evidence for increased risk of all leukemia for any solvent exposure. When looking at sub-types of leukemia, we found no association between exposure to any chemical class or specific solvent and AML. For this tumor, the ORs for exposure to benzene were 0.3 (95% CI: 0.1–1.0) for very low/low exposure and 0.9 (95% CI: 0.4–2.3) for medium/high exposure (compared to the unexposed). Although confidence intervals were wide, there were elevated point estimates for the association

TABLE I. Characteristics of Interviewed Subjects, Frequencies and Percentages, Italian Case–Control Study

	Leukemia (ICD IX: 204-208)		Multiple myeloma (ICD IX: 203)	
	Cases	**Controls**	**Cases**	**Controls**
No. interviewed	586	1,278	263	1,100
% of respondents	686 (85.4%)	1,796 (71.2%)	316 (83.2%)	1,446 (76.1%)
Gender				
Men	345 (58.9)	658 (51.5)	129 (49.1)	567 (51.6)
Women	241 (41.1)	620 (48.5)	134 (50.9)	533 (48.4)
Age (years)				
0-34	50 (8.5)	163 (12.8)	1 (0.4)	141 (12.8)
35–44	53 (9.1)	146 (11.4)	10 (3.8)	124 (11.3)
45–54	92 (15.7)	237 (18.5)	SAS1999 (14.4)	196 (17.8)
55–64	181 (30.9)	347 (27.2)	82 (31.2)	306 (27.8)
65–75	210 (35.8)	SAS19995 (30.1)	132 (50.2)	333 (30.3)
Missing	0	0	0	0
Education				
Illiterate	29 (5.0)	62 (4.9)	22 (8.4)	57 (5.2)
Primary school	286 (48.8)	621 (48.6)	175 (66.5)	529 (48.1)
Middle school	144 (24.6)	295 (23.1)	33 (12.5)	259 (23.5)
High school	94 (16.0)	233 (18.2)	23 (8.8)	196 (17.8)
University	33 (5.6)	67 (5.2)	10 (3.8)	59 (5.4)
missing	0	0	0	0
Smoking				
Yes	348 (59.4)	717 (56.1)	140 (53.2)	628 (57.1)
No	237 (40.4)	559 (43.7)	122 (46.4)	470 (42.7)
Missing	1 (0.2)	2 (0.2)	1 (0.4)	2 (0.2)
Area				
Florence	165 (28.2)	379 (29.7)	97 (36.9)	379 (34.4)
Forl′	62 (10.6)	135 (10.6)	29 (11.0)	135 (12.3)
Imperia	62 (10.6)	109 (8.5)	28 (10.7)	109 (9.9)
Ragusa	25 (4.3)	90 (7.0)	18 (6.8)	90 (8.2)
Turin	177 (30.1)	295 (23.1)	65 (24.7)	295 (26.8)
Verona	47 (8.0)	178 (13.9)		
Latina	48 (8.2)	92 (7.2)	26 (9.9)	92 (8.4)

between medium/high benzene exposure and all leukemia (OR = 1.3, 95% CI = 0.7–2.3), CLL (OR = 1.8, 95% CI = 0.9–3.9), and MM (OR = 1.9, 95% CI = 0.9–3.9). Risks of CLL were somewhat elevated, albeit with wide confidence intervals, from medium/high exposure to xylene (OR = 1.9, 95% CI = 0.8–4.5) and toluene (OR = 2.1, 95% CI = 0.9–4.7) as well.

Benzene, xylene and toluene exposures were correlated. Considering all levels of exposure, about 67% of subjects exposed to benzene were exposed also to toluene and/or xylene. For medium/high intensity exposure, the percentage of subjects exposed to benzene and also to toluene and/or xylene was about 33%. Risk of CLL appeared to be elevated from exposure to all three aromatic solvents: the OR was 3.2 (95% CI: 1.1–9.3, based on 7 out of 12 cases; data not shown). In contrast, the risk of MM seemed to be concentrated among subjects exposed only to benzene with an OR of 2.3 (95% CI: 1.0–5.4, based on 11 out of 14 cases; data not shown).

The effects of increasing duration of medium/high solvent exposures were investigated for MM and CLL (Table III). Associations were stronger for duration more than 15 years for several solvents and both malignancies. The numbers of cases and controls were generally quite small in these analyses, so that confidence intervals were often wide. Nevertheless, there was evidence of a positive trend with increasing duration of medium/high exposure for CLL and exposure to toluene (P-value for trend = 0.03), benzene ($P = 0.05$), and xylene ($P = 0.09$). For CLL, the risk from exposure to benzene was concentrated among subjects with

TABLE II. Exposed Cases and Controls, ORs, 95% CI for all Leukemia, Acute Myeloid Leukemia, Chronic Lymphatic Leukemia and Multiple Myeloma by Chemical and Intensity of Exposure—Italian Case-Control Study

		Leukemia (ICD IX: 204–208)				Acute myeloid leukemia (ICD IX: 205.0)				Chronic lymphatic leukemia (ICD IX: 204.1)				Multiple myeloma (ICD IX: 203)			
ICD: IX	Exposure intensity level	No. of cases	No. of controls	OR[a]	95% CI	No. of cases	No. of controls	OR[a]	95% CI	No. of cases	No. of controls	OR[a]	95% CI	No. of cases	No. of controls	OR[a]	95% CI
Unexposed[b]		*355*	*811*	*1.0*		133	811	1.0		103	925	1.0		*163*	*674*	*1.0*	
Chemical class																	
Solvents	Very low/low	43	86	1.0	0.7–1.5	18	86	1.3	0.7–2.3	12	113	0.7	0.4–1.5	19	74	1.3	0.7–2.3
	Medium/high	82	166	0.9	0.6–1.2	24	166	0.8	0.5–1.3	35	208	1.0	0.6–1.6	31	151	0.9	0.5–1.4
Aromatic hydrocarbons	Very low/low	*19*	*51*	0.7	0.4–1.2	6	51	0.6	0.3–1.6	7	79	0.6	0.3–1.4	10	47	1.0	0.5–2.2
	Medium/high	50	95	0.9	0.6–1.3	13	95	0.7	0.4–1.6	27	121	1.3	0.8–2.2	23	88	1.2	0.7–2.0
Chlorinated hydrocarbons	Very low/low	26	52	1	0.6–1.6	13	52	1.4	0.7–2.8	6	68	0.6	0.3–1.6	13	47	1.5	0.8–3.0
	Medium/high	37	67	0.9	0.6–1.4	13	67	1.0	0.5–1.8	17	90	1.1	0.6–2.0	16	62	1.1	0.6–2.1
Technical hydrocarbons	Very low/low	18	40	0.8	0.4–1.5	5	40	0.7	0.3–1.8	7	50	0.8	0.3–2.0	5	37	0.6	0.2–1.7
	Medium/high	52	95	0.9	0.6–1.3	14	95	0.7	0.4–1.4	29	125	1.1	0.7–1.9	22	92	0.9	0.5–1.7
Aliphatic hydrocarbons	Very low/low	13	33	0.8	0.4–1.6	2	33	0.4	0.1–1.6	7	53	1.0	0.4–2.4	3	28	0.5	0.1–1.7
	Medium/high	19	74	0.5	0.3–0.8	7	74	0.5	0.2–1.2	14	104	0.9	0.5–1.7	11	68	0.7	0.3–1.4
Derivative-oxygenate hydrocarbons	Very low/low	17	29	1.2	0.6–2.3	4	29	0.9	0.3–2.7	8	52	1.3	0.5–3.0	6	23	1.8	0.7–5.0
	Medium/high	34	84	0.8	0.5–1.2	10	84	0.7	0.3–1.3	19	107	1.1	0.6–2.1	14	76	0.9	0.5–1.7
Individual chemicals																	
Benzene	Very low/low	16	50	0.5	0.3–0.9	3	50	0.3	0.1–1.0	11	77	0.7	0.3–1.4	8	47	0.6	0.3–1.5
	Medium/high	25	32	1.3	0.7–2.3	6	32	0.9	0.4–2.3	12	35	1.8	0.9–3.9	14	29	1.9	0.9–3.9
Styrene	Very low/low	1	8	—		0	8			0	16			2	7	—	—
	Medium/high	2	11	—		0	11			2	12			2	9	—	—
Xylene	Very low/low	20	64	0.5	0.3–0.9	5	64	0.4	0.2–1.1	15	99	0.9	0.5–1.8	9	59	0.6	0.3–1.4
	Medium/high	10	27	0.7	0.3–1.5	2	27	0.4	0.1–1.8	9	34	1.9	0.8–4.5	6	23	1.2	0.4–3.2
Toluene	Very low/low	21	66	0.5	0.3–0.9	5	66	0.4	0.2–1.0	14	99	0.9	0.4–1.6	10	61	0.6	0.3–1.3
	Medium/high	13	28	0.9	0.4–1.7	2	28	0.4	0.1–1.7	10	35	2.1	0.9–4.7	5	24	0.9	0.3–2.7
Dichloromethane	Very low/low	7	21	0.7	0.3–1.7	3	21			2	28	0.4	0.1–2.0	4	20	—	—
	Medium/high	2	8	0.5	0.1–2.3	0	8			2	8	1.6	0.3–8.6	0	8	—	—
Tetrachloroethylene	Very low/low	6	17	0.6	0.2–1.6	2	17			3	29			3	15	—	—
	Medium/high	7	12	1.0	0.4–2.7	2	12			1	15			2	12	—	—
Trichloroethylene	Very low/low	17	34	1.0	0.5–1.8	6	34	1.0	0.4–2.5	8	47	1.2	0.5–2.7	9	28	1.5	0.7–3.5
	Medium/high	11	29	0.7	0.4–1.5	6	29	1.1	0.5–2.9	4	35	0.9	0.3–2.6	5	27	0.9	0.3–2.4
1,1,1-Trichloroethane	Very low/low	5	12	0.7	0.2–2.0	1	12			3	23			2	10	—	—
	Medium/high	5	7	1.4	0.4–4.7	2	7			0	9			1	5	—	—

[a]Adjusted by gender, age, education and area, ORs shown for at least five exposed cases.
[b]Reference group: subjects who never used any chemical (OR = 1).

TABLE III. Exposed Cases and Controls, ORs, 95% CI for Chronic Lymphatic Leukemia and Multiple Myeloma by Chemical and Duration of Exposure—Italian Case-Control Study

		Chronic lymphatic leukemia (ICD IX: 204.1)				Multiple myeloma (ICD IX: 203)			
Chemicals	**Years of exposure**	**No. of cases**	**No. of controls**	**OR[a]**	**95% CI**	**No. of cases**	**No. of controls**	**OR[a]**	**95% CI**
Unexposed[b]		*355*	*811*	*1.0*		*163*	*674*	*1.0*	
Classes									
Solvents	≤15 years	18	125	1.0	0.5–1.9	12	93	0.5	0.2–1.0
	>15 years	17	83	1.1	0.5–2.2	19	58	1.0	0.5–1.9
		P trend		0.82		*P* trend	0.85		
Aromatic hydrocarbons	≤15 years	15	76	1.7	0.8–3.5	10	58	0.6	0.2–1.4
	>15 years	12	43	1.9	0.9–4.2	13	28	1.4	0.6–3.0
		P trend		0.29		*P* trend	0.40		
Chlorinated hydrocarbons	≤15 years	8	54	0.8	0.3–2.0	6	41	0.5	0.2–1.4
	>15 years	9	35	1.2	0.5–3.1	10	20	1.5	0.6–3.9
		P trend		0.60		*P* trend	0.33		
Individual agents									
Benzene	≤15 years	9	31	1.8	0.7–4.6	9	26	0.8	0.3–2.2
	>15 years	3	4	4.7	0.8–26.5	5	3	4.1	0.8–20.0
		P trend		0.05		*P* trend	0.10		
Xylene	≤15 years	6	25	1.8	0.6–5.2	3	18	0.6	0.1–2.4
	>15 years	3	8	3.3	0.7–15.2	3	4	3.1	0.6–17.0
		P trend		0.09		*P* trend	0.29		
Toluene	≤15 years	6	26	1.7	0.6–5.0	2	19	0.4	0.1–1.9
	>15 years	4	8	4.4	1.1–18.0	3	4	3.1	0.6–17.2
		P trend		0.03		*P* trend	0.34		
Trichloroethylene	≤15 years	2	24	0.7	0.1–3.4	2	19	0.5	0.1–2.3
	>15 years	2	11	1.2	0.2–6.2	3	8	1.3	0.3–5.9
		P trend		0.87		*P* trend	0.82		

[a]Adjusted by gender, age, education and area.
[b]Reference group: Subjects who never used any chemical (OR = 1).

20–29 years since first exposure. The OR for this latency category was 13.5 (95% CI: 1.1–160.3) based on two cases (data not shown). No cases occurred in the latency category less than 20 years (data not shown). For MM the risk was concentrated among people who were exposed 10–19 years before incidence; the OR for this latency category was equal to 2.3 (95% CI: 0.6–9.0) based on three cases (data not shown).

DISCUSSION

High leukemia risk is associated with exposure to benzene as indicated by results from cohort studies of workers exposed in several activities including shoe and leather good production, printing, painting, rubber industry, petroleum production, refinery, and distribution. The association was stronger when considering specifically the acute myeloid sub-type. Levels of exposure to benzene producing such excesses were generally high and positive dose–response relationship was evidenced; however, more recent studies have suggested increased risks also at concentration levels lower than those described in the former studies. The latency period was generally low. Different updates of the follow-up of the Pliofilm cohort have shown that AML risk estimates declined through successive follow-up periods [Rinsky et al., 2002].

In this study we did not find the previously reported association between AML and exposure to benzene, although there were only nine cases, and so this result was not surprising. There were probably so few cases because our cases were collected in 1991–1993, about 30 years after benzene was effectively banned from manufacturing in Italy, and in particular in shoe and leather goods production and in printing. An Italian law in 1963 limited the concentration, as impurity, of benzene in most materials (glues, solvents) to a maximum of 2% in solvent mixtures. This limited opportunity for exposure, combined with the relatively short latency period with which AML occurs after benzene

exposure, may explain the lack of association in these data. When adjusting by possible confounders (Down syndrome and previous X-ray- and chemo-therapy), that are associated to the AML risk and could be reason of a reduced probability of being part of the workforce and then of being exposed to chemicals, we did not observe any difference in ORs. Results of studies concerning AML in industries where levels were very low gave conflicting results. A case–control study nested in a cohort of Australian petroleum workers showed an excess of leukemia for the highest benzene exposure category (>8 ppm-years), but lower than reported in previous studies. For CLL the risk was elevated also for cumulative exposures less than 8 ppm-years [Glass et al., 2003]. Evidence of increasing risk with increasing cumulative exposure was found for all leukemias and specifically for AML in the Monsanto cohort only for benzene peak exposures over 100 ppm for 40 days or more [Collins et al., 2003]. One cohort study on workers exposed to benzene revealed a weak trend of increasing SMRs for leukemia with increasing low-level cumulative exposure [Bloemen et al., 2004]. Others studies conducted in the UK, US, and Canadian petroleum refinery and distributions where benzene concentrations were generally low failed to evidence or provided weak evidence of an association [Wong and Raabe, 1995; Schnatter et al., 1996; Rushton and Romaniuk, 1997; Wong et al., 1999]. The pooled analysis concerning more than 300,000 subjects in petroleum workers did not reveal any increased risk of leukemia or MM [Wong and Raabe, 2000]. The authors attributed the lack of an increased risk of AML to the low levels of benzene exposure.

We found positive associations between CLL and exposures to benzene, toluene, and xylene, albeit with wide confidence intervals. When those with medium/high exposure to one of these agents were subdivided by duration of exposure there was a trend of increasing risk with increasing duration. For medium/high intensity exposure for more than 15 years, the ORs were: for benzene 4.7 (95% CI: 0.8–26.5); for xylene 3.3 (95% CI: 0.7–15.2); and for toluene 4.4 (95% CI: 1.1–18.8).

We do not think that a surveillance bias could contribute to the CLL findings, as suggested by Goldstein with regard to the Glass's cohort nested case–control study [Goldstein, 2004], as presumably a very small part of the CLL incidence could be explained by blood count examinations in workplace in our data-set.

A recent review of the literature on benzene exposure and leukemia sub-types suggested that elevated risks for CLL were seen in nested case–control studies that have advantages in terms of benzene exposure assessment [Schnatter et al., 1996, 2005]. In our study a good assessment of exposure was done, even if based on experts' judgments and not on environmental measures, so our results seem to be strong enough and support this association. It is noteworthy that we also found evidence for the association with two other aromatic solvents, toluene and xylene. Interestingly, for subjects exposed to all three aromatic solvents, the OR increased to 3.2 (95% CI: 1.1–9.3), based on 7 cases. We have previously reported strong associations between exposure to benzene, xylene, and toluene and the occurrence of small cell non-Hodgkin's lymphomas that include CLL as a subtype [Miligi et al., 2006]. In a recent review on benzene exposure and risk of NHL, epidemiological data strongly supporting the association between occupational exposure to benzene and risk of CLL—at now classified together with small lymphocytic lymphoma as a form of NHL—have been reported and discussed [Hartge and Smith, 2007].

An increased risk of MM was also suggested from these same solvents, and it was highest for people exposed for 15 or more years with 10- to 19-year latency period. It is noteworthy that the association was higher for those exposed only to benzene. The biological plausibility and the epidemiological evidence of the association between benzene exposure and MM was discussed by Goldstein [1990]. Our results, even if based on small numbers, are in agreement with the hypotheses that AML risk following benzene exposure declines in time while CLL and MM risks are not seen until a longer latency period has passed [Finkelstein, 2000; Rinsky et al., 2002].

Our results support the association between exposure to benzene, xylene, and toluene and risk of CLL and between benzene and risk of MM. Benzene is toxic for blood marrow where AML, CLL and MM originate from myelocytes, lymphocytes and plasma cells. Thus associations between benzene and CLL and MM seem biologically plausible. We did not observe clear evidence of an association between benzene and AML leukemia; however the absence of environmental measures and the small number of observations limited the interpretation of our results.

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