Leukemia in Relation to Occupational Exposures to Benzene and Other Agents: A Case-Control Study Nested in a Cohort of Gas and Electric Utility Workers

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Background *Many occupational and environmental exposures have been implicated in the etiology of leukemia, but only a few, such as benzene, are well-established leukemogens. The risk of leukemia in a large cohort of gas and electricity utility workers with exposures to several suspected or confirmed carcinogens was investigated.*

Methods *A case-control study nested within the cohort was conducted, with 72 leukemia cases identified among male workers, and 285 controls matched to the cases by year of birth. Only cases, and their matched controls, active in the company at the date of diagnosis were included. Exposure assessment was based on a job-exposure matrix (JEM) developed from expert judgment using a standardized procedure.*

Results *The risk of leukemia was increased in workers with an estimated cumulative exposure to benzene $\geq$ 16.8 ppm-years (OR = 3.6; 95% CI 1.1–11.7), and there was an indication of a dose-response relation (OR = 1.2; 95% CI 1.0–1.5 per 10 ppm-years increase in exposure). The link with benzene was more pronounced for acute leukemia than for chronic leukemia, but no association with a particular leukemia cell type was apparent. The risk of leukemia remained elevated for latency periods of 2, 5, or 10 years.*

Conclusions *From our evaluation, it could be estimated that the median TWA exposure to benzene among exposed workers was 0.16 ppm, i.e., within concentration ranges where an increased leukemia risk was usually not apparent in previous epidemiological studies. Although an increased leukemia risk may be real, it may also be related to other occupational factors not totally controlled for in the analysis, or to benzene exposures actually higher than expected.* Am. J. Ind. Med. 42:87–97, 2002. © *2002 Wiley-Liss, Inc.*

KEY WORDS: leukemia; occupational exposure; benzene; cohort; job-exposure matrix; utility workers

INTRODUCTION

Occupational exposures have often been implicated in the etiology of leukemia but the rarity of the disease, combined with the limited size of most occupational cohorts, have made difficult the study of the association between these exposures and leukemia. Well-established leukemogenic exposures include ionizing radiations and benzene. Exposures to other occupational factors, such as electromagnetic fields, styrene, or ethylene oxide have been suspected to increase the risk of leukemia [Linet and Cartwright, 1996].

The company ''Électricité de France-Gaz de France'' (EDF-GDF) is the only gas and electricity utility operating

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nationally in France. Salaried workers constitute a large population with many different occupations and exposures to potentially carcinogenic chemical or physical agents present in the company. The cases of leukemia have been recorded systematically among active workers since 1978, and the exposure to occupational carcinogens have been evaluated through an exposure assessment program [Thériault et al., 1994]. Therefore, this large population of workers provides an opportunity to test associations between several occupational exposures and leukemia risk. The number of cases available is relatively high, although only cancer diagnoses in non-retired workers can be identified. It has been shown that the incidence of leukemia in 1978–1982 among these workers was slightly higher than that in the French general population (standardized incidence ratio = 1.48; 95% CI 1.00–2.09) [Chevalier et al., 1996], but this excess risk has never been investigated in relation with occupational exposures.

Benzene is of special interest in this context, because it is a well-documented leukemogenic agent [IARC, 1982]. In this study, it was possible to investigate the leukemia risk in occupations where benzene exposure is not known to be particularly high. Furthermore, although benzene exposure in humans has been associated with an increased risk of acute myeloid leukemia (AML), it has also been shown in a literature review of epidemiological studies, that the link with other leukemia cell types is no less persuasive [Savitz and Andrews, 1997]. This question can be addressed in our study. Another unresolved problem concerns the temporal pattern between exposure and disease [Finkelstein, 2000] which will also be examined in this study.

MATERIALS AND METHODS

We conducted a case-control study nested within a cohort of 170,000 men employed at EDF-GDF for 1 year or more between 1978 and 1989.

Selection of Cases and Controls

All incident cases of leukemia (ICD-9 204–208) diagnosed in the cohort in the period 1978–1989, and still active in the company at the time of diagnosis, were included in the group of cases. Leukemia cases were identified from the company cancer register operated since 1978 by the health insurance system specific to active EDF-GDF workers. In this system, any diagnosis of cancer must be notified to the company's consulting physicians before health insurance benefits are provided to the diseased worker. For this reason, cancer registration is complete for active workers. All cases of cancer were coded according to ICD-O codes based on the pathology report. After the date of retirement, the social security system specific to EDF-GDF workers is replaced by the general system for all salaried workers in France, which does not permit cancer registration. Consequently only leukemia cases diagnosed among active workers, i.e., below the age of 60, could be included in the present study.

Controls were selected among other active, non-retired, EDF-GDF workers in the cohort, and were individually matched to the cases by year of birth. For each case, a set of possible controls was first created, which included the workers born on the same year as the case, who were actively working in the company and free of at the date of diagnosis. Four subjects per case were then selected at random from each of these sets to serve as the control group.

Assessment of Occupational Exposure

Occupational exposures were chemicals, groups of chemicals, physical agents, or industrial processes selected from the lists 1, 2A, and 2B of the International Agency for Research on Cancer [IARC, 1987], or other exposures of particular interest. These exposures were divided into five groups, according to the procedures used for exposure assessment (Table I).

For ionizing radiations (group 1), the individual lifetime cumulative exposure was obtained from the EDF surveillance program on ionizing radiations for workers in restricted areas of nuclear plants. Exposure to non-ionizing radiations (group 2), was assessed from exposure monitoring data, which have been described in details previously [Armstrong et al., 1994; Thériault et al., 1994; Guénel et al., 1996]. Briefly, exposure to extremely low frequency (ELF) fields and high frequency transient (HFT) fields was measured in a sample of 850 workers who wore a POSITRON meter during a full work week. This device recorded the electric, magnetic, and HFT fields every minute. The workers were selected after stratification in 37 occupational groups with a priori homogeneous exposure to electromagnetic fields. Mean exposures per group were calculated and included in a specific job-exposure matrix (JEM).

Occupational exposures in groups 3, 4, and 5 were assessed using a separate JEM. The job axis of the JEM consisted of 403 occupational groups defined by both the workers' occupational title (e.g., electrician, lineman, mechanics) and the sector of activity (e.g., nuclear plant, high voltage transmission lines, garage). Exposures were evaluated by professionals in occupational health (occupational health physicians, toxicologists, epidemiologists), employed in the different sectors of the company. Exposure assessment was based on expert judgment using a standardized procedure for collecting information. A list of work tasks entailing exposure was first established to serve as a basis for exposure assessment. When changes had occurred in the past, different time periods could also be defined for the same task. For occupational hazards entailing rare and/or very low exposure, the work tasks and associated jobs were simply classified into exposed or not exposed (group 3). For

TABLE I. List of the Occupational Exposures at EDF-GDF Estimated in the Job-Exposure Matrix (JEM)

Exposure	Unit of exposure estimate in the JEM	Unit of cumulative exposure for workers
Group 1[a]		
Ionizing radiations	—	Milli-sievert
Group 2[b]		
50-Hz electric fields	Volts/meter (V/m)	V/m-years
50-Hz magnetic fields	Microteslas (μT)	μT-years
HFT fields	ppm	ppm-years
Group 3		
Coal gasification	Exposed/ not exposed	N years exposure
Crystalline silica	Exposed/ not exposed	N years exposure
Herbicides	Exposed/ not exposed	N years exposure
Group 4[c]		
Cadmium	% Work time (% wt)	% Wt-years
Chlorinated solvents	% Work time (% wt)	% Wt-years
Coal tars	% Work time (% wt)	% Wt-years
Creosote	% Work time (% wt)	% Wt-years
Cutting fluids	% Work time (% wt)	% Wt-years
Epoxy resins	% Work time (% wt)	% Wt-years
Hydrazine	% Work time (% wt)	% Wt-years
Mechanical oils	% Work time (% wt)	% Wt-years
Polychlorinated biphenyls (PCBs)	% Work time (% wt)	% Wt-years
Polyurethane foams	% Work time (% wt)	% Wt-years
Unsaturated polyesters (styrene)	% Work time (% wt)	% Wt-years
Group 5[d]		
Asbestos	Fibers/cm^3	f/cm^3-years
Benzene	Arbitrary "unit"	U-years

[a]Cumulative exposure obtained for individuals from the EDF surveillance programme on ionizing radiation in radioactive areas.
[b]Measured with the Positron meter.
[c]Estimated indices are exposure frequency and exposure duration.
[d]Estimated indices are exposure frequency, exposure duration and exposure intensity.

chemicals in group 4, the frequency and duration of the work tasks episodes entailing exposure were evaluated for a typical worker in each job on a semi-quantitative exposure scale. These exposure indices were used to calculate the proportion of exposed work time (% work time), but exposure intensity was not estimated. For exposures in group 5 (asbestos and benzene), an index of exposure intensity was defined for each work task, in addition to exposure frequency and duration. These three exposure indices permitted to estimate the time-weighted average (TWA) exposure per job. Details of exposure evaluation for asbestos have been given elsewhere [Imbernon et al., 1995]. We report here in more details on the exposure evaluation for benzene, which is of special interest for this study on leukemia.

Benzene Exposure Assessment

"Use of solvents" for cleaning or degreasing materials, and "exposure to gasoline" from motor vehicles were the two work tasks that may have entailed exposure to benzene. Petroleum or aromatic solvents containing benzene in varying proportions [IARC, 1989a] have been widely used in the company. Examples of occupations with such exposures include plumbers of the gas distribution network, laboratory technicians, welders, sheet-metal workers, and mechanics in thermic or hydraulic electricity production plants. It was agreed by the group of experts that the intensity of exposure to benzene resulting from the use of these solvents, could be ranked on the basis of two regulations limiting the content of benzene in solvents, one in 1969 (benzene content $< 1\%$ volume) and one in 1986 (benzene content $< 0.2\%$ weight). As shown in Table II, the intensity of exposure associated with "use of solvents" was arbitrarily assigned a value of 1 U of benzene concentration before 1970. Exposure was considered to decrease by a factor of 5 for the same work task in 1970–1985, and again by a factor of 5 after 1985, leading to exposure intensity indices associated with the use of solvents of 0.2 and 0.04 U, respectively. Benzene exposure may also

TABLE II. Estimates of Benzene Exposure Intensity by Time-Period Resulting From Two Different Work Tasks (Arbitrary Units of Benzene Concentration)

Time period	Use of solvents containing benzene	Exposure to gasoline
<1970	1	2
1970–1985	0.2	1
>1985	0.04	0.4

have occurred from ''exposure to gasoline'' identified as the second exposed work task. Motor vehicle mechanics working in garages represented the main occupation with such an exposure. Benzene exposure intensities from gasoline were assigned higher values than for use of solvents in the same time period, because the recommended limits for benzene content in gasoline in Europe (for example 5% in 1970s) have been more elevated than in solvents [Runion, 1975]. In addition, gasoline may have been used as a solvent in garages, even though this practice is proscribed. Although the actual content of benzene in gasoline may have varied importantly within each period, the indices of benzene exposure intensity were assigned to workers in contact with gasoline as shown in Table II. They were chosen so that the ratio ''exposure to gasoline''/''use of solvent'' increases from 2 (= 2/1) before 1970 to 10 (= 0.4/0.04) after 1985.

The estimates for frequency and duration of ''use of solvents'' or ''exposure to gasoline,'' obtained for each occupation, were then combined to benzene exposure intensity to estimate the time-weighted average (TWA) exposure to benzene. Because the intensity indices were used for ranking work task and work periods on a relative exposure scale, but not for estimating absolute exposure levels, the TWA benzene exposure included in the JEM was expressed in an arbitrary ''unit'' of benzene concentration.

Analysis

Individual cumulative exposures to occupational hazards were calculated from the date of start of employment at EDF-GDF to the date of cancer diagnosis (for controls, to the date of diagnosis of the matched case) by summing the yearly exposure estimates in the JEM (Table I) of all the consecutive jobs in the individual's work history. To allow for a latency period (lag time) before the occurrence of cancer, we also assessed cumulative exposures after excluding from the calculations the exposures during the last 2, 5, or 10 years before the date of cancer diagnosis for the cases, or before the date of diagnosis of the matched case for the controls.

The analysis was performed with the EGRET software, using conditional logistic regression because of the matched design of the study. Exposure cutpoints depended on the exposure prevalence among controls, in order to avoid too small numbers of subjects in the different exposure categories. When the exposure prevalence was above 25%, we used the 50th, 75th, and 90th percentile of exposure distribution among exposed controls as exposure cutpoints, leading to five exposure categories including the category of non-exposed subjects (0; $>0<50$th; ≥ 50th <75th; ≥ 75th <90th; ≥ 90th). For an exposure prevalence among controls of between 5 and 25%, only the 75th percentile of the distribution among exposed controls was used as a cutpoint, leading to three exposure groups (0; $>0<75$th; ≥ 75th). Finally, for exposure prevalence below 5%, a simple 'ever/never exposed' classification was used. All exposure cutpoints were defined before the analysis was conducted. Linear trends were tested in models where subjects were attributed the mean value of their exposure group, which was then fitted as a continuous variable. Univariate analysis was first performed for each exposure separately. Multivariate analyses were then conducted by including in the model the exposure variables, which were associated with leukemia in the univariate analysis. Socio-economic status was determined from the first job at EDF-GDF according to the French classification of social class [INSEE, 1983].

RESULTS

During the study period, 72 leukemia cases were identified. From the 288 controls selected, 3 (1%) were excluded because their work history was missing in the personnel data files, leaving 285 controls available for the analysis.

Table III shows that the distribution of socioeconomic status did not differ significantly between cases and controls. Mean age at diagnosis was 45.5 years. The mean duration of employment at EDF-GDF was above 20 years for both cases and controls, indicating a stable population of workers. The age at start of employment and the period at start of employment at EDF-GDF did not differ between the two groups, as it was expected because of the matched design of the study.

Odds ratios for leukemia associated with cumulative exposure to potentially leukemogenic occupational hazards are shown in Table IV. Unadjusted odds ratios indicated that the risk of leukemia increased with cumulative exposure to benzene. Except for a slight decrease of the odds ratio in the second exposure category (<50th percentile), the odds ratios increased with exposure and reached the value of 3.6 in the highest exposure group (≥ 90th percentile). The test for trend indicates a linear increase in risk across exposure categories with a P-value of 0.02. Fitting a model with cumulative exposure to benzene as a continuous variable, provides an OR of 1.2 (95% CI 1.0–1.5) associated with an increase in exposure of 10 U-years (not shown in the table). Unadjusted odds ratios also showed some evidence of an increased risk of leukemia with exposure to asbestos (P for trend = 0.08),

TABLE III. Selected Characteristics of Leukemia Cases and Controls at EDF-GDF, France

	Cases	Controls	
Socioeconomic status			
Senior management/professionals	3 (4%)	18 (6%)	
Middle management/technicians	3 (4%)	23 (8%)	
Clerical workers	21 (29%)	67 (23%)	
Skilled blue collar workers	29 (40%)	128 (45%)	
Unskilled blue collar workers	16 (22%)	49 (17%)	X^2 4ddl = 3.48; P = 0.48
Age at diagnosis			
Mean (standard error)	45.5 (1.1)	45.5 (0.5)	t-test = 0.05; P = 0.96
Duration of employment at EDF-GDF			
Mean (standard error)	20.9 (1.2)	21.7 (0.6)	t-test = 0.66; P = 0.51
Age at start of employment			
Mean (standard error)	24.7 (0.7)	23.8 (0.3)	t-test = 1.26; P = 0.21
Period at start of employment			
Before 1970	54 (75%)	223 (78%)	X^2 1ddl = 0.35; P = 0.55
In 1970 or later	18 (25%)	62 (22%)	

chlorinated solvents (P for trend = 0.04), and coal tars (P for trend = 0.04). No evidence of an association with leukemia risk was seen for exposure to other chemicals and to ionizing or non-ionizing radiations.

Table IV also shows odds ratios after adjustment for benzene, asbestos, chlorinated solvents, and coal tars. Adjusted odds ratios for benzene decreased slightly, by about 15% in the highest exposure group, and the confidence intervals included 1. The test for trend was no longer significant. The decrease in risk was much more pronounced for asbestos, with an odds ratio in the highest exposure group below 1, as well as for chlorinated solvents and coal tars. Strong correlations between these exposures may have led to over adjustment, making the resulting odds ratios difficult to interpret. For the remaining analyses, we will consider that leukemia risks increased with exposure to benzene alone, and only unadjusted odds ratios will be presented.

Table V shows the effect of different benzene exposure components. We first focused on exposure to benzene arising only from the use of solvents, i.e., ignoring benzene exposure from gasoline. Although the OR in the high exposure category is no longer statistically significant when use of solvents only is taken into consideration, the risks are only slightly decreased and the test for trend had a P-value of 0.06 at the limit of statistical significance. These results indicate that benzene exposure from solvents contributes by its own to the excess risk of leukemia. Benzene exposure from gasoline occurred in two cases and three controls, and did not permit a detailed analysis due to small numbers. However, comparing the leukemia risk in ever versus never exposed to gasoline lead to an OR of 2.5 (95% CI 0.4–15.1) that also suggests an independent effect of gasoline exposure on leukemia risk.

In Table V, it can be seen that the risk of leukemia was increased only among workers with first exposure to benzene before 1960, although the odds ratio did not reach statistical significance. To distinguish between the two components of cumulative exposure (exposure duration and exposure intensity), Table V also shows the effects of each variable separately. Leukemia incidence was increased for exposure duration of 10 or more years, and reached statistical significance with an odds ratio of 3.73 for exposure duration greater than 20 years. The test for trend was statistically significant ($P = 0.02$). Mean exposure intensity also showed evidence of an association with leukemia risk, with non-significantly increased odds ratios in the two higher exposure categories. The test for trend was at the limit of statistical significance ($P = 0.05$).

The last three rows in Table V show odds ratios for leukemia after excluding benzene exposures in the 2, 5, or 10 years preceding the diagnosis of cancer. Clear increased risks and significant trends were observed for these latency periods. This suggests that exposures older than 10 years at diagnosis, may play a more important role in leukemia causation.

Table VI shows odds ratios associated with specific leukemia subtypes. An odds ratio of 4.6 was observed for all acute leukemia in the highest category of benzene exposure. Because the number of leukemia cases in each cytologic subtype was small, the analyses were done on exposure categories wider than for all leukemia. The odds ratios were increased for both cytologic subtypes of acute leukemia, myeloid, and lymphoid. No increased risk was observed for all chronic leukemia, and no case was observed in the highest exposure category (>90th percentile). The odds ratios of 4.4

TABLE IV. Odds Ratios Associated With Selected Occupational Exposures Among Electric Utility Workers

				Not adjusted		Adjusted[a]	
Exposure		**No. of cases**	**No. of controls**	**OR**	**95% CI**	**OR**	**95% CI**
Benzene (U-years)	0	48	207	1.0	—	1.0	—
	>0 <1.1	6	38	0.7	0.3–1.7	0.7	0.2–1.9
	≥1.1 <5.5	7	20	1.4	0.6–3.5	1.1	0.4–3.2
	≥5.5 <16.8	5	12	1.9	0.6–5.9	1.4	0.4–5.7
	≥16.8	6	8	3.6	1.1–11.7	3.1	0.3–30.4
				P for trend = 0.02		*P* for trend = 0.30	
Asbestos (f/cm^3-years)	0	47	220	1.0	—	1.0	—
	>0 <4.7	11	32	1.6	0.8–3.4	1.5	0.6–3.7
	≥4.7 <9.0	6	16	1.8	0.7–4.8	1.5	0.5–4.5
	≥9.0 <23.5	4	10	2.0	0.6–6.8	0.6	0.1–4.2
	≥23.5	4	7	2.5	0.7–8.7	0.6	0.1–8.0
				P for trend = 0.08		*P* for trend = 0.81	
Chlorinated solvents (%wt-years)	0	43	190	1.00	—	1.0	—
	>0 <35	11	47	1.0	0.5–2.1	1.0	0.4–2.5
	≥35 <124	6	24	1.1	0.4–3.0	0.9	0.3–2.9
	≥124 <240	6	14	1.9	0.7–5.2	1.6	0.5–5.4
	≥240	6	10	2.7	0.9–7.7	1.6	0.3–8.7
				P for trend = 0.04		*P* for trend = 0.51	
Herbicides (years exposure)	0	52	205	1.0	—	1.0	—
	>0 <5.9	10	39	1.0	0.5–2.2	0.7	0.3–1.8
	≥5.9 <9.7	3	20	0.6	0.2–2.1	0.4	0.1–1.7
	≥9.7 <15.1	4	12	1.4	0.4–4.9	0.9	0.2–3.9
	≥15.1	3	9	1.4	0.3–5.5	0.6	0.1–2.9
				P for trend = 0.78		*P* for trend = 0.35	
Coal tars (%wt-years)	0	59	251	1.0	—	1.0	—
	>0 <407	7	25	1.2	0.5–3.0	0.9	0.3–2.6
	≥407	6	9	3.0	1.0–9.3	1.9	0.5–7.7
				P for trend = 0.14		*P* for trend = 0.36	
Styrene (%wt-years)	0	70	276	1.0	—	1.0	—
	>0	2	9	0.9	0.2–4.0	1.1	0.2–5.9
				P for trend = 0.98		*P* for trend = 0.76	
Electric fields (V/m-years)	<256	38	142	1.0	—	1.0	—
	≥256 <335	20	71	1.0	0.5–2.1	1.4	0.6–3.2
	≥335 <405	11	43	0.8	0.3–2.2	1.1	0.4–3.1
	≥405	3	29	0.3	0.1–1.3	0.5	0.1–1.8
				P for trend = 0.12		*P* for trend = 0.26	
Magnetic fields (μT-years)	<3.7	41	142	1.0	—	1.0	—
	≥3.7 <4.8	14	71	0.6	0.3–1.3	0.6	0.3–1.2
	≥4.8 <6.7	9	43	0.7	0.3–1.6	0.4	0.1–1.1
	≥6.7	8	29	0.9	0.4–2.3	0.9	0.3–2.5
				P for trend = 0.93		*P* for trend = 0.93	
Ionizing radiations (mSv)	0	69	271	1.0	—	1.0	—
	>0	3	14	0.8	0.2–3.1	0.6	0.1–2.7
				P for trend = 0.80		*P* for trend = 0.50	

[a]Odds ratios are adjusted on benzene, asbestos, chlorinated solvents, and coal tars.
U-years=unit-years.

TABLE V. Odds Ratios Associated With Benzene Exposure Arising From the Use of Solvents, and According to Year of First Exposure, Exposure Duration, Mean Exposure, and for Different Latency Periods Before Cancer Diagnosis

Exposure to benzene		No. of cases	No. of controls	OR	95% CI	*P* for trend
Exposure to benzene due to the use of solvents only (U-years)	0	50	209	1.0	—	
	$>0<1.1$	6	37	0.7	0.3–1.7	
	$\geq 1.1<5.5$	7	21	1.3	0.5–3.2	
	$\geq 5.5<16.8$	5	12	1.8	0.6–5.5	
	≥ 16.8	4	6	3.1	0.8–11.8	0.06
Year of first exposure	Never exp.	48	207	1.0	—	
	<1960	11	25	2.1	0.9–4.7	
	1960–1969	7	27	1.2	0.5–2.8	
	≥ 1970	6	26	1.0	0.4–2.5	0.40
Duration of exposure (years)	Never exp.	48	207	1.0	—	
	0–9	10	52	0.8	0.4–1.7	
	10–19	7	17	2.0	0.7–5.2	
	≥ 20	7	9	3.8	1.3–11.1	0.02
Mean intensity[a] ("unit")	Never exp.	48	207	1.0	—	
	0–0.16	7	39	0.8	0.3–1.9	
	0.16–0.56	6	19	1.3	0.5–3.4	
	0.56–1.98	7	13	2.2	0.8–5.6	
	≥ 1.98	4	7	2.7	0.7–11.4	0.05
2-Years latency (U-years)	Never exp.	48	207	1.0		
	$>0<1.1$	6	39	0.7	0.3–1.6	
	$\geq 1.1<5.5$	7	19	1.5	0.6–3.7	
	$\geq 5.5<16.8$	5	13	1.8	0.6–5.3	
	≥ 16.8	6	7	4.3	1.3–14.8	0.01
5-Years latency (U-years)	Never exp.	49	211	1.0		
	$>0<1.1$	8	39	0.9	0.4–2.0	
	$\geq 1.1<5.5$	4	16	1.0	0.3–3.2	
	$\geq 5.5<16.8$	5	12	2.0	0.7–6.1	
	≥ 16.8	6	7	4.3	1.3–14.9	0.01
10-Years latency (U-years)	Never exp.	53	221	1.0		
	$>0<1.1$	7	32	0.9	0.4–2.2	
	$\geq 1.1<5.5$	2	14	0.6	0.1–2.7	
	$\geq 5.5<16.8$	4	11	1.7	0.5–5.6	
	≥ 16.8	6	7	4.2	1.2–14.2	0.02

[a]Exposure cutpoint are the 50th, 75th, and 90th percentiles of exposure distribution among exposed.

for chronic lymphoid leukemia was based on only one exposed case and was not statistically significant.

DISCUSSION

The data presented here were collected initially for a study on ELF fields and cancer [Thériault et al., 1994]. The findings did not show a clear association between exposure to ELF fields and leukemia among French gas and electric utility workers. The present study indicates that leukemia risk in this population may be related to other occupational exposures, primarily benzene. We have also examined exposures for which there has been at least a suspicion of a link with leukemia in previous case reports, epidemiological studies or meta-analyses. There was a priori only weak evidence of a leukemogenic effect of asbestos [Kishimoto, 1992], chlorinated solvents [Frangos and Peters, 1993], and coal tars [Partanen and Boffetta, 1994], which are linked to leukemia risk in this study. These associations, however, disappeared after adjustment for benzene. Odds ratios for benzene also did decrease after adjustment for these exposures, but to a smaller extent. No association was observed

TABLE VI. Odds Ratios Associated With Estimates of Benzene Exposure Among Electric Utility Workers by Leukemia Subtype

Exposure to benzene		No. of cases	No. of controls	OR	95% CI	*P* for trend
All acute leukemia[a] (U-years)	Never exp.	31	118	1.0		
	$>0<1.1$	1	18	0.3	0.1–1.6	
	$\geq 1.1<5.5$	1	13	0.3	0.1–2.3	
	$\geq 5.5<16.8$	2	8	1.2	0.2–6.8	
	≥ 16.8	6	6	4.6	1.2–17.4	0.05
Acute myeloid leukemia	Never exp.	20	74	1.0		
	$>0<5.5$	1	20	0.2	0.1–1.4	
	≥ 5.5	5	9	2.4	0.7–8.5	0.14
Acute lymphoid leukemia	Never exp.	9	37	1.0		
	$>0<5.5$	1	7	0.6	0.1–5.3	
	≥ 5.5	2	4	3.3	0.3–43.3	0.16
All chronic leukemia (U-years)	Never exp.	16	74	1.0		
	$>0<1.1$	4	18	1.1	0.3–3.8	
	$\geq 1.1<5.5$	4	6	3.2	0.7–13.9	
	$\geq 5.5<16.8$	2	3	1.7	0.3–9.3	
	≥ 16.8	0	2	—	—	
Chronic myeloid leukemia	Never exp.	7	35	1.0		
	$>0<5.5$	5	13	1.9	0.5–7.1	
	≥ 5.5	1	4	1.2	0.1–11.4	0.85
Chronic lymphoid leukemia	Never exp.	9	39	1.0		
	$>0<5.5$	3	11	1.3	0.3–6.3	
	≥ 5.5	1	1	4.4	0.3–77.1	0.75

One case of unspecified leukemia not included in the table.
[a]Three cases of acute leukemia of unknown cytology.

between leukemia and exposures to herbicides, styrene, ELF fields, and low doses of ionizing radiations.

Study Limitations

The follow-up of workers terminated at the date of retirement, because no diagnosis of cancer could be ascertained in older workers. This resulted in a smaller number of cases and in decreased statistical power, but an appropriate selection of controls among other non-retired workers guaranteed that the data were not biased.

Using a JEM to assess exposure always entails some degree of misclassification. In the present study, exposure misclassification may occur for different reasons. First, the workers were located in different plants or factories across the country, with possibly heterogeneous exposure situations. Second, the assessment of exposure to chemicals was based on expert judgment, since no exposure monitoring data was available. This method makes difficult the estimation of exposure intensity (e.g. air concentration), but exposure duration and exposure frequency were based on the observation of actual work tasks. In fact, exposure intensity was not estimated at all for some chemicals (group 4 in Table I). For benzene, we have used relative weights for each work task to estimate exposure intensity in different time periods. These assumptions put emphasis on the older exposure periods, which were assigned the highest exposure intensities. Although these assumptions may have influenced some results, they are realistic given the general improvement of exposure conditions at EDF-GDF during the last decades. In addition, we have considered that the decrease in benzene exposure was proportionally less pronounced for motor vehicle mechanics exposed to gasoline than for workers using solvents, because of the introduction in the 1980s of unleaded gasoline with high benzene content. The odds ratios for total benzene exposure were not changed meaningfully when only benzene exposure arising from the use of solvents was considered, i.e., disregarding benzene exposure from gasoline (Table V). This result indicates that the relative weights of benzene exposure intensities assigned to each work task had no marked effect on the results.

In total, any resulting error in exposure assessment was non-differential, as it should affect equally the cases and the controls. This type of misclassification generally results in odds ratios biased toward unity. It may entail a loss of statistical power to detect true elevations in risk, but in most usual

situations, it is not expected to account for false positive associations [Rothman and Greenland, 1998].

Confounding is a possible explanation for the observed association between benzene exposure estimates and leukemia. Confounding may result from other occupational exposures included in the JEM that may not have been totally controlled for in the analysis because of inaccurate estimations, or may result from unidentified risk factors. Garage mechanics, for example, are exposed both to benzene in gasoline and to engine exhaust (not estimated here) which contains other carcinogenic substances such as polycyclic aromatic hydrocarbons [IARC, 1989b]. However, they have not been shown to be strongly associated with leukemia risk, and they are unlikely to be strong confounders in our data.

Exposure Estimates

Because of uncertainties regarding the true exposure levels, we used arbitrary units of benzene concentration to estimate exposure intensity. However, our exposure ''units'' can be converted roughly into milligram per cubic meter or in parts per million, in order to compare our results with findings in other benzene exposed workers. From benzene monitoring data published in the literature, we can assume that 1 U of benzene exposure in this study is approximately equivalent to 1 ppm (3.2 mg/m^3), making our exposure estimates (for example 1 ppm for EDF-GDF workers exposed to gasoline in 1970–1985) in range with the published data (0.6 ppm in large garages in France and 0.7 ppm in small ones [Machefer et al., 1990]). Under this assumption of 1 U = 1 ppm, the median TWA exposure to benzene among exposed controls at EDF-GDF would be 0.16 ppm, with 90% of workers having exposure below 2 ppm. The median cumulative exposure would be 1.1 ppm-years, with 90% of exposed workers having cumulative exposure below 16.8 ppm-years.

Comparison With Previous Studies

Clear excess leukemia risks have been observed in workers exposed to levels of benzene higher than those estimated among the present workers. Earlier studies have reported the carcinogenicity and hematotoxicity of benzene for workers exposed well above 25 ppm [Aksoy et al., 1972; Vigliani and Forni, 1976]. In the cohort of rubber hydrochloride manufacturing workers (Pliofilm cohort), an increased risk of leukemia deaths was observed for exposures above 40 ppm-years (equivalent to 1 ppm over a working lifetime [Rinsky et al., 1987]. It can also be estimated from the risk assessment model described in that paper that the odds ratio of 3.6 observed in our high exposure group ($>$ 16.8 U-years or ppm-years, corresponding to a mean exposure of 40 ppm-years) would be observed in the Pliofilm cohort for an exposure of about 100 ppm-years. In a study carried out in 12 Chinese cities, workers were also exposed to relatively high levels of benzene [Dosemeci et al., 1994]. Significantly increased leukemia risks were observed for cumulative exposures in the range 40–99 ppm-years and above 100 ppm-years [Hayes et al., 1997], i.e., well above the mean cumulative exposures estimated here. The China study, however, also provided some evidence of an increased leukemia risk for exposures of less than 10 ppm, or cumulative exposures of less than 40 ppm-years.

Conversely, low levels of benzene have been documented in several studies among petroleum industry and distribution workers, with exposure close to the values estimated among present exposed utility workers [Rushton, 1993; Lynge et al., 1997; Rushton and Romaniuk, 1997]. These studies did not show elevated risks for leukemia [Lynge et al., 1997], or only slightly increased risks with cumulative exposure [Rushton and Romaniuk, 1997]. Therefore, assuming that gas and electricity utility workers had low exposures to benzene, as described above, the observation of an association between leukemia and the estimates of cumulative exposure to benzene in the present data is not totally in agreement with previous findings among workers with similar exposure.

Leukemia Subtypes

Although benzene exposure is thought to be linked with AML [Wong, 1995], it has also been shown in a literature review that an exclusive relationship with this leukemia subtype is based on insufficient evidence, and that an association with other leukemia subtypes is no less persuasive [Savitz and Andrews, 1997]. The relationship between benzene exposure and leukemia cell types is better addressed by leukemia studies based on cancer diagnoses rather than death certificates, because of the uncertainties in coding specific cell types of leukemia deaths. In the UK study on petroleum workers, there is some indication of an association between exposure to benzene and acute myeloid (and monocytic) leukemia, but no evidence of an association with acute or chronic lymphocytic leukemia [Rushton and Romaniuk, 1997]. The study in China also showed increased risks with a dose-response relation for acute non-lymphocytic leukemia (mainly acute myeloid) [Hayes et al., 1997]. In the present study, the increased risk of leukemia is primarily associated with acute leukemia subtypes. It is suggested that both acute myeloid and acute lymphoid leukemias are at increased risk. However, the analysis is limited due to small numbers.

Temporal Pattern

The temporal pattern between exposure to benzene and leukemia incidence has been a source of controversy. A recent

reanalysis of the Pliofilm cohort study indicated that the most recent exposures were more strongly associated with risk than the more distant ones [Finkelstein, 2000]. Similarly, cases with acute non-lymphocytic leukemia in the China study were primarily linked to benzene exposure in the 10-year period prior to diagnosis [Hayes et al., 1997]. Results from occupational cohorts with low levels of benzene exposure generally point to the opposite direction. Long latency periods of the order of 20–30 years have been generally observed for leukemia cases among workers in the petroleum industry [Wong and Raabe, 1989]. In the study of UK petroleum industry workers, the odds ratio for acute myeloid (and monocytic) leukemia tended to increase after excluding exposures occurring 5 or 10 years before diagnosis [Rushton and Romaniuk, 1997]. In the present study, results suggest that leukemia is more strongly associated with exposures to benzene after allowing for a 10–20 years latency period, i.e., with distant past exposures.

CONCLUSION

Our results seem to confirm that leukemia is associated with low exposure to benzene, as estimated from a JEM based on expert judgment. Associations with exposures to other occupational carcinogens were apparent, but they could be explained by confounding from benzene. Benzene exposure was estimated to be in concentration ranges where an increased leukemia risk has generally not been detected in previous epidemiological studies, possibly because of lack of statistical power. It is also possible that the actual benzene exposure in the present workers was underestimated. Although benzene was more clearly associated with acute leukemia than with chronic leukemia, no clear association with a specific leukemia subtype appear from our data. We also observe a long latency period between benzene exposure and leukemia, which is in contradiction with recent reports of stronger associations with the most recent exposures. Further follow-up of these workers, leading to more leukemia cases, combined with an update of the JEM, may help to clarify these results.

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REFERENCES

Aksoy M, Dincol K, Erdem S, Akgun T, Dincol G. 1972. Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. Br J Ind Med 29:56–64.

Armstrong B, Thériault G, Guénel P, Deadman J, Goldberg M, Héroux P. 1994. Association between exposure to pulsed electromagnetic fields and cancer in electric utility workers in Quebec, Canada, and France. Am J Epidemiol 140:805–820.

Chevalier A, Goldberg M, Godard C, Guenel P, Callet B, Antonini B, Medard A, Coing F. 1996. Incidence des cancers dans la population masculine des salariés en activité à Electricité de France et Gaz de France. (Cancer incidence among male salaried workers at Electricité de France and Gaz de France.) Rev Epidemiol Sante Publique 44:25–36.

Dosemeci M, Li GL, Hayes RB, Yin SN, Linet M, Chow WH, Wang YZ, Jiang ZL, Dai TR, Zhang WU. 1994. Cohort study among workers exposed to benzene in China: II. Exposure assessment. Am J Ind Med 26:401–411.

Finkelstein MM. 2000. Leukemia after exposure to benzene: Temporal trends and implications for standards. Am J Ind Med 38:1–7.

Frangos SA, Peters JM. 1993. Chlorinated hydrocarbon solvents: Substituting our way toward human carcinogenicity. Am J Ind Med 24:355–364.

Guénel P, Nicolau J, Imbernon E, Chevalier A, Goldberg M. 1996. Exposure to 50-Hz electric field and incidence of leukemia, brain tumors and other cancers among French electric utility workers. Am J Epidemiol 144:1107–1121.

Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, Li CY, Rothman N, Hoover RN, Linet MS. 1997. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group. J Natl Cancer Inst 89:1065–1071.

IARC. 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. In: Some industrial chemicals and dyestuffs. Vol 29: Lyon: IARC.

IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. In: Supplement 7: Overall evaluations of carcinogenicity: An updating of IARC monographs. Vol 1 to 42: Lyon: IARC.

IARC. 1989a. IARC monographs on the evaluation of carcinogenic risks to humans. In: Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. Vol.47: Lyon: IARC.

IARC. 1989b. IARC monographs on the evaluation of carcinogenic risks to humans. In: Diesel and gasoline engine exhausts and some nitroarenes. Vol 46: Lyon: IARC.

Imbernon E, Goldberg M, Bonenfant S, Chevalier A, Guenel P, Vatre R, Dehaye J. 1995. Occupational respiratory cancer and exposure to asbestos: A case-control study in a cohort of workers in the electricity and gas industry. Am J Ind Med 28:339–352.

INSEE. 1983. Nomenclature des professions et catégories socio-professionnelles PCS. (Classification of occupations and socio-economic categories.) Paris: INSEE.

Kishimoto T. 1992. Cancer due to asbestos exposure. Chest 101:58–63.

Linet MS, Cartwright RA. 1996. The leukemias. In: Schottenfeld D, Fraumeni JF, Jr, editors. Cancer epidemiology and prevention. New York: Oxford University Press. p 841–892.

Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, Boffetta P, Grandjean P, Heikkila P, Horte LG, Jakobsson R, Lundberg I,

Moen B, Partanen T, Riise T. 1997. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol 145:449–458.

Machefer J, Bidron P, Guigner PM. 1990. Exposition aux hydrocarbures benzéniques des carburants automobiles chez les mécaniciens et les pompistes. (Exposure to benzene from motor vehicle gasoline among garage mechanics and gas distribution workers.) Arch Mal Prof 51:89–94.

Partanen T, Boffetta P. 1994. Cancer risk in asphalt workers and roofers: Review and meta-analysis of epidemiologic studies. Am J Ind Med 26:721–740.

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. 1987. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:1044–1050.

Rothman KJ, Greenland S. 1998. Modern Epidemiology. Philadelphia: Lippincott-Raven 737 p.

Runion HE. 1975. Benzene in gasoline. Am Ind Hyg Assoc J 36:338–350.

Rushton L. 1993. A 39-year follow-up of the UK oil refinery and distribution center studies: Results for kidney cancer and leukemia. Environ Health Perspect 101 (Suppl 6):77–84.

Rushton L, Romaniuk H. 1997. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom [see comments]. Occup Environ Med 54:152–166.

Savitz DA, Andrews KW. 1997. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med 31:287–295.

Thériault G, Goldberg M, Miller AB, Armstrong B, Guénel P, Deadman J, Imbernon E, To T, Chevalier A, Cyr D, Wall C. 1994. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France 1970–1989. Am J Epidemiol 139:550–572.

Vigliani EC, Forni A. 1976. Benzene and leukemia. Environ Res 11:122–127.

Wong O. 1995. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. Occup Environ Med 52:380–384.

Wong O, Raabe GK. 1989. Critical review of cancer epidemiology in petroleum industry employees, with a quantitative meta-analysis by cancer site. Am J Ind Med 15:283–310.