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Occupational Risk Factors for Acute Leukaemia: A Case-Control Study

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A case-control study has been performed for occupational risk factors of acute leukaemia, based on 185 cases more than 30 years old and 513 matched controls. There was a significant excess of polyvalent farming and electronic engineers among professions of cases, and, in addition of metal workers when considering the professions pursued for more than 5 years. The corresponding exposures were analysed through a detailed questionnaire, and assessed by an industrial hygienist after blinding the case-control status. The odds ratios (OR) were computed after adjustment on matching variables and prior chemo- or radiotherapy treatment, and after stratification for the level and total duration of exposure. There was no excess of professional exposure to ionizing radiation among cases. A significant relationship was observed between acute leukaemia and high or medium exposure to benzene, as well as over 10 years high or medium exposure to exhaust gas. In addition a significant relationship was observed with exposure to pesticides—insecticides and/or weed killers—and to electric and magnetic fields (EMF). The relationship with pesticides was significant when considering high or medium exposure to weed killers and more than 10 years exposure to both subtypes of pesticides. The relationship with pesticides and EMF remained significant when confounding factors were taken into consideration and after adjustment on co-exposure to benzene.

The cytological studies showed that acute leukaemias following exposure to benzene (high or medium) and to EMF were only of myelogenous subtypes, whereas those following exposure to pesticides were divided between lymphoblastic and myeloblastic subtypes. Cytogenetic studies failed to show increased frequency of chromosomal abnormalities, as described in acute leukaemias secondary to anti-cancer treatments. Our study adds credence to the hypothesis that pesticides and EMF are leukaemogenic agents, together with benzene.

Besides genetic factors, certain exposures such as benzene, ionizing radiation and anti-neoplastic agents are known to cause acute leukaemia, through induction of irreversible DNA damage.[1,2] Iatrogenic exposure to radiation, which is especially leukaemogenic in utero and in childhood, has been reduced over the past decades, and most 'secondary' acute leukaemias occur following administration of alkylating drugs for a first cancer.[3] Meanwhile, occupational exposure to benzene and ionizing radiation still remain potential risk factors for acute leukaemia in Western countries, despite strict limitations and security rules. Acute leukaemias secondary to these exposures share several characteristics in common including predominant myelogenous cytological subtypes, latency of several years, and a dose-dependent relative risk.

Recent epidemiological studies have investigated the role of low-dose exposure to benzene,[4] ionizing radiation,[5] background radiation[6] and of other occupational and environmental factors: especially pesticides,[7] and non-ionizing radiation resulting from electric and magnetic fields (EMF).[8] These studies yielded controversial results, depending on the methods used, the size of the sample, and the geographical area under investigation. Some methodological aspects could partly explain contradictory results: many studies have used the ICD classification without distinguishing between leukaemia subtypes, or have not taken into account possible confounding factors. In addition, the level of exposure can vary from time to time, according to the introduction in work places of new agents with leukaemogenic potential or, conversely, the withdrawal or limitation of such agents.

The advantages of case-control studies of acute leukaemia as presented here are several, including the identification of multiple potential leukaemogenic

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agents, either through consecutive professional exposures, or acting simultaneously, the detailed analysis of their relative risk following evaluation of the levels of exposure and adjustment on confounding factors, as well as correlation between specific agents and certain cytological subtypes.

MATERIAL AND METHODS

Cases and Controls

This study performed from **1984** to **1988** involved **204** cases of acute leukaemia who were over **30** years old and resident in France. Most of them were hospitalized in the clinical department of haematology at Hôtel-Dieu, Paris, the others in the department of haematology of Hôpital Henri-Mondor in Creteil, near Paris. The age limit was selected to increase the chance of identifying occupational factors. The diagnosis of acute leukaemias, as well as the subtype classification, was made according to the French-American-British (FAB) Cooperative Group criteria.[9] During this period, there were **79** other cases of acute leukaemia satisfying the inclusion criteria who could not be interviewed. Of these patients, **34** had died within a week of arrival at the hospital, **43** were in a too serious condition to be interviewed (aplasia, infection . . .) and two were transferred to other hospitals. Hence in total **72%** of eligible cases were interviewed. During the same 4-year period, **561** controls, matched for sex, age (±5 years), ethnic group and usual residence, hospitalized in other departments of the same hospitals were interviewed. We have secondarily excluded from the analysis the cases and controls for which the interviewer had recorded poor cooperation (about 5% of cases and controls), the cases which were not matched with at least one control, and the controls which corresponded to excluded cases, leaving **185** cases and 513 controls. Among the **185** cases, **147** have three controls, **34** have two controls, and four have one control. The conditions of the controls were partly explained by the relative importance and cooperation of certain specialized departments in the same hospitals (ophthalmological: **30%;** cardiovascular and pulmonary: **17%;** diabetes and endocrinopathies: 16%; gynaecological: **12%;** orthopaedic: **10%;** cancer-excluding leukaemia and lymphomas: **7%;** miscellaneous: **5%;** undefined: **3%).**

Methods

Physicians trained in industrial health administered a standardized interview to cases and their appropriate controls. The questionnaire was designed to obtain information concerning: demographic data, information on occupation and health problems of the family, past medical history including any radiotherapy or chemotherapy treatment, drug use, a complete description of the occupational activities, and some assessment of the environmental and leisure exposure. The occupational history was assessed in detail by a separate questionnaire for each job including, apart from the job title and the branch of activity, recall of chemical and physical exposures with an estimation of exposure frequency and the use of any individual protection.

The analysis of occupations was carried out on all the different job titles of cases and controls. The 185 cases recorded **484** occupations and the **513** controls recorded **1364** occupations (which corresponds to an average of **2.6** per case and 2.7 per control respectively). For **95** cases **(51.4%)** and **280** controls **(54.6%)** there was no recorded industrial or agricultural exposure. For the rest, the number of separate exposures recorded (out of a list of **24)** was **447** for the cases and **1114** for the controls (average: 5.0 and **4.8** respectively).

Then, blinding the case-control status, the job exposures over the occupational history **(24** items) were reassessed by an industrial hygienist in a similar way to that used when building a job exposure matrix.[10] Whenever possible, the hygienist coded the exposure into low (<5% of the working time), medium (5–50%) and high (>50% of the working time). A weighted length of exposure (WLE) was defined on the basis of level and total duration of exposure: WLE = **0.025** × duration of low exposure + **0.25** × duration of medium exposure + **0.75** × duration of high exposure. The weights were chosen so as to represent approximately the average percentage of exposed working time in each of the three exposure categories. The analysis was performed only on the exposures assessed by the industrial hygienist. A standard case-control analysis was conducted." Results are reported first separately for each exposure and then significant risk factors are analysed jointly. Matching was included in the design of this study so as to ensure comparability of sociodemographic characteristics between cases and controls. The matching variables (hospital, sex, age, ethnic group and residence) have a fixed number of categories which is independent of the number of subjects in the study. Hence in the analysis, the matching can be taken into account either by including the matching variables as adjustment variables in an unconditional logistic regression for large strata[12] or by performing conditional regressions. After assuring ourselves of the similarity of results between the two approaches, we only report results corresponding to the first approach when each risk factor is analysed separately. For the

joint analysis of the significant risk factors, results for both unconditional and conditional logistic regression will be given. BMDP progams were used for the unconditional logistic regression and the SAS procedure pH-REG was used **for** the conditional analysis.

RESULTS

As expected there was no significant difference between the cases and controls for the matching variables: age (mean ***55.4 ± 14.9*** for both groups), sex (male/female: ***50.2*** versus 48.2), and residence (Paris, suburbs or outside). Further sociodemographic variables including ethnic origin of both parents (Europe: ***89.7%*** versus 93%), age at the end of education (mean: ***16.5*** ±5 versus 16.6), socioeconomic activity, and family situation were also comparable. The professional situation at time of study was similar (working: ***50.8%*** versus ***47.6%;*** out of work: ***2.2%*** versus ***1.8%;*** retired: ***36.2%*** versus ***38.1%;*** no profession: ***10.8%*** versus ***12.5%).*** There was, however, a small but significant difference for place of birth (France: ***83.2%*** versus ***88.7%;*** other European countries: ***3.2%*** versus ***5.3%;*** Africa: ***11.9%*** versus ***5.8%;*** other: ***1.6%*** versus ***0.2%*** for cases versus controls respectively) ($P = 0.004$).

Once 5% poor cooperation was excluded cooperation was evaluated as good in ***63%*** versus 60% and, medium in ***37%*** versus 40% respectively.

The analysis of job titles, coded according to the International Labour Office Classification ***(1968)*** showed a significant excess of polyvalent farming and electronic engineers among cases **as** compared to controls. When comparisons were made for professions pursued for more than ***5*** years, the same significant excesses were maintained, with, in addition, an elevated OR for metal workers among cases (Table ***1).***

The relative risk estimates concerning exposure to suspected professional agents are shown **in** Table **2. A** relatively low number of cases (8/185 = ***4.3%)*** and controls (18/513 = ***3.5%)*** had a previous history of chemotherapy or radiotherapy in a body area including active bone marrow. The **OR** was computed for comparison of professional exposures between cases and controls after adjustment for prior chemo- **or** radiotherapy and on the matching variables. The comparisons were made for all levels of exposures and, separately, for high or medium level exposure **(HM).** Professional exposure to ionizing radiation was not found to be linked to acute leukaemia in our study. Exposure to EMF is associated with an elevated **OR.** This OR is strongly increased and becomes statistically significant when exposure to EMF other than arc welding is considered separately. No association is found with exposure to solvents in general but **OR** for benzene **(HM)** and oxygenated solvents are significantly increased. Moderately increased OR not reaching statistical significance, are found for **HM** exposure to fuel and exhaust gas. All the **OR** measuring the association with pesticide exposure are elevated, with a high and significant risk attached in particular to **HM** exposure to weed killers. No subject (case or control) was coded for exposure to ethylene oxide.

TABLE 1 *Job titles showing a significant excess among cases*

	Cases No.	Controls No.	Odds ratio	χ^2	*P*
All professions					
Polyvalent farming[a]	8	5	4.6	6.5	0.011
Electronic engineers[b]	3	0	-	4.9	0.027
Professions pursued for more than 5 years					
Polyvalent farming[a]	8	4	5.6	7.7	0.006
Electronic engineers[b]	3	0	-	5.2	0.028
Metal workers[c]	5	3	4.6	3.8	0.065

N.B. The codes are indicated according to the International Labour Office Classification 1968: [a]: 611, [b]: 02310, [c]: 873. Comparisons were made against 465 5-digit ILO job title codes and 206 3-digit ILO job title codes.

Exposure to other agents which are not suspected in relation to leukaemia was also investigated as a way of checking whether our study could reproduce negative results. We did find OR close to ***1.0*** for various agents such as disinfectants, oils and grease, metallic dust, and other dusts (results not shown). There were fewer cases than controls with a history of exposure to asbestos dusts (2.7% versus 6.4%, OR = ***0.36, 95%*** CI : 0.14–0.96).

Other differences were noted between cases and controls when the comparison was made for weighted length of exposure which was significantly longer for benzene and exhaust gas (Table ***3).*** In addition the adjusted **OR** showed a significant link with acute leukaemia in case of exposure for more than ***10*** years to exhaust gas, weed killers, and insecticides.

As expected, professional exposures were more frequently observed for both groups in men than in women ***(22.6%*** versus 3.6%, $P < 0.001$). Double or multiple exposures to benzene **HM,** pesticides and/or EMF were more frequently observed in cases than in controls ***(3.78%*** versus 0.58%, OR = ***7.20, 95%*** CI : 1.79–28.9). For exposure to at least one of these

TABLE 2 ***Relative risk estimates concerning exposure to suspected agents***

		Cases		Controls		OR[a]	95% CI
		No.	%	No.	%		
Electric and magnetic fields							
- all types of exposure		14	7.6	23	4.5	1.7	(0.9–3.5)
Arc welding	(a) +	8	4.2	18	3.5	1.2	(0.5–3.0)
	(b) + +	4	2.2	9	1.7	1.3	(0.4-4.2)
Exposures other	(a)	7	3.8	5	1.0	3.9	(1.2–12.5)*
than arc welding	(b)	3	1.6	3	0.6	2.9	(0.6–14.4)
Ionizing radiation		4	2.2	17	3.3	0.7	(0.2–2.0)
Solvents							
- all types		71	38.4	188	36.7	1.1	(0.7–1.5)
Benzene	(a)	22	11.9	47	9.02	1.3	(0.8–2.3)
	(b)	15	8.1	16	3.1	2.8	(1.3–5.9)**
Other hydrocarbon	(a)	28	15.1	71	15.0	1.0	(0.6–1.6)
solvents	(b)	11	6.0	34	6.6	0.9	(0.4–1.8)
Halogenated	(a)	44	23.8	115	22.4	1.1	(0.7–1.6)
solvents	(b)	23	12.4	62	12.1	1.0	(0.6–1.7)
Oxygenated	(a)	42	22.7	82	16.0	1.5	(1.0–2.4)*
solvents	(b)	15	8.1	31	6.0	1.5	(0.7–2.7)
Fuel	(a)	25	13.5	50	9.8	1.4	(0.8–2.4)
	(b)	14	7.6	26	5.1	1.5	(0.7–3.0)
Exhaust gas	(a)	11	6.0	35	6.8	0.8	(0.4–1.7)
	(b)	8	4.3	13	2.5	1.7	(0.7–4.3)
Pesticides							
- all types		22	11.9	40	1.8	1.6	(0.9–2.8)
Weed killers	(a)	16	8.7	30	5.9	1.5	(0.8–2.8)
	(b)	7	3.8	6	1.2	3.5	(1.1–10.8)*
Insecticides	(a)	22	11.9	37	7.2	1.7	(1.0–3.1)
	(b)	8	4.3	11	2.1	2.1	(0.8–5.4)

[a] Adjusted OR on the matched variables and prior history of radiotherapy or chemotherapy.
+(a) All exposure.
+ + (b) High or medium exposure.
* OR significant at the 5% level.
** OR significant at the 1% level.

three agents the OR is still doubled: (OR = 1.95; 95% CI : 1.20–3.16).

Among the 31 cases and controls who had a history of exposure to benzene HM there was a significantly higher proportion of people exposed to EMF (9.7% exposed versus 1.35 non-exposed, $P = 0.0005$) and similarly to pesticides (22.6% versus 8.2%, $P = 0.006$), and to oxygenated solvents (38.7% versus 16.8%, $P = 0.002$). After adjustment for benzene HM, the OR for exposure to oxygenated solvents is reduced (OR = 1.4, 95% CI : 0.9–2.2); after further adjustments for exposure to EMF and weed killers HM its effects become weak and non-significant. The other three clearly significant exposures (benzene HM, EMF, weed killers HM) were then analysed simultaneously by logistic regression. Results from both un-

TABLE 3 *Comparison of duration of exposure to suspected agents between cases and controls*

		Cases	Controls	OR[a]	95% CI	*P* value[b]
Electric and magnetic fields						
Arc welding[c]						
WLE (m ± s)		3.0 ± 3.7	1.9 ± 2.9	-	-	NS
Exposures other than arc welding[c]						
WLE (m ± s)		2.9 ± 3.1	8.1 ± 12.9	-	-	NS
Solvents						
Benzene						
WLE (m ± s)		4.7 ± 5.1	3.3 ± 6.2	-	-	0.007
Years of HM exposure	0	170	491	1	-	
	≤10	7	5	4.3	(1.3–14.3)**	
	>10	8	11	2.1	(0.8–5.4)	
Other hydrocarbon solvents						
WLE (m ± s)		3.8 ± 6.8	2.6 ± 4.1		-	NS
Years of HM exposure	0	174	479	1	-	NS
	≤10	2	15	0.4	(0.1–1.6)	
	>10	9	19	1.3	(0.5–2.9)	
Halogenated solvents						
WLE (m ± s)		6.0 ± 8.4	3.6 ± 5.6			NS
Years of HM exposure	0	162	451	1	-	
	≤10	3	26	0.3	(0.1–1.1)	
	>10	20	36	1.5	(0.8–2.7)	
Oxygenated solvents						
WLE (m ± s)		2.3 ± 2.8	2.5 ± 3.8			NS
Years of HM exposure	0	170	482	1	-	
	≤10	4	12	1.0	(0.3–3.1)	
	>10	11	19	1.7	(0.8–3.6)	
Fuel						
WLE (m ± s)		6.3 ± 7.5	4.4 ± 6.4			NS
Years of HM exposure	0	171	487	1	-	
	≤10	3	8	1.0	(0.3–3.8)	
	>10	11	18	1.8	(0.3–3.9)	
Exhaust gas						
WLE (m ± s)		7.0 ± 6.5	2.3 ± 3.1			0.01
Years of HM exposure	0	177	500	1	-	
	≤10	1	6	0.4	(0.1–3.7)	
	>10	7	7	2.8	(1.0–8.3)*	
Pesticides						
Weed killers						
WLE (m ± s)		6.6 ± 12.3	1.5 ± 3.8			NS
Years of HM exposure	0	178	507	1	-	
	≤10	1	3	1.0	(0.1–9.7)	
	>10	6	3	6.0	(1.5–25.0)**	
Insecticides						
WLE (m ± s)		5.0 ± 10.7	1.5 ± 3.5			NS
Years of HM exposure	0	177	502	1	-	
	≤10	1	6	0.5	(0.1–4.1)	
	>10	7	5	4.0	(1.2–13.2)**	

[a] Adjusted OR on the matching variables and prior history of radiotherapy or chemotherapy
[b] Non-parametric Mann-Whitney test
[c] These categories had been already specified on the questionnaire. WLE is the weighted length of exposure defined in Material and Methods
* OR significant at the 5% level
** OR significant at the 1% level

matched and matched analyses are presented in Table 4. The three risk factors remain strongly associated with acute leukaemia. There is an overall similarity of results between both types of analyses, the matched analysis giving slightly higher relative risk estimates. The OR associated with EMF exposure is the largest but is estimated with much imprecision.

TABLE 4A. *Logistic regression analysing simultaneously three exposures adjusted for matching variables and prior history of chemotherapy or radiotherapy*

EXPOSURE	OR	CI (95%)
Benzene (HM)	2.49	1.16–5.34
Electric and magnetic fields	3.19	0.95–10.67
Weed killers (HM)	3.06	0.97–9.68

TABLE 4B. *Conditional logistic regression (matched analysis adjustment for prior history of chemotherapy or radiotherapy)*

EXPOSURE	OR	CI (95%)
Benzene (HM)	2.74	1.27–5.94
Electric and magnetic fields	3.99	1.06–14.69
Weed killers (HM)	3.45	1.05–11.34

Finally we present comparisons on morphology and cytogenetics within the case group, contrasting in particular professionally exposed and non-exposed cases. For this purpose we have chosen a global definition of 'exposed' as any patient for whom an exposure to one or more of the following agents—EMF, solvents (all types), fuel, exhaust gas and pesticides—is recorded. There were 26 cases of transformation of prior myeloproliferative or myelodysplastic syndromes. Fifteen cases corresponded to transformation **of a** previous chronic myelocytic leukaemia into acute leukaemia, six (7.3%) among the exposed and nine (8.7%) among the non-exposed cases. There was only one case exposed among the four cases of transformation of previous non-leukaemic myeloproliferative syndromes. On the other hand, six (7.3%) cases of transformation of previous myelodysplastic syndromes were exposed versus only one case (1%) non-exposed ($P = 0.025$). It is interesting to note that exposure to solvents other than benzene was found in the occupational history of all six cases of transformation of myelodysplastic syndromes. With our small number of cases of transformation, it is not possible to determine whether exposure promotes transformation or rather helps to create the primitive syndromes. To shed some light on this matter, we excluded the 26 cases of transformation from our analysis and ascertained again by joint logistic regression (conditional) the part played by benzene HM, EMF and weed killers HM. In comparison with Table 4, all the CI are increased, as expected since 26 cases and 68 controls are now excluded from the analysis. The OR for benzene HM is nearly identical to that reported in Table 4A (**OR** = 2.34, 95% CI : 1.02–5.37), those for EMF (OR = 3.58, 95% CI : 0.77–16.7) and weed killers HM (OR = 3.47, 95% CI : 0.95–21.1) are a little higher but the effect of EMF is now poorly estimated and significant only at the 10% level.

The distribution of the cytological types of acute leukaemia according to the FAB classification was in agreement with the one expected in adult patients, with 31 (16.5%) acute lymphoblastic leukaemia (ALL) and 154 (83.2%) acute myelogenous leukaemia (AML). All the 15 cases for whom an exposure to benzene HM and the seven cases for whom an exposure to EMF had been identified were of the AML type, whereas the 22 cases with a history of exposure to pesticides were split between **ALL** and AML. The relative risk was higher for ALL and pesticide exposure than it was for AML. The same pattern is also found for weed killers, insecticides and exposure to fuel (Table *5).* The distribution of cytological types of acute leukaemia was also investigated for other agents but no significant results emerged. The distribution of the cytological subtypes according to the FAB classification was not different from the one expected in this age group, taking into account the number of cases resulting from transformation of previous myeloproliferative or myelodysplastic disorders. The small numbers in each subtype precluded from finding significant differences between exposed and non-exposed cases. However the exposed cases have fewer L1, and more L2, M3 and M6 subtypes: (L1: 1.2% versus 3%; L2: 12.4% versus 9%; **M3:** 7.8% versus 5.2%; M6: 3.7% versus 1%).

Cytogenetics were available for 102 cases. There were no more global abnormal karyotypes in patients with a history of professional exposures than in those without such exposure (54% versus 50%). A trend was observed for more deletions of chromosomes 5 or 7, or trisomy 8 in the exposed cases (11% versus 5%), but the difference was not statistically significant. Philadelphia (Ph) chromosome was identified in 17 subjects, eight (17.4%) among the exposed and nine (16.1%) among the non-exposed. Twelve of the cases with a Ph chromosome corresponded to transformation of previous chronic myelocytic leukaemia (six exposed and six non-exposed); the other cases corresponded to primary AML or ALL with Ph chromosome. Overall, we found no notable difference in cytogenetics between the exposed and the non-exposed cases in our sample.

TABLE 5 *Cytological types of acute leukaemia according to the type of exposure*

	Acute lymphoblastic leukaemia (No. = 31)	Acute myelogenous leukaemia (No. = 154)
Electric and magnetic fields	0% (0)	4.55% (7) OR = 4.83 (1.48–15.80)*
Benzene (HM)	0% (0)	9.74% (15) OR = 3.61 (1.69–7.7)*
Fuel	22.58% (7) OR = 2.46 (0.93–6.55)	11.69% (18) OR = 1.23 (0.67–2.25)'
pesticides	19.35% (6) OR = 2.82 (1.01–7.92)	10.39% (16) OR = 1.38 (0.73–2.62)'
Weed killers	19.35% (6) OR = 3.61 (1.27–10.20)	6.49% (10) OR = 1.10 (0.52–2.36)*
Weed killers (HM)	6.45% (2) OR = 4.78 (0.81–28.0)	3.25% (5) OR = 3.15 (0.92–10.8)*
Insecticides	19.35% (6) OR = 3.29 (1.16–9.36)	10.39% (16) OR = 1.51 (0.79–2.89)*

The OR are calculated after adjustment on matching variables and prior history of radiotherapy or chemotherapy. All the agents included in Table 2 have been analysed but only those with increased OR either for ALL or AML are reported in this Table.
*** 95% CI.**

DISCUSSION

Our study shows a significantly higher frequency of past history of occupational exposure to EMF, benzene and pesticides in patients hospitalized for acute leukaemia than in control patients hospitalized for various other reasons.

As in all hospital-based case-control studies, selection bias cannot be totally excluded. The first to be addressed is a referral bias, since recruitment of neither cases nor controls is exhaustive for their respective diseases. Cases and controls were matched for place of residence in order to control this bias at the design stage. Furthermore, similarities in terms of demographic and socioeconomic characteristics were checked. In particular the proportions of shopfloor workers were nearly identical (23.9% for the cases versus 21.7% for the controls).

The second potential bias arises from the disease for which the controls were hospitalized, which could be related to some occupational exposure. The diversity of control diseases make it unlikely that any particular exposure is overrepresented among controls. Besides, no exposure difference between cases and controls was found for various agents such as disinfectants, oil and grease, metallic dust and other dusts which have not been associated with leukaemia in the literature. This strongly supports the validity of our results.

Concerning recall bias we note that both cases and controls were patients in a hospital and had similar motivation for answering. Patients who did not cooperate with the interviewer were excluded from the analysis, and for the others, degree of cooperation was similar. This study was designed to assess lifetime work exposure and to control for other types of work exposure with a complete work history questionnaire coded at a second stage by an industrial hygienist. This method is close to the approach described by Gerin *et al.*[13] for assessing industrial exposure which has been shown to work well.[14] Nevertheless a questionnaire only provides a surrogate measure of exposure with possible misclassifications which reduce the power of the study to detect a difference in the exposure of cases and controls.[15] However, the use of blind coding of each individual work history guarded against any differential misclassification.

Breaking down the analysis by 'intensity'—represented here by the frequency of exposure per unit of time—and for 'length'—total duration of exposure—has led to interesting observations: benzene was associated with leukaemia in case of high or medium intensity of exposure or longer weighted length of exposure. On the other hand a long duration of exposure of more than 10 years, was more frequently observed in cases than in controls for pesticides in-

cluding both weed killers and insecticides, and for exhaust gas.

The professions corresponding to these occupational exposures were mainly farming—including farm owners, tenants and labourers—electronic and metal workers. The corresponding activities were agriculture, equipment manufacture, iron and steel industries, and the chemical industry. Exposure to EMF was only significantly associated with acute leukaemia when electric arc welding was excluded; the corresponding exposed occupations were engineers or technicians involved in electrical engineering or electronics, furnace workers, work near an electronic bath and jewellery polisher. One X-ray technician was included in the EMF exposure as well as in ionizing radiation exposure.

Several case-control studies for occupational exposure of leukaemia patients have been reported recently.[5,16–20] They differ according to the definition of cases, either restricted to AML,[5,18] or extended to acute leukaemia + chronic myelocytic leukaemia.[17] The cases in other studies included related diseases such as myelodysplastic syndromes,[21]—which are generally considered as preleukaemic states—lymphomas and myelomas.[19] The sizes of samples, as well as the methods of recruitment also differ from one series to the other. The present study is among the largest in terms of the total number of cases and controls; one case-control study, from Lindquist et *al.* was devoted specifically to acute leukaemia, with a questionnaire addressed to 125 cases and 125 controls originating from a population register.[20] However, this study was selectively focused on exposure to organic solvents, and concluded that there was a significant risk of developing acute leukaemia in professions like painters, and other exposed occupations, suggesting an aetiological role for benzene. Two other case-control studies yielded similar results: Flodin et *al.* found, from questionnaires mailed to the next-of-kin of 42 cases who died from AML and 244 controls, a sixfold increase in the leukaemic rate ratio related to solvent exposure. The additional role of background radiation was also suggested.[18] Farrow et *al.* investigating 63 cases of myelodysplastic syndromes, found a significantly higher frequency of occupational exposure to petrol diesel fumes or liquids, and of hobbies involving chemical exposure, again suggesting an effect of benzene.[21] Another case-control study" explored specifically the link between leukaemia (all types) and farming or health-related occupations and failed to show a significantly higher relative risk.

Our study, based on a high number of cases and controls and on specificity of disease, shows a significant relationship between acute leukaemia and exposure to pesticides and EMF in addition to benzene. This relationship was confirmed by multivariate analysis.

Benzene is a well-known leukaemogenic and carcinogenic agent. It induces leukaemias and other haemopoietic neoplasms in several models in mice.[22] Several cohort studies have shown a significantly increased risk of death from leukaemia following exposure to benzene.[6,23,25] These leukaemias are mainly of acute myelogenous type, as in our study. The period of latency can be several years long: in the study from Yin et *al.* the cumulative mortality was in proportion to duration of exposure up to 20 years.[24] Standardized mortality ratios have demonstrated a marked, progressive increase with increasing cumulative exposure to benzene,[6] leading to recommendation of lowering exposure to less than 1 p.p.m. per year. Our study, however, like that performed by Rushton and Alderson on death certificates of male oil refinery employees,[25] concludes that an increased relative risk only occurs in cases of high or medium exposure or longer duration of exposure. Besides the difficulties related to assessment of exposure, this contradiction could be explained by some experimental observations according to which intermittent dosing leads to greater toxic response than chronic low-dose exposures.[26] In addition, many workers are exposed to benzene from exhaust gas, leading to persistent exposure even in countries with 'no benzene industries'[27]. Our study shows a higher risk of acute leukaemia in cases of prolonged exposure (> 10 years) to exhaust gas. This should reinforce the need for limiting exposure to benzene, whatever its sources.

Several studies have shown an increased risk of leukaemia in agricultural areas among farming-related professions.[28–33] Other cancer diseases were also related to these occupations, such as malignant lymphomas,[31,33,34] multiple myeloma[30] and various solid tumours including lip, prostate, stomach carcinomas[30,35,36] and soft tissue sarcomas.[32] The methods used in these studies were mainly based on death certificates or cancer registers, and the comparisons were made with other types of cancer or the general population, allowing evaluation of the proportionate (cancer) mortality ratio or the relative risk. Methodological differences or biases could explain why some of these studies have shown an increased relative risk of leukaemia following exposure to pesticides,[28,32] while others failed to show a significant relationship.[17,34,36] As emphasized by Linos et *al.* lack of association between leukaemia and farming in some studies, could be a result of the size of samples, over-matching and the

possibility that farmers were more likely to be chosen as control subjects than other occupational groups. Another possible bias could be due to changes over time: artificial fertilizers and pesticides have been extensively used since the 1960s, and the relative risk for several tumours has been shown to have increased over time in agricultural workers.[36] The responsibility of pesticides could be questioned since people working in agriculture are exposed to several other agents including chemicals (such as benzene) and, hypothetically, bovine leukaemia virus.[31,32] In our present series, a past history of exposure to pesticides alone was observed in 11 cases, to pesticides and benzene (with or without exposure to exhaust gas) in 10 cases, and to pesticides, benzene and EMF in one case. All the 16 cases exposed to weed killers also described contact with insecticides and only six out of 22 cases exposed to pesticides described contact with insecticides alone. Hence it is difficult to separate the effects of weed killers from those of insecticides. The specific role of pesticides is shown, following detailed job description and multivariate analysis, by the fact that OR for weed killers remains significant following adjustment for exposure to benzene. Another argument can be drawn from the cytological differences between acute leukaemias following the two types of exposures: those following exposure to benzene were mainly of AML subtypes, whereas those following exposure to pesticides were of ALL as well as AML subtypes. Furthermore it should be emphasized that pesticides, as other leukaemogenic agents such as benzene and ionizing radiation, can induce either bone marrow injury and aplastic anaemia following high-dose exposure, or leukaemia as a consequence of prolonged exposure.

The role of occupational or environmental exposure to EMF has been much debated during the recent Years. The hypothesis was first raised by Wertheimer and Leeper,[38] who reported an association in Colorado between residential electrical wiring configurations and childhood cancer, including leukaemia. Biological mechanisms which could be involved are largely hypothetical, since EMF, unlike benzene or ionizing radiation, are not mutagenic:[39] weak EMF, acting through a calcium-modulated mechanism, can alter membrane responses to surface-stimulating molecules.[40] Our results suggest a relationship between exposure to EMF and acute leukaemia, as shown in our Preliminary analysis.[41] Some caution is warranted, however, before drawing firm conclusions: the OR was statistically significant only when arc welding was excluded and there was no association with level or length of exposure. Several epidemiological studies have tried to correlate leukaemia with occupational exposure to EMF.[42-48] A meta-analysis of studies published by 1987 has been performed by Savitz et al.: out of ten studies, five showed an increased relative risk, and the overall relative risk computed in this meta-analysis was 1.2 (95% CI : 1.1–1.3).[8] The risk was highest for AML compared to acute leukaemias or leukaemias in general, an observation close to that of the present study. The largest risk elevation was for aluminium workers in one study,[41] but an excess risk was noted across most studies for electronics technicians, electrical engineers, telegraph, radio or radar operators, and for power and telephone linesmen. Other studies have been published since this meta-analysis, which mostly indicated an increased risk of leukaemia following occupational exposure to EMF. Only Tornquist et *al.* did not find an increased risk of leukaemia or cancer in general in Swedish power linesmen or power station operators,[49] while Stern et al. found an increased risk, especially for lymphoid leukaemias, among electricians, and for myeloid leukaemias among welders.[5] A recent study from Garland et *al.* has shown also an increased standardized incidence ratio among electrician's mates in US navy personnel.[50] Finally an increased risk of AML was observed by Flodin et al. among Swedish electrical workers including technicians, welders, and computer and telephone mechanics.[6] Our study supports the belief that EMF is an occupational factor for acute leukaemia: the OR indicate a strong association between acute leukaemia and EMF, once possible confounding factors have been taken into account, with adjustment for prior chemo- or radiotherapy treatment. Thus, despite the fact that, as in most other reports, exposure to EMF is only extrapolated from professional classification or job description rather than direct measurements of the fields, the hypothesis of EMF being leukaemogenic has reached consistency.

This study did not disclose any other occupational risk factor, except for oxygenated solvents. There was no relationship with such professions as health care, abattoir work, painting, or exposure to styrene or ethylene oxide as shown in other studies.[2] We also failed to show an increased risk of leukaemia following occupational or iatrogenic exposure to ionizing radiation. A clear relationship had been observed between moderate to high-dose ionizing radiation and occurrence of AML.[1,2] However, recent observations argued against considering limited fields or low-dose ionizing radiation as a major leukaemogenic factor: leukaemias—mostly AML—secondary to the treatment of a first malignancy, are mainly due to alkylating agents whereas radiotherapy induces solid

tumours rather than leukaemias.[51] In their recent study Flodin et *al.* have pointed out a significantly increased risk of AML after X-ray treatment, but not after X-ray examination and radiological work.[6] In a case-control study performed by Stern et al. in a naval nuclear shipyard for all leukaemias combined, an OR above 1.0 was seen only for those workers who had accumulated at least 1.0 rem of exposure, but this, however, was not statistically significant.[5] A recent review has shown the difficulty, for most recent studies, in confirming the classical link between occupational exposure to ionizing radiation and acute leukaemia, with, at a maximum, a rise in cases of exposure over long periods of time.[52] The fact that no significant difference was observed between cases and controls in our study for exposure to ionizing radiation could mean that the risk of exposure is currently low in France. This should not lead to the conclusion that ionizing radiations are not leukaemogenic, but case-control studies are somewhat limited in their ability *to* detect such associations since few workers accumulate lifetime moderate or high-dose radiation.

Finally our study does not provide evidence of a specific cytological subtype and cytogenetic pattern in AML following occupational exposure. This is contrary to other authors who have observed different distribution of cytological subtypes and more abnormal karyotypes, especially of group C, with more deletions of chromosomes 5 and 7 or trisomy 8, in AML patients with a history of occupational exposure.[53,54] However, we observed significantly more transformation of previous myelodysplastic syndromes in exposed than in non-exposed cases. The failure to observe different cytogenetic patterns in the exposed cases in the present study could be due, therefore, to the relative infrequency of these specific chromosomal abnormalities.

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