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Exposure to occupational and environmental factors in myelodysplastic syndromes. Preliminary results of a case–control study

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We performed a case-control study of occupational and environmental risk factors in myelodysplastic syndromes (MDS) diagnosed at our institution, using the method of Siemiatycki. A control for each MDS case, matched for age, sex, and residence area was chosen. The questionnaire asked demographic data, medical history, and information on life-time environmental and occupational exposures. Occupational exposures were first assessed by job titles, then by evaluating exposure to a list of 70 chemicals, and the level and duration of exposure to those chemicals (exposure index). In the first 100 cases and controls analyzed, a significantly higher incidence of smokers or ex-smokers was seen in MDS cases (odds ratio, OR = 1.83, $P = 0.03$). A significant excess of MDS was found in male patients with jobs (or previous jobs) generally exposing to chemical compounds, including plant and machine operators and assemblers (odds ratio, OR = 3.73, $P = 0.014$) whereas, on the contrary, technicians and associate professionals were more often seen in controls (OR = 0.17, $P = 0.002$). In males, there was also a trend for more skilled agricultural workers and coal miners in MDS cases. In females, there was a non-significant trend for more professionals in controls. After adjusting for sex, age and smoking habits, significantly more frequent exposure to stone dusts (OR = 3.06, $P = 0.011$), and cereal dusts (OR = 2.27, $P = 0.04$) was found. There was also a trend for higher incidence of exposure to exhaust gases and nitro-organic explosives. In addition, significantly higher exposure indices to petrol and diesel derivatives ($P = 0.03$) and to fertilizers ($P = 0.003$) were seen in MDS cases, as compared to controls. No significant difference in exposure to other chemicals was seen between MDS cases and controls. These preliminary results of our study, which is accruing more cases, suggest, as two previously published case-control studies of risk factors in MDS, that exposure to some chemicals may be involved in the pathogenesis of MDS.
Keywords: myelodysplastic syndromes; occupational exposure; acute myeloid leukemia

Introduction

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells, characterized by ineffective hematopoiesis leading to blood cytopenia, and by a high incidence or progression to acute myeloid leukemia (AML).[1]

Etiological factors of MDS remain poorly known. One of the reasons is that MDS have only recently been well characterized[2] and distinguished from aplasia and AML, especially in epidemiological studies or registries.[3,4] A familial predisposition has been found in the rare cases of MDS occurring in childhood[5] and, although to a lesser extent, in MDS occurring in young adults.[6] AML occurring after exposure to antineoplastic drugs (mainly alkylating agents) are preceded by a phase of MDS in the majority of cases.[7,8] Likewise, a review of cases of AML secondary to ionizing irradiation (especially in atomic bomb survivors)' and to benzene exposure[9,10] found that they were often preceded by a documented or suspected phase of MDS. Case–control studies or case reports have also incriminated exposure to several other compounds in the etiology of AML, including solvents other than benzene (xylene and toluene),"' ethylene oxide," pesticides and herbicides,[12,13] chloramphenicol,[14] radon,[15] and electromagnetic fields.[3,16] An increased risk of dying from AML has also been observed in farmers and other agricultural workers.[17] However, apart from alkylating agents, ionizing irradiation and benzene, a role for occupational or environmental exposure to other agents had not been demonstrated in the etiology of MDS until recently."' Two recent case–control studies, which included about 60 and 50 patients, respectively, addressed this issue. Farrow *et al*[19] found a higher incidence of exposure to ammonia, petrol and diesel fumes in MDS than in controls. Goldberg *et al*[20] on the other hand, found more frequent exposure to pesticides in MDS cases than in controls.

We performed a case–control study of occupational and environmental factors associated with MDS. Results of the first 100 patients analyzed are presented here.

Patients and methods

In September 1991, a case–control study of occupational and environmental risk factors of MDS was started at our institution. All cases of MDS (according to French–American–British (FAB) diagnostic criteria)' diagnosed in the Department of Hematology of the University Hospital of Lille were included, with the exception of MDS secondary to antineoplastic agents and patients who did not have the ability to answer the questionnaire. Data of the first 100 patients, diagnosed between September 1991 and July 1993, are analyzed here.

Overall, we used the same methodology as Farrow *et al.*[19] This method, described by Siemiatycki" for identifying carcinogens in an occupational environment, includes a control for each MDS case, matched for age (±5 years) and sex. One of the major differences with the study of Farrow *et al* was that the control for each MDS case was randomly chosen among the patients of the general practitioner of the MDS case rather than in outpatient clinics taking place in our hospital. Controls with cancers, blood or dermatological disorders, and those who did not have sufficient ability to answer the questionnaire were excluded.

A trained physician interviewed the cases and their appropriate controls using a questionnaire. The questionnaire was similar to that used by Farrow *et al*,[19] translated into French. All interviews were carried out in the patient's (or control's) home. Confidential information included demographic data, lifetime residence, medical history including drugs, diagnostic X-ray procedures, radiotherapy, operations, past illnesses, smoking habits, and hobbies. Occupational history was first

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assessed by job title (according to the classification of the International Labour Office).[22] Detailed analysis of each job was then made in order to estimate as precisely as possible exposure to a list of 70 chemicals whose list had been chosen based on literature data and on substances suspected of having causal links with leukemias. Finally, the level (Low level = 1: indirect exposure; Medium level = 2: direct contact; High level = 3: direct contact and inadapted conditions of use), frequency and duration of exposure to a given substance was evaluated. An exposure index was then calculated (Index = (hours a day × days a year × number of years × level of exposure)/10^3) for each substance. Exposure to potential toxic compounds during hobbies were also taken into account for the calculation or exposure indices. All questionnaires were blindly reviewed by the Medical Occupational Inspector of our region in order to reassess the job exposures over the occupational history according to the method of Siemiatycki.[21]

The total bone marrow dose irradiation from diagnostic radiology was evaluated using the mean dose calculated by Shlein *et al*[23] for each type of radiological examination (Σ (dose × number of examinations)).

Statistical analysis was performed with SAS software. For job titles, the analysis was performed on the entire population, and separately in males and females. Odds ratios (OR) were calculated without adjustment, for the different jobs held over at least 6 months, those jobs being included in major groups and subgroups according to the International Labour Office (ISCO 88).[22] Adjustment of OR for age and sex, using Mantel–Haenszel χ^2 tests, showed equivalent OR, and are not shown. For the analysis of exposure to the 70 chemicals and other substances, a logistic regression was used to adjust OR on age, sex and smoking habits. Finally, quantitative data (exposure indices) were compared using a non-parametric test (Wilcoxon test) as normality was not assumed.

Results

Initial characteristics of the patient and control populations

Median age of the patients was 70 years (range 31–87). Eighty patients were aged between 60 and 80, two were aged more than 80 and 18 less than 60. There were 56 males and 44 females. According to FAB classification, there were 28 cases of refractory anemia (RA), 10 cases of refractory anemia with ringed sideroblasts (RARS), 26 cases of refractory anemia with excess of blasts (RAEB), 12 cases of RAEB in transformation (RAEB-T), and 24 cases of chronic myelomonocytic leukemia (CMML). Median age of the control population was 69 years (range 32–91) and controls included 56 males and 44 females (Table 1).

As seen in Table 1, the socio-economic status was not significantly different in patients and controls, and remained so after adjustment for sex and age (Mantel–Haenszel χ^2: 3.02; $P = 0.082$).

Demographic data, medical history and environmental exposures

Eighty-nine of the patients and 89 of the controls had at least one child. The mean number of children in those persons was 2.9 ± 1.6 in MDS cases, and 3 ± 1.7 in controls (difference not significant).

Table 1 Socio-economic characteristics of the MDS and control populations

	MDS cases	*Controls*	P value
Sex			
Male	56	56	NS
Female	44	44	(χ^2 test)
Age (mean ± SD)	67.7 ± 12.5	67 ± 12.5	NS (Wilcoxon test)
Socio-economic status[a]			
Groups 0, 1, 2, 3	14	27	NS
Groups 4, 5	23	23	(χ^2 test)
Group 6	12	3	
Group 7	24	24	
Group 8, 9	22	17	
Unemployed	5	6	

[a]According to the International Labour Office major groups (ISCO-88) and based on the last job held at the time of the study

No documented familial history of hematological malignancy, aplasia or MDS was found in patients and controls. Past health was analyzed by classifying diseases in 14 specialty groups, but none showed significant association with MDS. No differences between patients and controls were found for previous medical or surgical treatments. Past immunizations could not be adequately analyzed in many patients and controls, who had forgotten those data and/or lost adequate medical documents. Fifty-nine of the MDS cases were current smokers or ex-smokers, as compared to 44 of the controls, and the difference was significant ($P = 0.03$, Table 2). On the other hand, the risk of MDS was not higher in heavy smokers than in light smokers, as there was no clear dose response pattern, even after adjustment for age and sex, using a logistic regression ($P = 0.164$).

When past radiodiagnostic procedures were examined and cumulative irradiation to the bone marrow calculated we found that, surprisingly, MDS patients had been submitted to a significantly lower cumulative dose than controls (13.4 ± 14.8 mGy and 18.5 ± 17.9, respectively, $P = 0.04$).

No differences in the life-time hobbies of the patients and controls (including gardening, decorating, car maintenance, hobbies using paints and glues) were statistically significant, but slightly more controls (85%) than MDS patients (75%) had been involved in gardening.

Occupational exposure

Analysis by job **titles:** We first analyzed job titles, classified according to the International Labour Office Classification (ISCO 88),[22] for major groups (Table 3) and for different jobs in those major groups. This was done in all cases and separately in males and females. The mean number of jobs held for at least 6 months was 1.93 (±1.3) in MDS patients, and 1.78 (±1.1) in controls (difference not significant, Wilcoxon test). By analyzing males and females together, the comparison of jobs held for at least 6 months showed an overall significant excess of MDS in plant and machine operators and assemblers (group 8) (odds ratio **(OR)** = 3.12, $P = 0.012$, χ^2 test) and, on the contrary a significant excess of technicians and associate professionals in controls (OR = 0.28, $P = 0.004$).

Table 2 Smoking habits

	MDS cases	Controls	Odds *ratio* (*95%* confidence interval)	P value
Smokers (Current and ex-smokers)	59	44	1.83 (1.04–3.21)	0.03 (χ^2 test)
Non-smokers	41	56	0.55 (0.31–0.96)	
Pack-years				
0	41	56	0.55 (0.31–0.96)	NS (χ^2 test)
1–10	15	12	1.29 (0.57–2.93)	
11–20	15	6	2.76 (1.06–7.24)	
21–30	8	7	1.15 (0.4–3.32)	
>30	21	19	1 13 (0.56-2.27)	

Pack-years, number of packs per day **x** number of years

The excess of MDS cases in group ***8*** was restricted to males (OR: 3.73, $P = 0.014$). In males, an excess of MDS cases as compared to controls was seen in several categories of this group, including metal plant operators (two cases, one control), wood and paper plant operators (two cases, one control), machine operators (three cases, one control), drivers (four cases, **two** controls) but differences were not significant, probably because of the low figures in each category. By contrast, technicians and associate professionals (group 3) were significantly more represented in controls in males (OR: 0.17, $P = 0.002$). The odds ratio **(OR)** for MDS cases were slightly increased in craftsmen (group 7) skilled agricultural workers (group 6) people with elementary occupations (group **9)** in males but differences with controls were not significant. Of note is that 13 of the MDS cases had been coal miners (a job included in group 7), as compared to seven of the controls, as coal mining was until recently a major economic activity in our region. The difference however, was not significant ($P = 0.16$).

In females, very few MDS and controls belonged to groups 3 and ***8*****,** which made comparison difficult in those groups. No differences were found between MDS cases and controls for group 7 (which included almost exclusively textile workers in females). There was a non-significant trend for more controls than MDS cases in females in group 2 (OR = 0.15, $P = 0.11$, Fisher's exact test). This group, in females, almost exclusively included teaching professionals.

Detailed analysis *of* exposures: We subsequently analyzed in a detailed interview previous occupational and environmental exposure **to** a list of 70 substances. **A** comparison between the number of exposed MDS and controls was studied when at least four persons in each group had been exposed. Odds ratio were adjusted for age, sex, and smoking, using a logistic regression. **As** seen in Table **4,** previous exposure to stone dusts (OR = 3.06; $P = 0.011$) and cereal dusts (OR = 2.27; $P = 0.04$) was significantly more frequent in MDS cases than in controls. There was also a trend for more frequent exposure of patients **to** exhaust gases (OR = 2.19) and nitro-organic explosives (OR = 2.46) but the difference with controls was not significant. Exposure to stone dusts mainly concerned coal mining, whereas exposure to nitro-organic explosives was only seen in that job.

Quantification of exposures: Finally, in MDS patients and controls with previous exposure to one of the 70 specific chemicals and substances analyzed, an exposure index, taking into account the time of exposure during life, its intensity and the route of exposure was calculated. Exposed MDS cases were found **to** have a significantly higher exposure index to petrol and diesel derivatives ($P = 0.03$) and to fertilizers ($P = 0.003$) than exposed controls (Table 5). These differences were related to differences in intensity rather than duration of exposure, as the mean duration of exposure was comparable for all the compounds analyzed in MDS cases and controls.

Discussion

To our knowledge, only two case-control studies investigating the relationship between MDS and previous occupational or environmental exposure to specific chemicals have been published.[19,20] Our case-control study was based on the protocol established by the Cardiff group which performed one of those studies, with few modifications.[19] We used the same structured questionnaire and the job exposure analysis based on the Siemiatycki methodology.[21]

In case-control studies, the choice of controls is of major importance. Contrary to Farrow et *al*,[19] we did not choose controls among outpatients referred to other departments of our hospital. The reason was due to differences in the British and French health care systems. Indeed, there is in France for most specialities (but not for Hematology, at least in our region), a large private sector which on average treats people with higher socio-economic status. The public hospital sector, on the other hand, treats a higher proportion of people belonging to the working class, ie with a potentially higher risk of occupational exposure to toxic compounds. Choosing controls in other departments of our hospital could therefore have created a recruitment bias. The choice of controls among the patients of the general practitioner of the MDS cases, among other advantages, allowed matching for the area of residence. Cases and controls were also matched for age and sex. The socio-economic status was not significantly different in MDS cases and controls, supporting the absence of selection bias. On the other hand, although the interviewer was normally blind as to the patient-control status, many patients and controls revealed their status, and one cannot exclude that this could have created some bias in the analysis. Still, the analysis was performed only on the exposures assessed by the occupational inspector who coded each questionnaire blindly to the status.

Table 3 Distribution of cases and controls for sex according to the International Labor Office major groups (for jobs held at least 6 months)

Group		Males			Females			Total		
		Cases	*Controls*	*OR*	*Cases*	*Controls*	*OR*	*Cases*	*Controls*	*OR*
0	Armed forces	1	1	1(0.06–16.4)	0	0		1	1	1(0.06–16.2)
1	Legislators, senior officials and managers	5	5	1(0.27–3.66)	0	0		5	5	1(0.28–3.57)
2	Professionals	5	5	1(0.27–3.66)	1	6	0.15(0.02–1)	6	11	0.52(0.19–1.44)
3	Technicians and associate professionals	4	17	0.17(0.06–0.52)[a]	3	4	0.73(0.15–3.5)	7	21	0.28(0.12–0.68)[c]
4	Clerks	4	9	0.42(0.12–1.36)	12	8	1.69(0.61–4.65)	16	17	0.93(0.44–1.97)
5	Service workers and shop and markets sales workers	8	9	0.87(0.31–2.45)	9	10	0.87(0.31–2.4)	17	19	0.87(0.42–1.80)
6	Skilled agricultural and fishery workers	12	7	1.91(0.69–5.25)	10	6	1.86(0.61–5.64)	22	13	1.89(0.89–3.98)
7	Craft and related trades workers	38	30	1.83(0.85–3.94)	13	13	1(0.4–2.5)	51	43	1.38(0.79–2.41)
8	Plant and machine operators and assemblers	15	5	3.73(1.31–10.67)[b]	4	2	2.1(0.37–11.83)	19	7	3.12(1.29–7.55)[d]
9	Elementary occupations	14	8	2(0.77–5.2)	10	11	0.88(0.33–2.36)	24	19	1.35(0.68–2.65)
	Unemployed	0	0		5	6	0.81(0.23–2.9)	5	6	0.82(0.24–2.80)

OR, Odds ratio without adjustment.
P, *P* value for the χ^2 test, or for Fisher's exact test when expected counts are less than 5.
[a]$P = 0.002$.
[b]$P = 0.014$.
[c]$P = 0.004$.
[d]$P = 0.012$

Table 4 Previous exposure to some of the 70 specific substances studied in the questionnaire in MDS patients and controls

Substance	No. of exposed persons		Odds ratio (95% confidence interval)
	MDS cases	Controls	
Explosives	13	6	2.46 (0.84–7.14)
Petrol and diesel	18	18	1 (0.47–2.15)
Oils and greases	16	14	1.46 (0.6–3.52)
Coal Tar	6	5	1.08 (0.3–3.85)
Exhaust gases	23	12	2.19 (0.95–5.06)
Solvents	28	27	1.08 (0.54–2.17)
Paint, varnishes	18	19	0.88 (0.4–1.9)
Glues, adhesive	10	8	1.2 (0.43-3.32)
Sulfuric or hydrochloric acid	6	7	0.91 (0.27–3.03)
Ammonia fumes	10	6	1.57 (0.53–4.18)
Insecticides	13	13	0.89 (0.38–2.14)
Pesticides	11	13	0.66 (0.27–1.61)
Herbicides	18	23	0.64 (0.31–1.31)
Fertilizers	21	19	1.1 (0.54–2.28)
Woodworm treatment	9	7	1.26 (0.43–3.67)
Copper	4	6	0.67 (0.17–2.68)
Metal dust	8	8	0.81 (0.28–2.37)
Asbestos	4	5	0.86 (0.2–3.6)
Stone dust	24	11	3.06 (1.28–7.32)[a]
Cotton dust	15	12	1.45 (0.61–3.47)
Cereal dust	24	12	2.27 (1.04–4.97)[b]

Odds ratio are adjusted for age, sex, and smoking, using a logistic regression.
[a] $P = 0.011$.
[b] $P = 0.04$

Table 5 Mean exposure indices in MDS cases and controls exposed to a given substance

Substance	Mean exposure indices (range)		P value (Wilcoxon test)
	MDS cases	Controls	
Explosives	18 (0.2–88)	17 (0.2–37)	NS
Petrol and diesel	85 (0.5–250)	35 (0.02–190)	0.03
Oils and greases	43 (0.2–195)	87 (4–334)	NS
Coal Tar	61 (14–167)	50 (0.6–230)	NS
Exhaust gases	66 (4–250)	90 (23–231)	NS
Solvents	8 (0.01–51)	8 (0.02–65)	NS
Paint, varnishes	29 (0.06–205)	17 (0.4–123)	NS
Glues, adhesive	57 (0.1–435)	5 (0.12–25)	NS
Sulfuric or hydrochloric acid	5 (0.03–14)	3 (0.06–10)	NS
Ammonia fumes	8 (0.3–40)	14 (0–38)	NS
Insecticides	2 (0.06–13)	3 (0.02–41)	0.03
Pesticides	2 (0.01–13)	0.4 (0.01–4)	NS
Herbicides	2 (0.01–13)	0.3 (0.01–4)	NS
Fertilizers	4 (0.01–47)	1 (0.01–14)	0.003
Woodworm treatment	4 (0.1–25)	0 4 (0.01–1)	NS
Copper	20 (0.9–40)	23 (1.1–69)	NS
Metal dust	17 (0.5–53)	25 (2.5–96)	NS
Asbestos	34 (0.5–111)	15 (0.8–41)	NS
Stone dust	92 (0.7–275)	94 (1.6–222)	NS
Cotton dust	31 (2.7–184)	57 (1.7–276)	NS
Cereal dust	19 (0.9–154)	14 (0.4–43)	NS

Farrow *et al*[19] observed significantly more celibates among male patients than controls, a finding we could not evaluate because marital status was not included in our questionnaire. We did not confirm, however, their finding that MDS patients were more often childless than controls. Insufficient information was obtained in patients and controls for past immunizations, and this did not allow us to confirm or not the higher incidence of previous poliomyelitis immunization found by Farrow *et al*[19] in controls. As these authors, we found no difference in medical history and previous treatments in patients and controls. We found a significantly higher incidence of smokers and ex-smokers in patients than in controls, which had not been previously reported in MDS, to our knowledge. However, two case-control studies have shown a significantly higher risk of AML in cigarette smokers.[24,25]

We found, unexpectedly, that controls had a higher calculated bone marrow irradiation by X-ray diagnostic procedures than MDS patients. An explanation to this difference could have been that patients chosen as controls for the study were often regular patients, who possibly had more frequent medical surveillance (including X-ray procedures) than a general population of the same age.

The odds ratio for job titles showed an excess of cases in jobs usually associated with exposure to chemicals. However, possibly owing to the small number of patients in each major group, no specific jobs could be incriminated. By contrast, jobs where less exposure to chemicals is generally observed were more frequent in controls. A relatively high odds ratio was found in skilled agricultural workers but the difference with controls was not significant. Several previous studies have shown an increased risk of AML among farmers, and suggested that this could be the consequence of chemical exposures.[13,17]

Evaluation of exposure to a list of 70 chemicals during lifetime, including occupation time and hobbies, found significantly more frequent exposure to stone dusts and cereal dusts and a trend for more frequent exposure to exhaust gases in MDS patients, as compared to controls, after adjustment on sex, age, and smoking habits. The excess of exposure to exhaust gases in MDS cases is in agreement with the findings of Farrow et al[19] and those of Richardson in AML.[13] Contrary to the report of Farrow et al,[19] the number of MDS cases and controls previously exposed to petrol and diesel fumes or liquids was equivalent, but the mean exposure index was significantly more elevated in MDS cases. This stresses the interest of calculating the exposure index for each chemical, and suggests that the toxicity of some chemicals may occur above a certain threshold or is cumulative over time. A previous case control study had demonstrated a higher incidence of AML in petrol station attendants, and a potentiation of the leukemogenic effects of benzene by other petrol or vehicle exhaust components had been suggested.[26] In the report of Goldberg et al,[20] a trend for higher incidence of exposure to solvents (including benzene) was found in MDS patients, as compared to controls, but the difference was not significant.

Significantly more frequent exposure to stone dusts was also found in MDS patients than in controls. Stone dusts were generally silica and exposure mainly involved coal mining, a major industrial activity in our region until recently. Coal miners were somewhat more frequent (although not significantly) in MDS cases than in controls. Coal mining exposes not only to stone dusts, but also to exhaust fumes and to nitro-organic explosives, for which a non-significantly higher incidence of exposure was seen in MDS cases. Nitro-organic explosives include nitroglycerine, ethylene glycol dinitrate and trinitrotoluene, and the two latter chemicals have been incriminated in the pathogenesis of leukemia and aplastic anemia, respectively.[27,28] Therefore the nature of the compounds which could be responsible for the excess of MDS in coal miners remains uncertain.

In the present study, there was no increased exposure to herbicides, pesticides or insecticides in MDS cases, as compared to controls, both for the number of cases and the exposure index, and this did not confirm the results of Farrow et al[19] who found that the number of MDS patients and controls exposed to insecticides, herbicides, and pesticides did not differ, but that their exposure indices were significantly higher in MDS cases. A history of exposure to pesticides was also significantly more often found in MDS cases than in controls by Goldberg et al,[20] and in AML preceded by an MDS phase than in AML of acute onset in another report.[29] Insecticides and pesticides had also been previously incriminated in leukemogenesis.[12,13] On the other hand, in our study, a larger number of MDS cases had been exposed to cereal dusts and mean exposure to fertilizers was significantly higher in MDS cases, these findings being in agreement with the larger number of farmers in MDS. No excess of exposure to cereal dusts had previously been reported in MDS.[19,20]

Finally, Farrow et al reported a significantly higher incidence of exposure to ammonia, a non-significant trend for chromium, lead and tin compounds and higher exposure indices to copper compounds in MDS patients, but we could not confirm these findings.

In conclusion, these preliminary results suggest, as the reports of Farrow et al[19] and Goldberg et al[20] a possible link between exposure to some chemicals and MDS. In spite of preventive measures, benzene or other suspected substances including aromatic polycyclic hydrocarbons, contained in exhaust gases and petrol derivatives, could be incriminated in some cases. Fertilizers, insecticides and pesticides used by gardeners and/or agricultural workers, could also be implicated. Our findings of a higher incidence of MDS in smokers (and to a lesser extent in coal miners) will have to be confirmed, and the nature of the causative chemical(s) determined. Recent reports have suggested an increase in the incidence of MDS over the last few years[1,30] and, in a British Registry of Hematological Disorders thought to be associated with occupational hazards, MDS was the most frequent.[11] if this increase does not only correspond to improved diagnosis of MDS in recent years, better identification of the chemicals possibly involved in the pathogenesis of MDS will have to be made, and preventive measures taken. Final results of this case–control analysis, which should include a total of 300 patients and 300 controls, should contribute to the answer to this question.

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