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Survey of Exposure to Genotoxic Agents in Primary Myelodysplastic Syndrome: Correlation with Chromosome Patterns and Data on Patients without Hematological Disease[1]

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ABSTRACT

Exposure to genotoxic agents such as insecticides, pesticides, and solvents correlated with abnormal karyotypes and development of acute nonlymphocytic leukemia (ANLL) similar to, but to a lesser degree compared to, patients exposed to irradiation and alkylating drugs in several reports. Because of the natural progression of myelodysplastic syndrome (MDS) to ANLL, we investigated the relationship of exposure to these carcinogens in patients with primary MDS by having 52 such patients diagnosed and referred to our center answer an occupational/environmental questionnaire. We excluded all secondary MDS patients with exposure to previous chemotherapy and radiation for a previous malignancy. In addition, we prospectively gave the same questionnaire to a similar number of age- and sex-matched comparable control patients from the same socioeconomic group based on their residence, health insurance coverage, and occupation.

We found a 46% exposure rate to implicated genotoxic agents in our patients with MDS. Patients with MDS who were exposed had 75% incidence of a poor prognosis French-American-British classification compared to 57% in the nonexposed group but the difference was not significant ($P = 0.089$). However, the karyotypic abnormalities that were associated with exposure in ANLL were found equally in both exposed (55%) and nonexposed groups (50%) of our MDS patients and our control group had a similarly high exposure rate at 40% to genotoxins.

Implicating a relationship between exposure to pesticides and solvents in ANLL and MDS is difficult. All the previous studies indicating such a relationship did not use a control group of patients. Our findings indicate the pitfalls of historical data without investigating the bias of obtaining an exposure history. However, our findings that the majority of our MDS patients came from the middle socioeconomic group which has a high exposure rate as shown by our control group indicate a relationship and that prospective follow-up of the exposed cohort of control patients should be done to determine if ANLL and MDS will increase after a latent period compared to the nonexposed controls.

INTRODUCTION

A number of studies have looked at the relationship of occupational exposure to carcinogens and chromosomal abnormalities in patients with ANLL[4] (1–4). Mitelman *et al.* (1) examined 162 patients with ANLL and found that 32% had occupational exposures to insecticides, solvents, or petrol products and that 75% of these patients had a chromosomally abnormal clone of cells in the marrow as compared with 32% of the nonexposed group. Chromosomal abnormalities in leukemia and myelodysplastic syndromes following previous therapy for another malignancy are well documented (5, 6). Because such abnormalities are generally associated with a poor prognosis in such conditions, they can be an important aspect of classification.

Several studies have addressed exposure to pesticides, chemicals, and solvents through hobbies as a possible risk factor. Golomb *et al.* (2) in looking at the relationship between ANLL, occupation, and karyotype did not see a higher incidence of cytogenetic abnormalities when comparing patients with hobbies that might be associated with mutagenic exposure to those with no reported exposures, although he did note that 43% of the "exposed" hobby group had abnormalities of chromosome 5 or 7 in their leukemic cells compared to 16.7% of those in the "nonexposed" hobby group. These two abnormalities have been particularly associated with known exposures to genotoxic agents. The Fourth International Workshop on Chromosomes in Leukemia (1982) (7) reviewed 716 patients with ANLL, comparing 660 with *de novo* ANLL and 56 with secondary (therapy-related) ANLL. Abnormal chromosomes were found in 54.5% of patients with *de novo* ANLL compared to 75% of those with secondary leukemia. In the secondary leukemia group, 45% had abnormalities involving chromosome 5 and/or 7, which are associated with a poor prognosis, while in only 12.8% of the *de novo* cases were these chromosomes involved. ANLL secondary to benzene exposure is also known to be associated with karyotype abnormalities (8).

Thus, strong correlation between exposure to known mutagenic and carcinogenic agents and chromosomal abnormalities in the neoplastic cells of patients with hematological malignancies has been well supported in the literature. This correlation has not been as well documented in preleukemic disorders. Utilizing an environmental/occupational exposure questionnaire devised by the American Lung Association, we examined the relationship between cytogenetic findings and exposure to potential mutagens in 52 patients with myelodysplastic syndrome. In addition, we determined the incidence of a positive exposure history, using the same questionnaire in a retrospective control-matched study. This represents the first attempt to examine the frequency of positive exposure history in a control population without hematological disease.

PATIENTS AND METHODS

Fifty-two patients with a MDS who fulfilled the criteria for this diagnosis as defined by the FAB group have been entered in our study since 1976 (9). Eighteen patients were classified as either RA or RARS, which are diseases associated with a more indolent course. Twenty-one patients had either CMML or RAEB and 13 had RAEB-T, all of which are associated with more aggressive behavior with regard to progression

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[4] The abbreviations used are: ANLL, acute nonlymphocytic leukemia; MDS, myelodysplastic syndrome; FAB, French-American-British classification; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; CMML, chronic myelomonocytic leukemia; RAEB, refractory anemia with excess blasts; RAEB-T, RAEB in transition; NS, not significant.

to acute leukemia and survival. Patients with MDS secondary to cytoreductive therapy (chemotherapy and/or radiation therapy) or with a history of occupational benzene exposure were excluded. Ages ranged from 28 to 88 years old with a median age of 64.6 years; 59% (28 of 52) of the patients were males. As the treatment protocols differed among patients, survival was not included in the current study. Initial evaluation of the patients was done under the direction of one author (E. B.) including the results of physical examination, hematological laboratory studies, karyotypic evaluation of bone marrow cells, and detailed environmental and occupational histories. For cytogenetic studies, direct preparations and 24-h-cultures, without mitogen, were done on marrow aspirates. Slide preparation and chromosome banding, by the trypsin-Giemsa method, were carried out as described previously (10). In all cases, at least 25 counts and three karyotypes analyses were obtained. In this series, no clone was identified that constituted less than 20% of the metaphases examined, and in most patients all or nearly all of the bone marrow was replaced by the chromosomally abnormal cells. Chromosome studies were unsuccessful in 4 of the 52 patients studied.

Information about exposures to chemicals, solvents, asbestos, and insecticides both through occupation and hobby were obtained using the Occupational/Environmental History Form developed by the Occupational Health Task Force of the American Lung Association of San Diego (11) to all MDS patients after diagnosis was confirmed. Significant exposure was defined as a report of 5 or more contacts with these agents per lifetime as approximated by the number of contacts per year and number of years of use of the agents. There is also a record of all previous occupations. Patients and controls were also questioned on their history of tobacco use.

Demographic, health insurance, and occupational data of the patients were obtained from the Institution's finance database and assigned a socioeconomic level based on residence (inner city *versus* suburban), health insurance (Medicare and public assistance *versus* third party), and occupation.

Fifty-two controls from the primary care and cardiology clinics in our hospital and one of its affiliates were matched for age and sex and comparable socioeconomic group and selected after the MDS patient population was characterized. The control patients had cardiac problems related to coronary disease or hypertension and patients were excluded if they had a malignancy or blood dyscrasia. The controls were interviewed by one author (H. G.). None of the MDS or 4 control patients refused to answer the questionnaire. Statistical analysis was done using the test of proportion or the Fisher exact test.

RESULTS

Clinical characteristics and exposure histories of the patients and their age-matched controls are shown in Tables 1 and 2. Only 4% of MDS patients (2 of 52) compared to 24% of our practice belonged to the lower socioeconomic group as based on their residence, health insurance, and occupation ($P = 0.0001$). Data on chromosomal analysis of the patients are included. Exposure was considered significant if the person came in direct contact more than once with the chemical in question. Information was obtained on the duration and frequency of exposure when known. Data regarding frequency of exposure were limited by the recall ability of the patient and how far in the past the exposure occurred. Exposures to pesticides including insecticides (sprays used for indoor and garden insects), weed killers, and fungicides for fruit trees were all less than 5 times a year in subjects who were exposed by hobby.

As summarized in Table 3, the questionnaire elicited a similar high total incidence of positive exposure to known and potentially genotoxic agents in both control (40%) and MDS (46%) groups (P = NS). However, more MDS patients had exposure to pesticides alone (71%) compared to the control patients (29%) ($P = 0.002$). Routes of exposure were similar, the most common being gardening. Only one control patient, a tree surgeon (CC27), and one MDS patient, an exterminator (G-1), were exposed to pesticides by occupation and had more than 5 exposures/year.

Exposure to solvents differed greatly with a higher incidence of solvent alone (43% *versus* 20%) ($P = 0.089$) and both pesticide and solvent in the control group (29% *versus* 8%) ($P = 0.121$) compared to patients with MDS. Hobbies that involved exposures to chemicals and solvents included painting and model building. Occupational exposures to asbestos, welding fumes, and fibers are included in the tables but were not included in our analysis because of no demonstrated association with hematological disease. Where available, details were obtained as to duration, frequency, and intensity of the exposure. In separating the exposures to solvents based on whether these occurred via occupation or from participation in a hobby, we found that 21% of the MDS patients compared to 33% of control patients with exposure history had occupations that exposed them to the substances under question.

Chromosome analysis among MDS patients with positive exposure histories revealed that 12 of 22 patients (55%) compared to 13 of 26 patients (50%) (P = NS) without exposures had abnormal karyotypes in the marrow (Table 4). The karyotypic abnormalities involved multiple or involving chromosomes 5 and/or 7 were observed in 18 and 27% of patients with positive histories and in 31 and 23% of patients with no exposure histories (P = NS).

Dividing the FAB classes into 2 broad groups based on prognosis, more patients with a positive exposure history (75%) compared to patients with no exposure history (57%) were in the poor prognostic classes of RAEB, RAEB-T, and CMML *versus* the better prognostic classes of RA/RARS ($P = 0.08$) using a one-tailed test.

DISCUSSION

In our study we questioned whether the use of pesticides or solvents in the home or garden or occupationally increased the risk of myelodysplastic syndrome and whether this exposure led to a higher incidence of chromosomal abnormalities. We elicited by questionnaire a positive history of exposure to pesticides, solvents, or both in about one-half of primary MDS patients being accrued to our clinical trial. To determine whether this observation might be of etiological significance, we gave the same questionnaire to an age-, sex-, and socioeconomically matched group of control patients without any malignancy or hematological abnormalities. We were surprised to find a similarly high incidence of overall exposure in this group of patients. However, most of the exposure in the control group was from solvents while there was a higher incidence of pesticide exposure in the MDS group. There was a preponderance of the poor prognostic FAB groups in the pesticide-exposed compared to the nonexposed MDS patients, but it was not statistically significant. Furthermore, there was no correlation with pesticide exposure to the type of cytogenetic abnormalities, unlike some previous reports in patients with acute leukemia (1, 2).

The use of a control-matched study is unique to the literature as it pertains to hematolgical malignancies. Our results demonstrate the importance of taking a more in depth exposure history focusing on several means of exposure through occupation and hobbies with emphasis on duration, frequency, and intensity of exposure rather than the routine approach which tends to focus primarily on pulmonary toxins such as asbestos.

Table 1 *Characteristics of MDS patients with exposure history and controls*

UPN[a]	Sex	Age (yr)	Diagnosis	Chromosome	Exposure	Means of exposure	Tobacco	Occupation
B4	F	28	RAEB-T	46,XX	Miscellaneous[b] chromates, silica	O	No	Packaging/bookkeeper
CC1	F	28				Pot-tery	No	Doctor
D-3	M	71	CMML-T	46,XY	Pesticides and solvents	H	No	Office supervisor
CC2	M	71			No	None	Yes	Policeman
A-2	F	62	RAEB	46,XX	Pesticide	O	No	Electric factory worker
CC3	F	62			No	None	No	Homemaker
A-3	M	64	RARS	46,XY	Solvent	H	No	Reporter
CC4	M	64			No	None	No	Doctor
A-24	M	60	RAEB	46,XY	Pesticide	H	No	Education administra-tion
CC5	M	60			No	None	No	Lawyer
B-6	M	84	RAEB	46,XY	Pesticide	H	No	Hotel manager, barten-der
CC6	M	84			No	None	Yes	Accountant
E-1	F	55	RARS-T	46,XX	Pesticide	H		Homemaker
CC7	F	55			No	None	No	Office work
A-15	M	64	RAEB	46,XY	Pesticide	H		Computer programmer
CC8	M	64			No	None	No	Container manufacturer
B-3	F	56	RARS	46,XX	Pesticide	H	No	School teacher
CC9	F	56			No	None	Yes	Homemaker
A-5	M	62	RAEB-T	46,XY	Pesticide	H		Building contractor
CC10	M	62			Acids, asbestos	O	Yes	Tile setter
A-10	M	71	RAEB	47,XY,+8	Pesticide	H	Yes	Office work
CC11	M	71			No	None	Yes	Naval officer
A-12	M	66	RAEB	46,XY,11q−	Pesticide	H	No	History professor
CC12	M	66			Fibers, asbestos	O	Yes	Textiles
H-3	M	83	CMML	47,XY,+8	Pesticide	H	No	Theology professor
CC13	M	83			No	None	No	Messenger
A-23	M	72	RARS	46,XY, isochromosome 14	Pesticide	H		
CC14	M	72			No	None	No	Insurance
J-3	F	67	RARS	46,XX, 5q−	Pesticide	H		Soldering
CC15	F	67			No	None	No	Homemaker
B-13	M	78	RAEB	46,XY, abnormal 18	Miscellaneous	O		Woodworker
CC16	M	79			Formaldehyde, acids	O	Yes	Leather tanner
B-12	F	47	CMML	47,X,−X,−17,−20,5q−,+4	Pesticide	H	Yes	Teacher
CC17	F	47		markers	No	None	Yes	Banker
F-6	M	64	RAEB-T	45,XY,5q−,−3,−2C,−E,+3	Solvent	H	No	Commercial painter
CC18	M	64		markers	Pesticides, CCl_4, acids	H	Yes	Truck driver
A-9	F	68	RA	47,XX, 5q−,+6	Pesticide	H	Yes	Teacher
CC19	F	68			Pesticides	H	No	Homemaker
A-8	M	74	RA-	46,XY, t(2:11)	Pesticide	H	No	Drill press operator
CC20	M	74	RAEB		No	None	No	Sales
A-6	M	60	RARS	45,XY, −7	Pesticide	H		Executive
CC21	M	60			Pesticides, solvents, toluene	H, O	Yes	Cabinetmaker
H-1	M	56	RAEB-T	46,XY,−7,−15,−21,+15p+, +t(21;21),5q−,+ ring 49,XY,−7,−15,−21, +13,+15p+,+15p+, +t(21;21),+22,+ ring	Solvents	O	Yes	Maintenance supervisor
CC22	M	56			Pesticides (malathion)	H	Yes	Secretary
H-2	M	77	RAEB-T	Unsuccessful	Pesticides and solvents	H	No	Mechanic
CC23	M	77			Acids	O	No	Paper worker
G-1	M	58	CMML	Not done	Pesticide	O	Yes	Exterminator
CC24	M	58			Pesticides (malathion), benzene	H, O	Yes	Printer

[a] UPN, unique patient number (CC = matched control patient); H, hobby exposure; O, occupational exposure.
[b] Polymeric isocyanate, polyether polyol resin.

Table 2 *Characteristics of MDS patients without exposure history and controls*

UPN[a]	Sex	Age	Diagnosis	Chromosome	Exposure	Means of Exposure	Tobacco	Occupation
A-26	M	64	CMML	46,XY			No	Repair/gardening
CC25	M	64			Pesticide (malthion 1/m)	H	No	Doctor
B-10	M	78	CMML	46,XY			Yes	Engineer
CC26	M	72			Asbestos	O	No	Construction
A-14	M	48	RARS	46,XY			No	Teacher
CC27	M	48			Pesticides (chlordane, lindane, DDT, malathion)	O	Yes	Tree surgeon
D-1	F	85	CMML-T	46,XX			No	Office work
CC28	F	85			Turpentine, paints	H	No	Payroll
A-17	M	65	CMML	46,XY			Yes	Unemployed
CC29	M	65			Welding fumes	O	Yes	Welder
A-7	M	69	RAEB-T	46,XY			No	Accountant
CC30	M	69			Solvents (polychlorinated biphenyl)	O	Yes	Oil worker
F-4	M	63	RAEB	46,XY			Yes	Laborer
CC31	M	63			Dyes, fibers	O	Yes	Textile worker
A-21	M	61	CMML	46,XY			Yes	Engineer
CC32	M	61			Solvents	H	No	Psychology research
H-4	F	60	CMML	46,XX				
CC33	F	60			Pesticide (1xm)	H	No	Homemaker
A-22	F	76	RARS	46,XX			No	Homemaker
CC34	F	76			No	None	No	Homemaker
H-5	F	71	RARS	46,XX			Yes	Homemaker
CC35	F	71			Pesticide (Sevin), solvents	H, O	No	Commercial artist
B-7	F	68	RA	46,XX			No	Sales
CC36	F	68			No	None	No	Bookkeeper
I-1	F	83	RARS	46,XX				Homemaker
CC37	F	83			No	None	No	Executive designer
A-25	M	88	RARS	47,XY, +8			No	Chemist, businessman
CC38	M	88			Asbestos	O	No	Hotel manager
D-5	M	87	CMML-T	47,XY, +8			Yes	Chemist, businessman
CC39	M	87			Pesticide (chlordane-3x/y), benzene, lead	H, O	No	Engineer
F-3	F	42	RAEB	47,XX, +C			Yes	Homemaker
CC40	F	42			No	None	Yes	Office work
B-5	M	70	RARS	47,XY, 20q−			Yes	Sales, serviceman
CC41	M	70			Pesticide (1/m)benzene, asbestos	H	Yes	Truckdriver
A-13	F	69	RARS	45,XX, −7			No	Homemaker
CC42	F	69			Asbestos	O	No	Office worker
D-2	F	86	CMML-T	46,XX, −7,+14			No	Homemaker
CC43	F	86			No	None	No	Homemaker
J-2	F	85	RA	47,XX, triploid with 2 markers			No	Homemaker
CC44	F	85			No	None	No	Homemaker
G-3	F	70	RA	46,XX, 5q−,22p+, abn 11			No	Homemaker
CC46	F	70			No	None	No	Telephone operator
J-4	F	61	RAEB	48,XX,+6,+8,3p−,(?5q−),			Yes	Housewife
CC47	F	61		?7q−,10p+,?abn 12,19q+	Fibers	O	Yes	Textile worker
F-1	F	67	RAEB	46,XX,−4C,+4 markers,1p+,			No	Homemaker
CC48	F	67		Bq+,7q−	Pesticide (malthion-1/m)	H	No	Homemaker
C-1	M	70	RA	47,XY,−9,+2 mar, (?9q−)			No	Priest
CC49	M	70			Solvents, asbestos	O	Yes	Construction
A-20	F	73	RARS	45,XX, −7,3+			No	Billing clerk
CC50	F	73			No	None	Yes	Caterer
F-5	F	78	RAEB-T	45,X, −X, Dq−, abn small C			No	Tobacco factory worker
CC45	F	78			No	None	Yes	Bookkeeper
B11	F	62	RAEB	Not done			No	Teacher
CC51	F	62			Toluene, turpentine	H	Yes	Nurse
B-1	M	50	CMML-T	Unsuccessful			No	
CC52	M	50			Cyanide, toluene	O	No	Refrigerator repair

[a] UPN, unique patient number (CC = matched control patient); abn, abnormal; H, hobby exposure; O, occupational exposure.

Table 3 *Type and mode of genotoxic agent exposures in MDS and control patients as obtained through an environmental and occupational history questionnaire*

	MDS patients (%)	Control patients (%)	*P* value (2-tailed)[a]
Positive exposure	46 (24/52)[b]	40 (21/52)	NS
Agents			
Pesticides	71 (17/24)	29 (6/21)	0.002
Solvents	20 (5/24)	43 (9/21)	0.089
Both	8 (2/24)	29 (6/21)	0.121
Exposure by			
Occupation	21 (5/24)	33 (7/21)	NS
Hobby	79 (19/24)	48 (10/21)	0.024
Both	0	19 (4/21)	0.04

[a] Where NS is noted when $P > 0.1$.
[b] Number exposed/total.

Table 4 *FAB classification and chromosomal abnormalities in MDS patients with and without exposure history to pesticides and solvents*

	MDS with exposure (%)	MDS without exposure (%)	*P* value (2-tailed)[a]
FAB classification			
RA/RARS	25 (6/24)[b]	43 (12/28)	0.12
Pesticide	21 (5/24)		
Solvents	4 (1/24)		
RAEB/CMML	75 (18/24)	57 (16/28)	0.16
Pesticide	50 (12/24)		
Solvents	8 (2/24)		
Both	8 (2/24)		
BM karyotype			
Normal	45 (10/22)	50 (13/26)	MS
Abnormal	55 (12/22)	50 (13/26)	NS
Single abnormality	36 (8/22)	19 (5/26)	0.18
Pesticide	32 (7/22)		
Solvents	9 (2/22)		
Multiple abnormality	18 (4/22)	31 (8/26)	0.32
Pesticide	9 (2/22)		
Solvents	9 (2/22)		
Chromosome abnormality of 5 and/or 7	27 (6/22)	23 (6/26)	MS
Pesticide	18 (4/22)		
Solvents	9 (2/22)		

[a] Where NS is noted when $P > 0.1$.
[b] Number exposed/total.

As more becomes known about the role of the environment and carcinogenesis this information is likely to be vital.

Previous work (2, 4, 12, 13) has shown a relationship to exposure to potentially mutagenic agents by occupation or through hobbies; these groups had a higher incidence of chromosomal abnormalities and ANLL. Details of the degree of exposures were not provided, although most were via painting as a hobby. Lindquist *et al.* (14) found an increased risk of acute leukemia in professional painters, but in nonprofessional painting only when it was engaged in daily.

Table 4 shows the higher incidence of RAEB/RAEB-T/CMML in our MDS patients with exposure histories and 58% of these patients were exposed to pesticides. This is very important prognostically because the higher incidence of progression to acute leukemia is well known in this group. These classes of MDS are also higher in cases seen secondary to previous chemotherapy and radiotherapy. One can postulate a similar correlation between exposures to pesticides, albeit much weaker.

The chemical compounds in question most often are halogenated alkanes and alkenes. Many of our patients and controls questioned were unaware of the chemicals they use or had used in the past but the pesticides most often mentioned were lindane and malathion. Lindane is a broad spectrum insecticide that is a γ isomer of benzene hexachloride and has been associated with cases of agranulocytosis and aplastic anemia (15, 16). Malathion is also used as a broad spectrum insecticide especially in the home and garden. While there is an anecdotal report of a brief exposure to malathion followed by aplastic anemia, the mutagenicity tests were questionable and limited. There are no evidences of carcinogenicity in mice and rats, nor are there sufficient data to evaluate chromosomal effects in humans with this compound (17). Malathion was reported in 10% of pesticide exposure in our control group and none in the MDS group.

Subtle abnormalities were observed in the peripheral blood counts such as a decrease in hemoglobin levels, polymorphonuclear band forms, and lymphocyte counts in a group of workers occupationally exposed to pesticides compared to the nonexposed control workers (18). Wang and MacMahon (19) looked at the mortality of pesticide applicators in a cohort study of professional pesticide applicators and saw no significant increase in cancer. However, few had been studied for 10 years or more after their first exposure and considering the importance of latency for development of chemically induced tumors may far exceed this time period. This group is to be followed prospectively for a greater period of time as a cohort to determine rates of development of leukemia and other malignancies.

Cole and Goldman (20) point out that occupation is very closely related to social class which in itself is a risk for many cancers, as is race. It is of interest that only 4% of our MDS patients was of the lower socioeconomic class while 24% of the patient population without MDS are of that class in the medical school Hematology-Oncology clinic where the MDS patients were seen. Most of the MDS patients were of middle to upper middle socioeconomic classes referred for our studies from suburban areas. These possible differences in exposure to environmental agents may contribute to development of the disease. Perhaps working in the garden, refinishing furniture and other hobbies which may differ by social class may play an etiologic role. Ideally, a cohort study following prospectively an exposed and nonexposed group of a comparable socioeconomic background might help determine if these risk factors are indeed related to MDS. One would need detailed information as to nature and duration of exposures.

Our findings indicate the importance of having a control group in studies implicating exposure by history in the pathogenesis of these disorders. However, our observation that the majority of the MDS patients were coming from the middle socioeconomic class and the high exposure rate to genotoxic agents in this class of patients should be further investigated. Studies associating exposures to insecticides and solvents in leukemia and MDS should evaluate a control group from the general population to see if eliciting the history of exposure by itself may be a confounding variable. This socioeconomic cohort of controls with a high exposure rate should be prospectively studied taking into consideration the long latent period to determine the true relationship of insecticide and solvent exposures with MDS and leukemia. Multivariate analysis using all the mentioned prognostic factors should be examined in a prospective manner using a larger population to determine the relationship of these agents in inducing the preleukemic condition.

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