Increased Risk of Developing Acute Leukemia After Employment as a Painter

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A case-control interview study of 125 adult patients with acute leukemia and 125 controls matched with respect to age (± four years), sex, and residence was carried out in central Sweden during the period from September 1980 to May 1983. Their history of organic solvent exposure is described. A significant overrisk of developing acute leukemia was found when comparison between patients and controls revealed a difference in the solvent exposure rate, which was significantly higher in patients than in controls, with an estimated odds ratio (OR) of 4.9, 95% CI (2.2 to 12.1). The most frequently exposed profession, painters, exhibit a relative risk of 13 (2.0 to 554). These results suggest that an etiologic relationship exists between organic solvent exposure and the development of acute leukemia in man.

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IN THE SEARCH FOR a causal relationship between the effect of chemical compounds on bone marrow cells and the development of leukemia, early studies on workers exposed to the aromatic solvent benzene revealed a possible relationship between benzene exposure and myelotoxicity (Santesson 1897).[1] In 1928, Delore and Borgomano[2] described the first case of acute leukemia in heavily exposed workers and in 1932 Lignac found six leukemias and two lymphomas among 54 white mice exposed to benzene, whereas there was no leukemias among 1465 control mice. Later studies have confirmed that, in rodents, benzene inhalation produces myelogenous leukemia.[3]

Although benzene may be the most important organic solvent associated with leukemia development,[4] occupational exposure to organic solvents is usually complex. Therefore, results of epidemiological studies are usually based on information concerning the exposure to a mixture of organic solvents and not to benzene alone. A few such studies have been carried out and an increased risk of developing acute leukemia[6–9] after organic solvent exposure has been suggested. The sources of information were registers,[6,7] questionnaires to the next of kin[8] and case records supplemented by interviews of patients or of their relatives.[9]

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The aim of the present study was to compare the exposure of organic solvents in patients with acute leukemia and in matched controls to evaluate the significance of such exposure in the etiology of acute leukemia.

Material and Methods

Patients

During the period from September 1980 to May 1983, 125 patients with acute leukemia, who were treated in one of the five hospitals taking part in the collaborative treatment protocols of the Leukemia Group of Middle Sweden,[10] were interviewed. Because of the way health care is organized, the majority of patients with leukemia in this region of Sweden are admitted to these hospitals for diagnosis and treatment. There are no private clinics for leukemia treatment in Sweden. If a control had developed leukemia, he/she would have been treated in the same hospital as the patient. Fourteen patients who were in too poor a condition to be interviewed or who had too poor a memory to recapitulate information were excluded. One further patient refused to take part.

An alternative to interviewing the patients is to interview the next of kin. The information obtained was not comparable with the information obtained directly from the patients and controls and could not be used in this study.

The patients were of rural and urban origin. Seventy-six were men and 49 were women. The mean age was 49 years (range, 15 to 84 years). The mean age of the women was 51 years (range, 16 to 84 years) and of the men 48 years (range, 15 to 84 years). FAB classification according to Bennett *et al.*[11] was carried out with a slight

modification." There were 14 patients with M1 acute leukemia. 41 patients with M2, four patients with M3, 17 patients with M4, 21 patients with M5, 24 patients with acute lymphocytic leukemia and four patients with acute undifferentiated leukemia.

Controls

One control per patient was obtained from the population register of the taxation authorities. where all inhabitants are listed according to their addresses. district by district. Starting from the name of the patient in this list, the closest situated name of the same sex and age (±4 years), as the patient was taken as a control. One control refused to take part, one was not able to cooperate because of a recent cerebral hemorrhage and one could not be found. Instead of these three, the next closest persons in the population registers were interviewed. When possible, the patient and the corresponding control were interviewed at about the same time.

Questionnaire and Gatherirg of Dara

The patients and controls were all interviewed *in person* by one of the authors (R.L.), according to a strictly standardized questionnaire. The questions were 'addressed to each subject in the same way and with the same words. Information was obtained concerning all occupations during the person's life-time, and of exposures to specific chemicals. A list of professions. in accordance with the principles of the Swedish Central Bureau of Statistics, was checked systematically with every subject to make it possible for everyone to recall former occupations. The questionnaire also contained questions about hobbies, tobacco use. use of medicines, exposure to x-rays. vaccines, former diseases, and living conditions. The educations and the professions of the subjects were given in chronological order to describe the total life-span up to the interview. They were asked *to* describe working instructions and environmental exposure concerning inhalation. skin exposure and ingestion. They were also asked about different tasks within occupations and the way they performed the work. Different activities within the profession of painters can easily be described and it is unlikely that the subjects did not recall their activities. Exposure to organic solvents. paints and solvents. are uniformly used all over the country and well known by their users. The Swedish National Board of Health and Safety has performed analyses of their content. As far as possible. quantitatively and qualitatively exact answers that could be directly coded for computer processing. were obtained. The chemical agents and the professions were listed and coded for computing purposes. The questionnaire dealt with professional and nonprofessional activities. These hvo parts are not combined in the analyses or in the presentation of the results, except in table 6 concerning frequencies of skin exposure.

TABLE 1. Definition of Odds Ratio*

Patients	Referents	No. of pairs
Exposed	Exposed	a
Exposed	Nonexposed	b
Nonesposed	Exposed	c
Nonexposed	Nonexposed	d

* The odds ratio $\left(OR = \frac{b}{c}\right)$ is calculated as the ratio of the number of discordant patients and controls.

Epidemiological and Statistical Methods

The analyses of the material have been performed by comparing bound patient-control pairs. Odds ratios (OR) were estimated (Table 1) and tested for the discordant pairs according to Breslow and Day.[13-14] Concordant pairs, pain with solvent exposure of both patient and control. are disregarded.

Multivariate analysis with logistic regression on matched data was also performed."

Definitions

Constant daily occupational exposure to paints and/or organic solvents and/or organic solvent-containing glue(s) during a defined period of time in life is termed professional exposure. Skin exposure is defined as skin cleaning with aromatic and aliphatic solvents. Therapeutic x-ray is defined as low-dose gamma irradiation for joint or back pain, *e.g.*, *2500* rad as surface dose four times as a course of treatment. Petroleum products is defined as fuel (diesel. gasoline, aircraft fuels) and its combustion products.

Results

Painters

Thirteen patients and one control had been painters. All painters reponed daily exposure to organic solvents by vapoun. All of them cleaned their hands with solvents containing a mixture of aromatic and aliphatic hydrocarbons. The majority, 11 painters and the control. were exposed by direct skin application one or more times daily. while two painters were exposed at least by direct skin application every week arid by other means of skin cleaning daily (Table 2). The estimated odds ratio was 13 with a 95% confidence interval (CI) (2.0 to 554). 'The median duntion of exposure for painters was 16 years (range, 1 to 50 years) and the

TABLE 2. Data Gathered by Questionnaire From Painter Patients

Patient & control no.	Age*/sex	Type of painters	Occupation at the time of diagnosis	Solvent exposure (yr)†	Interval from end of exposure to start of disease‡	Skin exposure to solvents	Smoking duration years	Type of leukemia (FAB)
Patients								
1	41/F	Spray painter	Shoe factory (glue)	18	0	Daily	0	AL L
2	72/M	Painter + hobby artist painter	Painter	50	0	Daily	49	ALL
3	32/M	Car painter	Car tester	16	1	Daily	17	ALL
4	20/M	Painter (metal, machines)	Railway. shunting yard worker	1	2	Daily	0	M2
5	53/M	Painter. rubber factory + paint manufacturer	Paint manufacturer	18	0	Daily	30	M4
6	70/M	Painter + hobby artist painter	Painter	50	0	Daily	46	M4
7	19/M	Painter	Painter	3	0	Daily	0	ALL
8§	58/M	Boat painter	Salesman	16	25	Daily	46	M1
9	59/M	Car painter	Baker	3	7	Weekly	43	M2
10§	66/M	Boat and building painter	Pensioner	10	28	Daily	0	ALL
11	45/M	Boat painter	Clerk	4	22	Daily	19	M4
12	73/M	Spray painter (anticorrosive agents)	Pensioner	5	6	Weekly	40	M2
13	71/M	Warm and cool asphalt painter	Pensioner	41	4	Daily	50	M5
Control								
1	39/M	Car painter	Assistant nurse	6	12	Daily	0	—

ALL: acute lymphocytic leukemia: FAB: French-American-British classification of the acute leukemias.
* Median age. 58 years.
† Median exposure, 16 years (range. 1 to 50 years).
‡ Median interval, 2 years (range, 0 to 28 years).
§ Exposed to therapeutic X-ray treatment to shoulders.

median interval from the end of exposure to the development of disease was two years (range 0 to 28 years). Five were occupationally exposed at the time of leukemia diagnosis. Patients 8 and 10 had received x-ray treatment, Patient 8 twice, eight years (right shoulder) and six years (left shoulder and back). before the diagnosis of leukemia and Patient 10, eight years before (one shoulder) diagnosis. Excluding the *two* individuals exposed to x-rays. OR = 11 ($P = 0.012$, sign test). The shortest exposure to solvents (1 year) was seen in one young painter (Patient 4) who painted warm machines with anticorrosive agents and lacquers. Two painters (Patients 2 and 6) also painted as a hobby (artists) with a long duration of exposure prior to the diagnosis of leukemia.

Nonprofessional Painting

There was no overall statistical difference between the nonprofessional painting activities of patients and controls. In fact 77 patients and 89 controls had been exposed to solvent-containing paints. The intensity of the nonprofessional exposure was ranked from single occasions in life to periods of once a year, once a month. once a week and daily painting. There was no significant statistical difference between the patients and controls as regards the low-grade exposure, but the more intense exposure, with frequencies of once a week to daily activity. was seen significantly more often among discordant pairs of patients compared to controls ($P = 0.03$) (Table 3).

Exposure by inhalation of solvent-containing air from restoration of the patients' and controls' homes during single brief periods during the previous 5 years was not significantly different in the two groups.

Organic Solvent Exposure in Different Occupations

Organic solvents are used as constituents of paints. glues, and cleaning fluids in many different professions (Table 4). If excluded all patient-control pairs of painten. 26 patients and seven controls were occupationally exposed to paints and/or solvents and/or glues during a certain period of life, disregarding four exposed

TABLE 3. Frequency of Nonprofessional Painting Activities Amonn Patients and Controls

Frequency of activity	No. of discordant pairs of patients	No. of discordant pairs of controls	*P* value of comparison between discordant pairs of patients and controls
Daily	3	1	*0.03.*
Weekly	6	1	NS
Monthly	6	6	NS
Yearly	21	24	NS
Once	23	39	NS
Never exposed	35	23	NS

NS: not significant.
• One-tailed significance test.

concordant pairs. The ratio 26 to 7 is highly significant (*P* = 0.0013) when tested for the equality of proportions in matched samples (by sign test, 1947).[15] The OR of the overall exposure to solvents is estimated to be 3.7, with the 95% CI limit calculated by binomial distribution to be 1.6 to 10.1 (Table 5). The median time of exposure of discordant patients was longer than that of discordant controls (nine years compared to four years). The median time from cessation of exposure to the development of leukemia was 15 years (range, 0 to 40 years). Median time from cessation of exposure to interview for controls was 16 years (range 0 to 24).

Skin Exposure to Organic Solvents

The distribution of patients and controls regarding the frequency of skin cleaning with organic solvents show that there was no difference in low frequency exposure, but daily exposure was noted in 18 patients and six controls (Table 6). They were using white spirit 17% to 22% aromatic hydrocarbons) and/or gasoline with a high aliphatic hydrocarbon content and about 5% aromatic hydrocarbons. The aromatic hydrocarbon fraction is composed of xylene. toluene, trimethylbenzene, and benzene.[16]

TABLE 4. Distribution of Occupations Exposed to Organic Solvents According to the Interviews

Occupation	No. of discordant patients	No. of discordant controls
Painter	13	1
Rubber industry worker	1	0
Pharmaceutical industry worker	1	0
Upholsterer	1	1
Car wax cleaner	1	0
Printing worker	1	1
Dry cleaner	1	2
Car repairman	3	0
Woodworker	4	0
Shoe factory worker	2	1
Book binder	1	0
Textile printing worker	1	0
Train/bus wagon repairman	2	1
Shipyard worker	1	0
Sign painter	1	0
New building cleaner	1	0
Isolation worker	1	1
Metal industry printing worker	1	0
Dispensing chemist	1	0
Nurse	1	0
	39	8

Ether Anesthesia

The exposure to ether anesthesia was the same in patients and controls (58 patients exposed compared with 57 controls; discordant pairs, 27 patients and 26 controls). The solvent-exposed patients were not significantly more often exposed to this form of anesthesia than other patients.

Smoking Habits

Thirty-one percent of the painters had not been smokers. Considering all patients and controls, the smoking habits were similar (Table 7). Forty-two percent of all the patients and 48% of the controls had not been smokers. Neither differences between discordant pairs nor strata of patients and controls proved to be of statistical significance when the duration of smoking,

TABLE 5. Exposure to Organic Solvents*

Occupational organic solvent exposure	Patients					Controls						
		Time of exposure (yr)		Time from end of exposure to diagnosis (yr)			Time of exposure (yr)		Time from end of exposure to interview (yr)			
	No.	Median	Range	Median	Range	No.	Median	Rang	Median	Range	*P*	OR (CI)
Painters	13	16	1–50	2	0–28	1	6		12		0.002	13 (2–554)
Professions other than painters	26	9	0.1–60	15	0–40	7	4	1.5–40	16	0-24	0.001	3.7 (1.6–10.1)
Total	39	10	0.1–60	7	0–40	8	5	1.5–40	14	0-24	<0.001	4.9 (2.2–12.1)

OR: odds ratio: CI: confidence interval.
* Number of patients and controls exposed to organic solvents, median time of exposure (years/range), median time from end of exposure to diagnosis/interview (years/range), OR with CI (binomial distribution) and *P* values.

TABLE 6. Frequency Skin Exposure of Professionals and Nonprofessionals to Organic Solvents

Frequency of exposure	No. of patients	No. of controls	P	OR CI (binomial distribution)
Daily	18	b	<0.05	3.0 (1.14–9.24)
Weekly	12	11	NS	
Some occasions/year	34	41	NS	
Single occasions/year	17	10	NS	
Single occasions	18	20	NS	
Never exposed	31	37	NS	

OR: odds ratio; CI: confidence interval; NS: nonsignificant.

number of cigarettes consumed, pipe smoking. or snuff use were tested.

Multivariate Analysis

Multivariate analysis expressed as logistic regression on matched data showed no interaction between organic solvent exposure, smoking habits, x-ray exposure and petroleum products (Table 8).

FAB Classes

The distribution of French-American-British classification of the acute leukemias (FAB) classes[11,12] among patients exposed to organic solvent-containing compounds showed that no single patient had the diagnosis of promyelocytic leukemia (M3) or erythroleukemia (M6) (Table 9). Leukemias of the MI + M2 types were found significantly more seldom among solvent-exposed than among non-exposed patients ($P = 0.01$, chi-square test) and the M4-M5 leukemias were found significantly more often among exposed patients ($P = 0.02$).

Discussion

Our results indicate that regular exposure to solvents is associated with an increased risk of developing acute leukemia. Heavily exposed persons, such as painters. exhibit the greatest OR (13). while solvent-exposed persons other than painters have an excess risk of 3.7 when compared with nonexposed persons. Multivariate analysis showed no interaction between solvent exposure, tobacco use. therapeutic x-ray exposure, or petroleum products.

TABLE 7. Tobacco Use (During any Period of Life) by Patients and Controls*

Category	No. of patients	No. of controls
Cigarrette smoken	63	62
Pipe smokers	20	20
Snuff takers	18	19
Nonsmokers	52	60

* The same individual may have consumed tobacco in different forms.

TABLE 8. Multivariate Analysis

Variable	β	P
Therapeutic x-ray	1.51	0.008
Organic solvents	1.96	<0.001
Petroleum products	1.42	0.020

β: regression coefficient.[13]

* Multivariate analysis using logistic regression on matched data showed no interaction between exposure to therapeutic x-ray treatment, solvents, or petroleum products. All variables were coded 0–1: 0, not exposed: 1. exposed. Another considered (NS) variable was tobacco use.

The solvents used occupationally by painters consist of mixtures of aromatic and aliphatic hydrocarbons.[16] Although knowledge of the toxic effects of benzene has resulted in its prohibition in Sweden as a pure solvent, it is impossible to prevent complete prohibition. It often occurs as an impurity in other solvents, in paints and is used as an additive in gasoline.

Benzene is metabolized to benzene epoxide, a highly reactive compound, which in turn is metabolized to phenol, which is oxidized to alkylating agents.[17,18] This could be one mechanism for cellular damage. For example, Snyder *et al.* have shown that a benzene metabolite is bound to bone marrow cells.[19] and Karigaya *et al.* have noted stemcell injury leading to diminished cell replication and other cellular abnormalities in *in vitro* liquid bone marrow cell cultures exposed to benzene.[20]

Toluene (methylbenzene) and xylene (dimethylbenzene) can be metabolized by the same pathway but to a lesser extent, because they are also metabolized on methyl groups into carboxyl acids, which can be conjugated and excreted.[21] Human leukemia and aplasia of the bone marrow following inhalation of vapor from toluene-containing glue was' observed in youngsters assembling model building set~.""--It is therefore proba-

TABLE 9. Distribution of FAB Classes Among Patients Exposed to Organic Solvents and Nonexposed Patients*

	Nonexposed		Exposed		All patients	
	No.	Percent	No.	Percent	No.	P†
MI-MI	42	78	12	22	54	0.01
M3	4	100	0	0	4	0.36
M4 + M5	20	51	19	49	39	0.02
ALL	13	52	12	48	25	0.12
AUL	3	100	0	0	3	0.55
	82	66	43	34	125	

ALL: acute lymphocytic leukemia; AUL: acute undifferentiated leukemia; FAB: French-American-British classification of the acute leukemias.

* A comparison of the number of patients, exposed and non-exposed of the different FAB groups.

† Chi-square test.

ble that the metabolism to epoxides and phenols is sufficient for the induction of bone marrow cell damage and leukemia.

Cytogenetic analyses of human lymphocytes have indicated mutagenic properties of benzene[25-28] and trichloroethylene.*' Also, increased chromatid exchange and chromatid breakages were found in laboratory and printing works employees who were exposed to solvents as compared to nonexposed controls."' Chromosome breakages are increased in blood lymphocytes of plastic factory workers exposed to styrene." Thus, a substantial amount of data shows that many organic solvents and their metabolites are mutagenic. This may explain why exposure to them increases the risk of developing leukemia. However, the mechanism behind the mutagenic action is complex, and there is little knowledge about the relative risk of each specific organic solvent or its metabolite/s.

For painters, the median time of solvent exposure was 16 years (range, 1 to 50 years), but the median interval from the end of exposure to onset of disease was two years (range, 0 to 28 years). Five painters acquired leukemia while still engaged in professional activity after 18, 18, 50, 50, and 3 years of exposure, respectively. Thus, the results suggest that there is an excess risk after a short period of exposure. Furthermore, we find that onset of the disease can occur in association with the exposure as well as after cessation of exposure. The same result was obtained by Rinsky *et al.* who studied leukemia in benzene workers."

Organic solvent exposure has been associated with the development of both myelocytic and lymphocytic leukemias and lymphomas. In a report from Turkey[33] on 34 patients chronically exposed to benzene, Aksoy *et al.* found both myelocytic and lymphocytic leukemias. McMichael *et al.* reported a sevenfold increase in the relative risk of developing acute lymphocytic leukemia in workers exposed to solvents? Two case-control studies, by Hardell *et al.*[34] and by Olsson and Brandt,[35] show an increased risk of developing lymphoma after exposure to organic solvents. This was also found by Ohlin and Ahlbom[36] concerning cancer mortality among Swedish chemists exposed to solvents. Aksoy *et al.*[33] reported an incidence of leukemia of 13.5 per 100,000 individuals with chronic exposure to benzene, compared to the overall incidence of six per 100,000, a significantly greater risk ($P < 0.001$). when exposed. The OR was 13.5/6 = 2.25. When estimating the OR of malignant lymphoma. Hardell *et al.*[34] found that in patients with high-grade exposure to organic solvents, the OR was 11.1, 95% CI (1.9 to 11.4). The high-grade exposed group is comparable with the group of painters in our study, whose OR = 13(1.95 to 554). The results are consistent. suggesting the estimation of the ovemsk to be in the lower span of the confidence interval.

A comparison of the distribution of FAB classes (Table 9) among our patients exposed to organic solvents and nonexposed persons indicates that the FAB M4 and M5 subtypes of leukemias are more frequently observed among exposed persons ($P = 0.02$, chi-square test) and FAB MI and M2 subtypes less frequently ($P = 0.001$, chi-square test).

A Swedish death certificate cohort study of 416 paint-industry workers exposed to organic solvents, has been presented by Lundberg *et al.*[37] Cause–specific mortality was studied. Among 96 workers who died, three died of multiple myeloma, compared with 0.6 expected deaths. Five deaths of disease of the lymphatic and hematopoietic systems were observed compared to 2.4 expected deaths with an estimated OR of 2.12, 95% CI (0.68 to 4.96).

The alkylating agents of metabolized aromatic compounds, such as epoxids, have an effect most probably consistent with cancer initiator, inducing DNA damage and turning the normal cell into a malignant cell. An initiating agent, if sufficiently strong, *can* theoretically express its capacity after a single exposure, thus explaining the occurrence of leukemia in individuals with a short exposure time. The same DNA-damaging property can also induce chromosome abnormalities which may predispose second event/hit to induct the malignancy.

The mechanisms of bone marrow carcinogenesis giving rise to acute leukemias is still obscure. In the case of alkylating agents, the situation seems to have much in common with the expenmental model for rat liver carcinogenesis, called the resistant hepatocyte model.[38,39] In this model, initiated cells are generated by the use of mutagens in the presence of cell proliferation. The initiated cells are selectively favored in their proliferation during the promotion phase because they are resistant to the mitoinhibitory effect of the promotor." This differential sensitivity concentrates the mitogenic power to the initiated cells, permitting them to clonally expand to focal cell populations with a high rate of basal cell proliferation and a high risk of rare mutation-like events that pushes them another step forward in the process of cancer development. In the bone marrow, alkylators form DNA adducts that probably give rise to mutation-like events in rare cells. Alkylators have also been shown to be mitoinhibitors for bone marrow stem cells,[41] depressing the production of leukocyte and thrombocytes. Thus, it is possible for resistant cells to develop (mutation/initiation) and the prerequisites (organic solvents), are at hand matching the analogy with experimental models obvious. In experimental carcinogenesis and in other examples of human cancer development, the process is slow and takes a considerable part of the lifespan to reach the terminal stage of malignant transformation. During that time, the subject does not have to be to the

carcinogen exposure constantly. In the optimized experimental liver models, dependent of both initiation events and promotion. initiation is a one-dose event and promotive treatment is performed for 2 weeks. Cammomas in this model are Seen 10 months after initiation. Potent carcinogen exposure in young animals with a high rate of liver cell proliferation results in hepatoma development within 2 to 3 months.

Our results point to a greatly increased risk of developing acute leukemia after exposurc to organic solvents Furthermore. noxious effects of these compounds on *the* kidneys,[42] *the* nervous system[43] and the liver" have been reported. Today, occupational exposure to organic solvents is widespread and complex. and it is important that further efforts be made to minimize such exposure.

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