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Occupational Exposures of Parents of Children with Acute Nonlymphocytic Leukemia: A Report from the Childrens Cancer Study Group[1, 2]

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ABSTRACT

The Childrens Cancer Study Group conducted a case-control study of occupational exposures of parents of 204 children (under 18 yr of age) with acute nonlymphoblastic leukemia. The most consistent finding was an association of acute nonlymphoblastic leukemia risk with pesticide exposure. Controls matched by date of birth and race were obtained through random digit dialing. Odds ratio (OR) for paternal pesticide exposure in jobs held for longer than 1000 days was 2.7 (95% confidence interval, 1.0 to 7.0; trend, $P = 0.06$), and seven case mothers and no control mothers had prolonged exposure (trend, $P = 0.008$). Risk estimates for parental pesticide exposure were substantially increased for children under age 6 at diagnosis (OR for prolonged exposure to either parent = 11.4; trend, $P = 0.003$) and for those with myelomonocytic and monocytic subtypes (OR, 13.6; trend, $P = 0.007$). Moreover, there were significantly elevated risks for direct exposure of the child to pesticides in the household (OR for exposure most days = 3.5; trend, $P = 0.04$) and for maternal exposure to household pesticides at the time of pregnancy (eight case mothers *versus* no controls for exposure most days; trend, $P = 0.05$). Paternal exposures to solvents (OR, 2.1; $P = 0.003$) and petroleum products (OR, 2.4; $P = 0.002$) were reported more commonly for cases than controls. Other occupational exposures reported significantly more often by case parents were paternal exposure to plastics or lead and maternal exposure to paints and pigments, metal dusts, and sawdust. These data provide further evidence for a role of occupational risk factors in the etiology of childhood cancer.

INTRODUCTION

ANLL[6] displays two age peaks; there is an early peak for children under age 3, an essentially constant incidence until early adulthood, and then a progressive increase in incidence with age, as ANLL comes to be the predominant form of acute leukemia. In children, ANLL is substantially less common than acute lymphocytic leukemia, accounting for only 15% of leukemias. Occupational exposures to radiation (1–3), benzene (4–6) and other solvents (7), and petroleum products (8) have been associated with leukemia in adults and children (9). In addition, there is evidence from animal studies (10, 11) and in human populations (9, 12–15) to suggest that exposure to pesticides may be a risk factor. These associations have not been examined in detail for ANLL within the pediatric population and, for this reason, we conducted a case/control study of factors related to ANLL in children, with particular emphasis on the effect of parental occupational exposures.

METHODS

Cases were ascertained through the registration files of the CCSG, a cooperative clinical trials group with approximately 100 member and affiliate institutions in the United States and Canada. All patients under age 18, newly diagnosed with ANLL between 1980 and 1984, were considered for study entry. Additional eligibility criteria were that the patient's biological mother lived in the United States or Canada at the time of diagnosis, owned a telephone, and spoke English. Of 331 cases identified, 262 met all eligibility criteria. Most cases were enrolled on a CCSG therapeutic study, although this was not an entry criterion.

Permission for interview was first obtained from the patient's physician and then from the parents. Of 262 eligible cases, 204 mothers were interviewed with reasons for noninterview being physician refusal (19), inability to locate family (15), and parental refusal (24). Once consent was obtained, the parents were sent an interview guide containing hand cards which listed medications, occupational hazards, common illnesses, and other factors that were to be part of the interview. The mother and, where available, the father of the case were separately interviewed by telephone. One hundred fifty-four case fathers and 138 controls fathers were interviewed, and surrogate interviews were obtained for 36 case fathers and 51 control fathers; in these instances, when the father was either not available or refused to participate, the mother was asked to complete the questionnaire. These interviews provided 178 case-control pairs for analysis of paternal occupational exposures. To check whether the use of surrogate information influenced the findings, analyses were repeated excluding surrogate interview data; for these analyses, it was necessary to break the matching to maintain an adequate sample size.

Controls were obtained by random digit dialing. A single matched control was sought for each case, using the area code and first five digits of the case's telephone number in a series of randomly generated telephone numbers. Up to nine attempts (including morning, afternoon, evening, and weekend calls) were made to contact a household before a number was abandoned. Controls were matched on date of birth (within 24 mo for children over age 4, within 12 mo for children 1 to 3 yr of age, and within 6 mo for those younger) and race (white and nonwhite). If a control family with a matched child did not consent to interview, random dialing continued to the next match. When the first matched control refused to participate (29 instances), another control was sought. The second chosen control was used in 23 instances, the third chosen in four instances, and a fourth match was needed to be found for two cases. In a small number of instances in which a race-matched control could not be found, controls were matched on age only. Eligibility criteria and procedures for contacting and interviewing the controls were the same as those for cases. Direct exposures to the child were only recorded if they occurred before a reference date, which was 2 yr prior to diagnosis for children over age 3 at diagnosis, 1 yr prior to diagnosis for children aged 24 to 36 mo, and 6 mo before diagnosis for those less than 24 mo old at diagnosis. The same reference age was used for the matched control.

The mother's interview lasted approximately 1 h and included questions on demographic factors; the index pregnancy; exposures to infec-

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[6] The abbreviations used are: ANLL, acute nonlymphoblastic leukemia; OR, odds ratio; CI, confidence interval; CCSG, Childrens Cancer Study Group.

tions, X-rays, and medications during the pregnancy; household exposures and parental smoking; occupational exposures; reproductive and medical history; contraceptive practices; complications of delivery and early postnatal illnesses of the child; and congenital abnormalities of the child or first degree relatives. The father's interview concentrated on occupational factors, possible Agent Orange exposure, medications, and X-rays. Questionnaires were identical for case and control parents, and interviewers were not informed on case/control status of the subject nor of the major study hypotheses.

A life-time occupational history was obtained. This consisted of questions on the employer, job title, specific duties, start and termination date for every job held (of at least 6-mo duration; part- or full-time, including self-employment), and inquiry about possible exposure to 52 specific agents in 9 major categories (Table 1). Parents were asked whether they "came in contact" with each substance, through either direct use or working in the presence of others using the substance. For specific exposures reported by a parent, the average frequency of exposure and nature of exposure were recorded, and exposures were linked to the appropriate jobs to provide information on duration and timing with respect to the index pregnancy. There was no verification of exposures with the employers. Analysis of occupational exposures was based primarily on self-reported exposure. In addition, all employers and job titles were coded using the Standard Industrial Classification Manual (16) and the Dictionary of Occupational Titles (17), and exposures were inferred through the linkage system developed by Hoar *et al.* (18), which provides a matrix of occupation-exposure correspondences for 375 substances, including many known or suspected chemical carcinogens. The specific substances were grouped into general categories of pesticides, petroleum products, and other solvents for the analysis.

Pathologists in the treating institutions determined the morphology of the diagnostic marrow according to the French-American-British classification system. All original karyotypes were reviewed by two cancer cytogeneticists.

Conditional logistic regression was used to test for case-control differences and to estimate ORs and CI (19). Linear weights were used in calculation of trend statistics. Unless otherwise stated, the adjective "significant" refers to results that reached the two-sided 0.05 level of statistical significance.

RESULTS

Demographic Characteristics

The case and control groups were similar with respect to age, race (Table 2), sex (51% and 49% male in the two groups, respectively), maternal age at the date of birth of the child (median age, 25 yr for both groups), paternal age (median age, 28 for both groups), and paternal education (Table 2). The distribution of cases by morphological type is given in Table 2.

Occupation/Industry Classification

One case father, two control fathers, 24 case mothers, and 21 control mothers had never been employed. Occupations and industries were coded from the job descriptions, and the parents were classified as ever/never employed in each occupation and each industry. Three ratios were significant: non-auto mechanics (14 cases, 4 controls; OR = 3.5, $P = 0.02$) and painters (7 cases, 1 control; OR = 7.0, $P = 0.02$) for fathers, and metal manufacturing (10 cases, 3 controls; OR = 4.5; $P = 0.03$) for mothers.

Exposures Inferred from Job Title

Inferred exposures were examined, first using all job titles and then restricting the jobs to those held from 1 yr prior to the index pregnancy until the reference date. The only general category found to be significant was pesticide exposures for fathers (OR = 2.3, $P = 0.05$).

Self-reported Exposures

The duration, frequency, and timing of exposure for each of the substances listed in Table 1 were analyzed to determine whether there was any association between exposure, as reported by the parent, and ANLL occurrence.

Duration of Exposure. For each occupational exposure, the lengths of all jobs involving that exposure were summed, and the exposure was categorized as none, short (1000 days or less between the start and end dates of the job(s) in which the exposure occurred), or prolonged (more than 1000 days). Both the broad exposure groupings and the more specific named substances were tested for association with ANLL, and the significant associations are shown in Table 3. For fathers, solvent exposures were significant (OR = 2.1 for prolonged exposure; trend, $P = 0.003$). Since relatively few respondents were able to name the solvent used, the only statistically significant subcategory of solvent exposure was "other solvents." Three subgroups of the paternal "plastics" category were individually significant: polyethylene ($P = 0.002$); polystyrene ($P = 0.02$); and "other plastics" ($P = 0.03$). The paternal oil and coal products grouping was significant overall (OR = 1.5 and 1.9 for short and prolonged exposures, $P = 0.01$), and although three subcategories (coal and graphite, OR = 2.5; coal, tar, soot, pitch, or smudge, OR = 2.0; and petroleum products, OR = 2.4) had similar elevated OR for prolonged exposure, only for petroleum products was the number exposed large enough to provide statistical significance. The OR for prolonged exposure to pesticides was 2.7 (trend, $P = 0.06$).

Table 1 *Occupational exposures included in the questionnaire*

- Solvents, degreasers, cleaning agents
  - Carbon tetrachloride
  - Trichlorethylene
  - Perchlorethylene
  - Methyl ethyl ketone
  - Toluene or toluol
  - Xylene or xylol
  - Freon
  - Benzene
  - Naphtha
  - Other solvents
- Plastic materials
  - Polyvinylchloride[a]
  - Polystyrene[a]
  - Polyethylene[a]
  - Polyurethane[a]
  - Other plastics[a]
- Paints or pigments
  - Spray paints
  - Other paints
  - Dyes or pigments
  - Printing inks
  - Lacquers or stains
  - Turpentine
  - Paint remover
  - Paint thinner
  - Lacquer thinner
  - Other paints or pigments
- Oil or coal products
  - Cooling, cutting, or lubricating oils
  - Coal or graphite[a]
  - Coal tar, soot, pitch, or smudge
  - Petroleum products
- Metals
  - Chromium[a]
  - Arsenic[a]
  - Beryllium[a]
  - Cadmium[a]
  - Lead[a]
  - Mercury
  - Nickel[a]
  - Metal dusts or fumes
- Insulation materials
  - Asbestos
  - Fibrous glass or rock wool
  - Other insulation
- Nonionizing radiation
  - Radar
  - Microwave ovens
- Miscellaneous
  - Epoxy resins
  - Formaldehyde
  - Rocket fuel
  - Sulfuric acid
  - Other acids or alkalis
  - Pesticides or weed killers
  - Synthetics, such as nylon[a]
  - Sawdust
  - Wood preservative
  - Grain dust
- Radiation or radioactive materials
- Other substances

[a] Excluding exposures to finished product.

Table 2 *Characteristics of the case and control groups*

	Cases (%)	Controls (%)
Age		
0–2	32	32
3–6	18	18
7–10	16	14
11–14	22	21
15+	13	15
Race		
White, non-Hispanic	85	87
Hispanic	5	6
Black	6	5
Other	4	2
Morphology		
M1/M2	53	
M3	7	
M4	18	
M5	12	
M6	2	
M7	1	
Unknown	7	
Paternal education		
College graduate	28	30
High school graduate	49	47
Less than Grade 12	15	14
Unknown	8	8

The results of an unmatched analysis excluding surrogate paternal interviews produced comparable results: association with ANLL risk remained significant for solvents ($P = 0.03$), petroleum products ($P = 0.003$), and pesticides ($P = 0.01$), but was nonsignificant for plastics ($P = 0.28$) and lead ($P = 0.08$).

Significant associations for occupational exposures of the mothers are included in Table 3. Paints and pigments as a general category were significant, and use of spray paints was the the most significant subcategory (OR = 3.0 for prolonged exposure; trend, $P = 0.03$). Use of turpentine (four case mothers *versus* no control mothers, $P = 0.04$) and paint thinners (OR = 4.0, $P = 0.16$) had also elevated odds ratios within this category, but these associations largely disappeared when the analysis was adjusted for reported use of spray paints. Maternal metal exposures overall were significant (OR = 3.5 for both short and prolonged exposure; trend, $P = 0.02$), but frequencies for specific metals were small, and most mothers simply reported exposure to the subgroup of "metal dusts and fumes." The most significant maternal exposure was to pesticides (seven case mothers and no control mothers had prolonged exposure; trend, $P = 0.008$). One additional factor, not shown, was exposure to insulating materials which was protective (trend, $P = 0.05$), due largely to the fact that all five mothers reporting prolonged asbestos exposure were control mothers (asbestos; trend, $P = 0.03$). This factor has not been included in subsequent analyses since, in the absence of any plausible mechanism for a protective effect, the association was considered to be due to chance.

The most important of the factors found not to be significantly associated with ANLL was occupational exposure to ionizing radiation. Exposure was considered to be potentially significant if the parent was required to wear a dosimetry badge. There were only four case mothers and four control mothers reporting such exposure. Seventeen case fathers and nine control fathers worked in jobs that required that a dosimetry badge be worn (OR = 1.9 for prolonged exposure; $P = 0.22$).

Frequency Times, Duration, and Nature of Exposure. Cumulative exposure measures were calculated as sums (for each substance) over all jobs of the product of exposure frequency by job duration. These measures did not show stronger associations with disease risk than did the simpler measures based on duration alone (results not shown). Exposures were also classified being due to direct use of the products or working in the presence of others using the product. For the statistically significant factors (shown in Table 3), the proportion of exposures reported that were direct varied from 47% (for maternal exposure to pesticides) up to 88% (for paternal exposure to solvents). Removing indirect exposures from the analysis reduced all the significance levels. Since there were few mothers classified as exposed in any of the categories, restricting the definition of exposure to exclude indirect exposure left too few to provide useful risk estimates; for the maternal exposures, all results became nonsignificant. For the fathers, the restricted exposure definition reduced significance levels, but did not substantially alter the odds ratios: solvents OR for prolonged exposure = 2.0 (trend, $P = 0.007$); plastics OR = 2.2 ($P = 0.06$); petroleum products OR = 1.8 ($P = 0.04$); pesticides OR = 2.9 ($P = 0.09$); lead OR = infinite ($P = 0.09$).

Timing of Exposure. Odds ratio estimates for exposures before, during, and after the index pregnancy are shown in Table 4. These three measures (coded as any *versus* none) are highly correlated, since many individuals had exposures that spanned two or more intervals, either in a long-held job or because exposures in different jobs for a given individual were often quite similar. It is not clear that risk associated with exposures in any one period is consistently higher than the other periods.

Clinical Factors

Age. To determine whether there were stronger associations when the ANLL occurred at an early age, analyses of self-reported exposures were repeated excluding all patients aged over 10 (and their matched controls), and then eliminating patients over age 5. Of the 188 pairs with both maternal and paternal occupational data, 118 included patients aged 10 and under, and 82 included patients aged 5 and under. Associations within the restricted age groups were quite similar to those seen for all ages, except for pesticide exposure for which the OR for

Table 3 *Parental occupational exposures associated with ANLL risk*

Exposure	Total duration (days)	Case	Control	OR	95% CI	*P* trend
Paternal exposures						
Solvents	None	89	117	1.0		
	1–1000	32	19	2.6	1.3–5.5	
	>1000	57	42	2.0	1.2–3.8	0.003
Plastics	None	152	164	1.0		
	1–1000	11	7	1.8	0.7–4.8	
	>1000	15	8	3.3	1.0–10.3	0.02
Petroleum products	None	93	118	1.0		
	1–1000	32	29	1.4	0.8–2.5	
	>1000	53	31	2.4	1.3–4.1	0.002
Pesticides	None	151	158	1.0		
	1–1000	10	13	1.0	0.4–2.4	
	>1000	17	7	2.7	1.0–7.0	0.06
Lead	None	167	173	1.0		
	1–1000	5	5	1.0	0.3–3.5	
	>1000	6	0			0.03
Maternal exposures						
Paint and pigments	None	174	186	1.0		
	1–1000	15	11	1.5	0.6–3.3	
	>1000	15	7	2.2	0.9–5.4	0.05
Metal dusts	None	194	202	1.0		
	1–1000	4	1	4.0	0.5–35.8	
	>1000	6	1	6.0	0.7–49.8	0.02
Sawdust	None	198	202	1.0		
	1–1000	1	2	0.0		
	>1000	5	0			0.03
Pesticides	None	193	200	1.0		
	1–1000	4	4	1.0	0.5–2.9	
	>1000	7	0			0.008

Table 4 *Odds ratio estimates for occupational exposures before, during, and after the index pregnancy*

	Period of exposure relative to the index pregnancy		
	Before	During	After
Paternal			
Solvents	2.2[a]	2.1[a]	1.5[b]
Plastics	1.8	1.5	2.4[b]
Petroleum products	2.0[a]	2.8[a]	1.6[b]
Lead	2.3	[1][c]	6.0[a]
Pesticides	1.7	1.9	1.8
Maternal			
Paints and pigments	2.3[a]	1.5	0.9
Metal dusts	5.5[a]	3.0	1.5
Sawdust	[2]	[3]	1.5
Pesticides	3.0[b]	6.0[a]	7.0[a]

[a] $P < 0.05$.
[b] $0.05 < P < 0.10$.
[c] [1], three exposed cases and no controls; [2], four exposed cases and no controls; [3], two exposed cases and no controls.

prolonged exposure of either parent was increased to 11.38 in the youngest age group (Table 5). Although the magnitude of the OR estimate increased within the subgroup, the lower 95% confidence limit remained unchanged. Similar, although less marked, results were obtained for separate maternal and paternal analyses.

Morphology. Patients with the acute myelocytic (M1/M2) morphology ($n = 94$) and those with myelomonocytic (M4) or monocytic (M5) morphology ($n = 53$) were also analyzed separately for evidence that the risk factors might be specific to either of these major ANLL subgroups (Table 5). Odds ratios within the M1/M2 subgroup were not substantially different from those given in Table 3 for all patients combined, but the M4/M5 subgroup showed some specific associations of interest. For paternal exposure to solvents, the odds ratio for short (<1000 days) exposure was relatively unchanged at 3.7, but for prolonged exposure, the ratio became 5.6 ($P = 0.0004$ for trend). The association with pesticide exposure was substantially stronger in the M4/M5 subgroup than in the M1/M2 group. The high OR estimates and very wide confidence interval for the M4/M5 subgroup reflect the fact that two of the three individuals in the control group who reported pesticide exposure were matched to exposed cases, leaving only one pair discordant for exposure *versus* nonexposure. We attempted to refine the analysis further through restriction to M5 cases only, but the sample size was too small to provide useful results.

Although the variations in risk estimates across age and morphology groups were substantial, the numbers of exposed individuals in the subgroups were small, and the heterogeneity of odds ratios was not statistically significant.

Cytogenetic Abnormalities. There were 66 cases for whom cytogenetic analyses were performed and were considered adequate after central review of the karyotypes. Within this group, all but 16 had abnormal karyotypes, including several recurring abnormalities observed in myeloid leukemias: t(15;17) (6 cases); t(8;21) (9 cases); t(9;11) (4 cases); −7 (3 cases); +8 (11 cases); and +21 (4 cases). No significant associations of specific recurring abnormalities and occupational exposures were found. However, given the limited number of cases on whom data were available in conjunction with the low frequency of individual abnormalities and of specific exposures, this analysis had very little power to detect moderate correlations.

Household Exposures

Among the questions on nonoccupational exposures of child or parents were several that were directly relevant to this analysis. These included questions on maternal exposure to household flysprays, pesticides, garden or agricultural sprays, and petroleum products, in the month before the last normal menstrual period or during the index pregnancy. Treatment of the house by insect exterminators over the same period was also ascertained. Similar questions were asked concerning direct exposure of the child to household pesticides, garden sprays, and insect exterminations. Significant associations were present for *in utero* and postnatal pesticide exposure as well as postnatal exposure to petroleum products (Table 6). The frequency categories refer to frequency of use in the home.

Multivariate Analyses

The occupational exposures listed in Table 3 were reanalyzed while controlling for the possible confounding effects of the household exposures (for the variables shown in Table 6) and maternal marijuana use. Maternal marijuana had been found on an earlier analysis of this data set to be a significant risk factor (OR = 10.0, $P = 0.005$) (20). The only significance level to change substantially in the adjusted analyses was paternal exposure to solvents, which increased from 0.003 to 0.03 (OR = 1.4). Since solvent and petroleum product categories overlap, the effect on each factor of controlling for the other was examined: both significance levels decreased (to 0.05 and 0.03, respectively). The association of paternal solvent and ANLL risk became nonsignificant (OR = 1.2, $P = 0.23$) when controlled for both the household exposure (including marijuana

Table 5 *Odds ratio estimates for pesticide exposure (either parent) for restricted age groups and morphological subtypes*

Group	Total duration[a] (days)	Case	Control	OR	95% CI	*P* trend
All cases	None	142	156	1.0		
	1–1000	13	15	1.2	0.5–2.7	
	>1000	23	7	3.8	1.5–9.7	0.004
Age >5	None	77	80	1.0		
	1–1000	7	10	0.9	0.3–2.7	
	>1000	12	6	2.1	0.6–1.35	0.31
Age <5	None	65	76	1.0		
	1–1000	6	5	1.4	0.4–4.9	
	>1000	11	1	11.4	1.5–88.7	0.003
M1/M2 morphology	None	78	81	1.0		
	1–1000	5	8	0.8	0.2–2.8	
	>1000	11	5	2.3	0.7–7.8	0.20
M4/M5 morphology	None	42	50	1.0		
	1–1000	5	2	6.6	0.7–63.1	
	>1000	6	1	13.6	1.0–182.3	0.007

[a] Duration coded as >1000 if either the mother or the father was exposed for >1000 days.

Table 6 *Odds ratios for significant household exposures*

Exposure	Frequency	Case	Control	OR	95% CI	*P* trend
Pesticide[a] (mother)	None	134	148	1.0		
	<1/wk	50	40	1.4	0.8–2.2	
	1–2/wk	12	15	0.9	0.4–2.1	
	Most days	8	0			0.05
Pesticide (child)	None	128	148	1.0		
	<1/wk	46	33	1.8	1.0–3.0	
	1–2/wk	13	9	2.0	0.8–5.0	
	Most days	8	3	3.5	0.9–13.8	0.04
Petroleum products (child)	None	166	184	1.0		
	<1/mo	9	6	1.7	0.6–4.8	
	1–3/mo	14	4	4.7	1.3–16.6	
	More often	15	10	1.8	0.7–4.3	0.02

[a] *In utero* exposure of the child.

use) and paternal petroleum product exposure. In only one of the 11 families in which the mother reported marijuana use was there any report of parental occupational exposure to pesticides, indicating that these factors were not related. There was greater overlap between reported use of marijuana and household use of pesticides, but in an unmatched analysis of the risk associated with marijuana use, stratifying on levels of exposure to pesticides in the home, there was little change in the risk estimate.

Correlation of maternal and paternal occupational exposures is also possible, since work histories may be related. For this reason, the significance of maternal exposure to paints (which may represent solvent exposure) was assessed when controlling for paternal solvent exposure and was found to be no longer significant. The reverse was not the case: controlling for paint exposure did not decrease the significance of solvent exposure. In contrast, maternal exposure to metal dust, when controlled for paternal lead exposure, remained significant at $P = 0.03$. Controlling paternal lead exposure for maternal metal dust exposure similarly had little effect on the strength of association.

Finally, a forward stepwise logistic regression analysis was used to reduce the occupational factors (based on self-report) and related household exposures to a subset of independently significant variables. Variables were coded as shown in Tables 3 and 6, and at each step the variable with the smallest P value for trend (adjusted for all previously selected variables) was selected. The most significant univariate association was with parental occupational pesticide exposure ($P = 0.004$). The second variable to be included in the model was household pesticide exposure of the child, with a significance level of 0.01 (adjusted for parental occupational pesticide exposure). Three more variables were selected by the stepwise procedure: maternal metal dust and fume exposure (adjusted $P = 0.02$); paternal petroleum exposure (adjusted $P = 0.03$); and paternal exposure to plastics (adjusted $P = 0.04$). The most significant of the remaining (unselected) variables was maternal exposure to paints and pigments (adjusted $P = 0.06$).

DISCUSSION

In the search for environmental factors that could cause cancer in children, attention in recent years has been focused on the role of parental exposures and, particularly, on occupational factors (9, 21–30). Results from these studies have shown limited consistency and, in general, have not provided data to indicate how the occupational exposure might affect an offspring. Alternative mechanisms include a germ cell mutation prior to conception, transplacental fetal exposure, exposure through breast milk, or direct exposure postnatally to chemicals brought home on clothing. One reason for uncertainties in this area is that many of the studies have been limited in patients numbers, have grouped together diverse tumor types, or have attempted to infer exposure on the basis of a single job title, recorded in a medical record or on a birth or death certificate.

We report the results of the first large case-control study of children with ANLL. Since this malignancy in adults has been conclusively linked to several occupational exposures including benzene and other solvents (4, 5), and more tentatively associated with other factors including pesticides (12) and ionizing radiation (1), the possibility of an association between the child's illness and occupational exposures of either parent was examined in detail. Both parents were interviewed where possible, and a life-time job history obtained. Parents were asked about each job held and about possible exposure to 52 specific substances. The results show paternal solvent and petroleum product exposure and maternal pesticide exposure to be the most significant statistically ($P < 0.01$ for trend), with pesticide exposure being the only occupational risk factor common to both fathers and mothers. The largest relative risk estimates were for prolonged exposures to lead (father), and metal dusts, sawdust, and pesticides (mother), but the small number reporting prolonged exposures make these risk estimates subject to large random errors. It was not possible to pinpoint the period in relation to the pregnancy when exposure gave the greatest increase in risk, since patterns differed for the various substances, and the high correlation of exposure before, during, and after the pregnancy generally ensured that risk estimates for these periods were similar. We did not see higher ORs when the definition of exposure was confined to direct use of the products. For the mothers, this was not surprising, since the study had limited power to detect differences for occupational exposures that occurred infrequently (less than 2% of controls reported exposure to three of the factors found to be significant), and tightening the definition of exposure resulted in too few individuals exposed to be of practical use. For fathers, the elimination of indirect exposure (that is, exposure to chemicals used nearby but not directly handled by the respondent) had little effect on risk estimates.

Risk estimates related to pesticide exposure were substantially greater within the subgroup of cases with M4 and M5 morphology, and for those with disease occurring at young age, although formal tests of odds ratio heterogeneity were not significant. Since the M5 subtype is more common in younger children, the relationship with morphological subtype may be secondary to an age effect, or vice versa. We did not have a central review for pathology, and future studies should probably be designed to include pathology review to validate the institutional morphological classification. No relationship of exposure to a specific cytogenetic abnormality could be demonstrated, although the small number of cases with adequate karyotypes provided limited power to detect such associations. Of note, however, is that the recurring chromosomal abnormalities that are frequently present in the malignant cells of adult patients with ANLL who have occupational exposures (loss or deletion of chromosomes 5 and/or 7) were rarely observed in either the exposed or unexposed patients in this study.

Since we excluded families that were not English speaking or did not have a telephone, migrant farm laborers, who would be expected to be at high risk of heavy pesticide exposure, were presumably underrepresented in both the case and control samples. The likely effect of these exclusions is to bias the risk estimates towards unity and to reduce statistical significance. Another concern is with potential recall bias, due to better recall by case parents of either a wide range of past exposures or, more specifically, to certain exposures that have been linked in the media to cancer in general or leukemia in particular. The effect of any nonspecific recall bias must be small, since no systematic differences in responses were found for the vast majority of questions asked. Similarly, a general perception that chemicals such as pesticides are potentially hazardous to health should also be reflected in the results of our other studies on childhood cancers, which used very similar methodologies and questionnaire formats, and we have seen no evidence for this (results not shown). Recall bias is aggravated by the use of surrogate interviews, since information provided by mothers relating to their husbands' occupational exposures is likely to be less detailed and less accurate than that obtained directly from fathers, and there were more surrogate interviews for controls than for cases. We checked the possibility that the associations of solvents, petroleum products, and pesticides for

fathers were due to use of surrogate information, but found similar results in the unmatched analyses (excluding surrogate interviews). We did not attempt to verify exposures since it was felt that information obtained from employers by mail would generally be less reliable than that obtained from the case or control parent, and on-site visits were clearly not a practical proposition.

It is more difficult to discount the possibility of differences in recall that were confined specifically to leukemia and the substances found to be significant. Use of a job exposure matrix has the potential advantage of being less susceptible to recall biases and we had hoped that results from this analysis would support the self-report data. In fact, while the job exposure matrix results provided some support for the fathers' self-reported exposure for pesticides, such was not the case for the other findings. This could be interpreted as evidence for biases in the self-reporting of exposures. Alternatively, and we consider more probably, it could reflect a high level of misclassification for exposures inferred from job titles. It is important to appreciate that a job exposure matrix associates a group of individuals with a common job title, but perhaps quite varying responsibilities and environments, to a possible exposure. It does not necessarily link a specific person (in that job) to the exposure; only through further enquiry can it be determined whether or not a given individual was exposed.

Several direct exposures of the child were relevant to this analysis. Household pesticide and petroleum product exposures were statistically in the univariate analyses. A less direct household exposure, that was also significant, was maternal exposure to pesticides during the pregnancy. To assess the extent of confounding of these variables with the occupational factors, both sets of variables were included in the stepwise multivariate analysis. The selection of two measures of pesticide exposure (occupational and direct exposure of the child) as the first two variables reflects the relative strength of the dose-response relationship for these variables and indicates that the occupational and household exposures were largely independent. The other household exposures were not selected in the stepwise multivariate analysis.

The results from this study concerning maternal drug use have been published elsewhere (20), and the strongest association was with marijuana use during pregnancy. Interestingly, young children and those with M4/M5 morphology were disproportionately overrepresented in the marijuana-exposed group, a pattern also seen for the pesticide-exposed group. These observations were quite independent, however, since there was no overlap between the individuals with prolonged pesticide exposure (of the parents) and those exposed *in utero* to marijuana. Neither was the risk estimate for marijuana use altered substantially when the level of household use of pesticide was used as a controlling variable. Marijuana has been shown to have a direct effect on the immune system, particularly on monocytes (31), and it may be directly leukemogenic. An intriguing alternative is that smoking marijuana may provide a significant additional exposure to pesticides. Drug enforcement agencies have used aerial paraquat spraying of marijuana fields to combat marijuana growers, and paraquat contamination of marijuana has been measured in 4 to 21% of confiscated samples (32). Further, there are clearly no controls on the type and dose of pesticides that growers use on their marijuana crops to control insects and weeds.

The categories of substances that were inquired about (Table 1) are not mutually exclusive. For example, paints and pesticides may include organic solvents, and many petroleum products may be classified as solvents. Thus, the observed association of pesticides, solvents, and petroleum products (fathers), pesticides, paints, and pigments (mothers), and petroleum products (child) may represent a common exposure to solvents. In the multivariate analysis, both pesticide exposures and petroleum product exposures were seen to be important.

The association of cancer risk with maternal exposure to fabrication processes that involve metals is intriguing, since this occupational exposure has been previously reported for Wilms' tumor (25) and was found to be a significant risk factor for hepatoblastoma in a recently completed CCSG study.[7] In the multivariate analysis, maternal metal dust exposure remained significantly associated with ANLL risk after adjustment for pesticide and petroleum product exposure. We are not aware of supporting data from animal studies, nor of any commonality of ANLL with these two embryonal tumors, but clearly this association is one that warrants further research.

One of the three specific hypotheses for this study was that occupational exposure of the parent to ionizing radiation or exposure of the child to medical X-rays might increase risk. We found little evidence for an association with occupational exposure, although the number of mothers reporting exposure to ionizing radiation was small, and a larger study would be needed to detect small or moderate risk increases. A nonsignificantly elevated OR was found for occupational exposure of the fathers to radiation. There was no association with use of medical X-rays; findings from this study relating to nonoccupational exposures will be reported elsewhere.

In a case-control study of acute childhood leukemia in Shanghai (33), which included 94 ANLL cases, there was a significantly increased risk of ANLL for children of women working in metal refining and processing (OR = 4.6). This study also found significant associations with maternal exposure to benzene (OR = 4.0) and gasoline (OR = 2.1). Maternal pesticide exposure was associated with both acute lymphocytic leukemia (OR = 3.5) and ANLL (OR = 2.4), but only the former was statistically significant.

The results of this study provide a consistent pattern of association of ANLL risk with pesticide exposure and with a broadly defined "solvent" category that includes petroleum products and paints. The two-sided significance levels reported throughout must be regarded as conservative, since in most instances only one of the two alternatives to the null hypothesis was considered likely. This applies particularly to the three factors (pesticide exposure, solvent exposure, and ionizing radiation exposure) that were the primary focus of the study, based on *a priori* data implicating these factors as potential leukemogens; more caution must be exercised in interpreting the other positive findings, since examination of a relatively large number of possible exposures is likely to have produced some statistically significant findings by chance. Since both the mothers and fathers were asked about 9 major categories of exposure and 52 more specific exposures, there was a total of 122 exposures to be tested. Some of these were examined in a variety of ways (duration of exposure, direct *versus* indirect exposure, etc.), thus increasing the number of statistical tests carried out.

Solvents and pesticides are widely used in both industrial and domestic settings, and both categories include a large number of diverse chemicals. Unfortunately, we could not identify with any confidence the specific solvents or pesticides associated with ANLL risk. A priority for future research must be to narrow the search, either to one of the major classes of pesticides or solvents, or to a single agent.

[7] Unpublished observation.

APPENDIX

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