HALOGENATED SOLVENTS INDUSTRY ALLIANCE

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TO: HEALTH AND SCIENCE COMMITTEE

ARTICLE ON CHILDHOOD LEUKEMIA

Attached is a copy of a recently published case-control study linking childhood leukemia to parents exposure to solvents, spray paints, dyes, and other chemicals in the workplace and at home. This study may pose difficulties for us and should be taken seriously. We do not believe, however, that an adequate analysis can be performed by reviewing the data in the paper. Rather, investigators who are experienced in epidemiological surveys need to review the primary data (telephone interview protocol, survey materials, data tapes, etc.) for confounding factors and sources of bias. An independent analysis of this primary data is needed, whether internal experts or an outside consultant is utilized. We should discuss this paper at the next Committee meeting.

Daniel M. Byrd III
Director of Scientific Affairs

Attachment

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Childhood L ukemia and Par nts' Occupational and Hom Exposures [1,2]

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ABSTRACT—A case-control study of children of ages 10 years and under in Los Angeles County was conducted to investigate the causes of leukemia. The mothers and fathers of acute leukemia cases and their individually matched controls were interviewed regarding specific occupational and home exposures as well as other potential risk factors associated with leukemia. Analysis of the information from the 123 matched pairs showed an increased risk of leukemia for children whose fathers had occupational exposure after the birth of the child to chlorinated solvents [odds ratio (OR)=3.5, P=.01], spray paint (OR=2.0, P=.02), dyes or pigments (OR=4.5, P=.03), methyl ethyl ketone (CAS: 78-93-3; OR=3.0, P=.05), and cutting oil (OR=1.7, P=.05) or whose fathers were exposed during the mother's pregnancy with the child to spray paint (OR=2.2, P=.03). For all of these, the risk associated with frequent use was greater than for infrequent use. There was an increased risk of leukemia for the child if the father worked in industries manufacturing transportation equipment (mostly aircraft) (OR=2.5, P=.03) or machinery (OR=3.0, P=.02). An increased risk was found for children whose parents used pesticides in the home (OR=3.8, P=.004) or garden (OR=6.5, P=.007) or who burned incense in the home (OR=2.7, P=.007). The risk was greater for frequent use. Risk of leukemia was related to mothers' employment in personal service industries (OR=2.7, P=.04) but not to specified occupational exposures. Risk related to fathers' exposure to chlorinated solvents, employment in the transportation equipment-manufacturing industry, and parents' exposure to household or garden pesticides and incense remains statistically significant after adjusting for the other significant findings.—JNCI 1987; 79:39–46.

Several investigators have found a relationship between parents' occupation and cancer in children (*1–12*), while others have failed to demonstrate such a relationship (*13–16*). It has been suggested that the fathers' exposure to hydrocarbons during employment as motor vehicle mechanics, machinists, miners, painters, or motor vehicle drivers is responsible for an increased risk of childhood leukemia (*1, 4, 9*). In addition, mothers' exposure to hydrocarbons including paint, petroleum products, and unspecified chemicals during pregnancy is associated with a significantly elevated risk of leukemia (*12*).

Such studies of parental occupation and childhood cancer generally have relied on exposures inferred from job titles or industries, which may inadequately reflect actual exposures. Only one study has examined the relationship between specific parental exposures and childhood leukemia, but only up to the birth of the child (*12*).

We investigated possible etiologic factors for childhood leukemia in a matched case-control study. Specific exposures of both parents that occurred from 1 year before conception until shortly before the diagnosis of leukemia as well as other suspected risk factors for childhood leukemia were evaluated.

SUBJECTS AND METHODS

Selection of cases.—Cases were identified from the Los Angeles County Cancer Surveillance Program, a population-based cancer registry (*17*). Cases of acute leukemia were eligible for inclusion if they were 10 years of age or less at the time of diagnosis from 1980 through 1984 and if the biological mother was available for interview. All races were included.

The Cancer Surveillance Program identified 216 potential cases. The hospitals and attending physicians granted us permission to contact 202 (94%). We interviewed the mothers of 159 cases (79% of 202). Information about 154 case fathers was obtained: 124 fathers were interviewed directly and 30 case mothers answered questions about the fathers. Information could not be obtained for 5 case fathers. Of the 202 case families we attempted to contact, 23 were lost to follow-up, and 20 refused to participate.

ABBREVIATIONS USED: ALL=acute lymphocytic leukemia; ANLL=acute nonlymphocytic leukemia; CCl_4=carbon tetrachloride; ICD-O=International Classification of Diseases for Oncology (Morphology); MEK=methyl ethyl ketone; OR=odds ratio; PCE=perchloroethylene (tetrachloroethylene); TCE=trichloroethylene.

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Selection of controls.—Controls were selected when possible from among friends of the case. Early in the interview, each case mother was asked to name children who were her child's age, with whom the child spent time, or who were known to the family approximately 1 year before the date of diagnosis. If no such control child was available, a control was selected by random-digit dialing (*18*).

We interviewed the mothers of 136 controls: 65 were identified from among friends, and 71 were identified by random-digit dialing. Information about 130 control fathers was obtained: 87 fathers (67%) were interviewed directly, and 43 control mothers (33%) answered questions about the fathers. Information about the father could not be obtained for 6 control fathers (4%).

Each control was matched to the case on age, sex, race, and Hispanic origin for whites. All matching criteria were met for friend controls, but for random-digit-dial controls, matching criteria for race or ethnicity and sex were relaxed if no control was found after 150 telephone calls. This resulted in 3 controls who were not matched to cases on sex and 10 controls who were not matched to cases on race or ethnicity. All controls met specific age-matching criteria within 3 years of the case's age for cases older than 6 years of age at diagnosis, within 2 years of the case's age for cases 4–6 years old, and within 1 year of the case's age for cases under 4 years of age. The race of the child was determined by the race of any nonwhite parent. Caucasians who spoke Spanish as their native language were considered Hispanic. Matching by these criteria resulted in matching by socioeconomic status as determined by census tract of residence (*19*) in 84% of the case-control pairs. The socioeconomic status of the remaining 16% of controls was equally distributed above and below that of the cases.

Of 154 cases and 130 controls with interview information for both parents, 4 cases and 5 controls were eliminated from the analysis because complete occupational histories could not be obtained. Used for this analysis were 123 case-control pairs with complete information about both parents, including occupational histories.

The interview.—Our initial contact with each family was a telephone call in which we explained the study and asked the parents to participate. If they agreed, we scheduled a telephone interview with each of them. Interviews were conducted in English or Spanish by one of two trained interviewers during the years 1983–85. It was not feasible for interviews to be conducted blindly, but all questions were asked in a standard manner with the use of a structured interview.

Questionnaires sought information from the parents of cases and controls on experiences they had before, during, and after the index pregnancies and on experiences the children had from birth to the reference date. The reference date was defined to be 1 year before the date of diagnosis if the case was older than 2 years at diagnosis, 6 months before the diagnosis if the case was between the ages of 1 year and 2 years at diagnosis, and the same as the date of diagnosis if the case was under the age of 1 year at diagnosis. A complete occupational history was requested to the reference date. Questions were asked concerning job title, industry of employment, and time period in which parents worked with regard to the index pregnancy.

We asked about occupational exposures to the specific substances listed in table 1 and the frequency of exposure. The questionnaires also included questions on family and personal medical history, use of alcohol, tobacco, household and personal products, and exposure to x-rays. The mother's questionnaire included additional questions about the pregnancy, including medical complications, use of drugs and dietary consumption during pregnancy, and questions about the child's medical history and exposure to ionizing radiation.

Occupations and industries were coded using the 1970 U.S. Census Classification System. Occupations were grouped according to potential hydrocarbon exposure with the use of the narrow definition of Zack et al. (*14*). Occupations and exposures that occurred prior to 1 year before conception were excluded from the analysis.

Statistical analysis.—We maintained the matched-pair design in all aspects of the statistical analysis. Univar-

TABLE 1.—*List of specific occupational exposures on questionnaire*

Category	Specific occupational exposures
Solvents or degreasers	CCl_4 (CAS: 56-23-5), TCE (CAS: 79-01-6), PCE (CAS 127-18-4), MEK (CAS: 78-93-3), benzene (CAS: 71-43-2), toluene (CAS: 108-88-3), xylene (CAS: 1330-20-7), freon, other
Plastic materials[a]	Polyvinylchloride (CAS: 9002-86-2), polystyrene (CAS: 9003-53-6), polyethylene (CAS: 9002-88-4), polyurethane (CAS: 9009-54-5), other
Paints or pigments	Spray paints, other paints, dyes or pigments, printing inks, lacquers or stains
Oil or coal products	Cooling-cutting-lubricating oils, coal or graphite,[a] coal tar-soot-pitch-smudge, petroleum products-gasoline-kerosene
Metals[a]	Chromium (CAS: 7440-47-3), arsenic (CAS: 7440-38-2), beryllium (CAS: 7440-41-7), cadmium (CAS: 7440-43-9), lead (CAS: 7439-92-1), mercury (CAS: 7439-97-6), nickel (CAS: 7440-02-0), metal dust-fumes
Insulation material	Asbestos (CAS: 1332-21-4), fibrous glass, other insulation
Miscellaneous	Epoxy resins, formaldehyde (CAS: 50-00-0), rocket fuel, sulfuric acid (CAS: 7664-93-9), other acids-alkalies, pesticides-weed killers, synthetics (nylon, rayon, polyester),[a] sawdust, wood preservatives (creosote), grain dust, other
Radiation	Ionizing, nonionizing: radar, microwave ovens
Specific activities	Welding, soldering, rubber processing, rock crushing-drilling-polishing, leather processing

[a] Handling of finished product not included as an exposure.

iate and multivariate analyses and tests for trend were performed by the conditional logistic regression method [20]. A pair was eliminated from a particular analysis when either the case or the control parent did not answer the relevant question(s). All statistical significance levels quoted (P-values) are one-sided, with a P-value less than .05 considered statistically significant.

RESULTS

There were 61 male and 62 female cases whose mean age at diagnosis was 4 years. The racial and ethnic distribution of the cases was 52% non-Hispanic white, 38% Hispanic white, 4% black, and 6% Asian. This distribution is similar to that of all children with leukemia identified by the Cancer Surveillance Program. There were 107 cases with ALL (ICD-O codes 9820, 9821) and 16 cases with ANLL (ICD-O codes 9801, 9861, 9866, 9891).

Cases in the study versus cases not in the study showed similar ages (4 yr old vs. 4 yr old), similar sex distribution (50% females vs. 53% females), and a somewhat higher proportion of ALL (87% vs. 73%).

Fathers' Occupational Exposures

Table 2 shows the ORs for leukemia associated with industries in which the fathers worked at any time beginning 1 year prior to conception until the reference date. A statistically significant risk was associated with manufacturing of transportation equipment and machinery.

Fathers' exposure to chlorinated solvents, MEK, spray paint, dyes or pigments, and cutting oils after the birth of the child is significantly associated with leukemia (table 3). None of the other exposures about which we inquired (table 1) are statistically significant. Spray paint is the only statistically significant fathers' exposure that occurred during the mother's pregnancy with the index child (OR=2.2, P=.03), though the ORs for the other 4 substances in table 3 are elevated. For exposure that occurred prior to conception, no associations are statistically significant.

Case fathers with exposure to chlorinated solvents were exposed more frequently, on average, than control fathers in each of the 3 periods studied (table 4). Most of the case fathers and all of the control fathers were exposed during all 3 periods examined.

Frequency of occupational exposure to these substances was classified according to whether the substance was used less than 50 times per year or at least 50 times per year. Table 5 shows a statistically significant trend in the ORs with increasing exposure of the fathers to each of these substances.

The OR for chlorinated solvents remains statistically significantly elevated after adjusting for each of the other significant fathers' exposures. The ORs associated with the other 4 significant groups of substances remained elevated, although not statistically significant, after adjusting for exposure to chlorinated solvents (spray paint: OR=1.7, P=.07; dyes: OR=3.0, P=.08; MEK: OR=1.7, P=.23; cutting oil: OR=1.4, P=.16).

TABLE 2.—*Industries in which the father worked from 1 year prior to conception of the index child to reference date and risk of childhood leukemia*

Industry	Discordant pairs	OR	P-value	Confidence limits
Agriculture	6/6	1.0	.50	0.27-3.74
Construction	9/16	0.6	.92	0.22-1.35
Business[a]	25/36	0.7	.92	0.40-1.19
Personal service	4/0	∞	.39	0.66-∞
Entertainment	11/24	0.5	.98	0.20-0.97
Transportation[b]	13/9	1.4	.20	0.57-3.83
Manufacturing	36/18	2.0	.008	1.11-3.74
Transportation equipment[c]	15/6	2.5	.03	0.92-7.87
Aircraft	11/6	1.8	.12	0.62-6.04
Machinery	15/5	3.0	.02	1.04-10.55
Textiles	7/5	1.4	.08	0.38-5.59
Foods and drink	9/4	2.2	.09	0.63-9.99
Petroleum-chemicals	8/8	1.0	.50	0.33-3.06

[a] Includes trade, finance, business, and administration.
[b] Includes transportation, communication, and utilities.
[c] Includes aircraft, ship, boat, motor vehicle, and motor home manufacturing.

We reexamined the industries in which the fathers worked during this period after adjusting for the 5 exposures in table 3 after the delivery of the child. Only the fathers' employment in the transportation equipment-manufacturing industry remains significant (OR=2.4, P=.05). The excess risk may be partially explained by the following reported exposures: degreasing solvent—type unknown, 4/0 (cases/controls); epoxy, 1/0; freon, 2/0; or gasoline, 3/1. The degreasing solvents are likely to be chlorinated solvents, representing additional risk due to this class of solvent.

We grouped fathers' occupations according to whether the job might entail hydrocarbon exposure. Those occupations classified as hydrocarbon related are machinists, automobile mechanics, miners, lumbermen, painters, dyers, or cleaners. Although all ORs are elevated, we find no statistically significant association between hydrocarbon-related occupations and childhood leukemia for exposures that occurred within 1 year of conception (OR=1.7, P=.07) or for those that occurred during (OR=1.8, P=.07) or after (OR=1.6, P=.11) the index pregnancy.

Mothers' Occupational Exposures

Most of the mothers worked at some time: 1 year prior to conception, 73/69 (case/controls); during pregnancy, 70/67; or after pregnancy, 74/81. The mothers' employment in the personal service industries is associated with increased risk of childhood leukemia (OR=2.7, P=.04), with the following distribution of industries within this category: beauty shops, 4/0 (cases/controls); domestics in personal households or other lodgings, 7/4; and laundries, 1/1. Of the mothers who worked in these industries, 9 of 12 of the respective case fathers and 3 of 5

TABLE 3.—*Significant occupational exposures of the fathers and risk of childhood leukemia*

Exposure	Time period of exposure related to pregnancy									
	One year before pregnancy			During pregnancy			After delivery			
	Discordant pairs	OR	*P*-value	Discordant pairs	OR	*P*-value	Discordant pairs	OR	*P*-value	Confidence limits for after delivery
Chlorinated solvents	9/4	2.2	.09	9/4	2.2	.09	14/4	3.5	.01	1.10–14.60
CCl_4	2/3	0.7	.33	2/3	0.7	.33	5/3	1.7	.24	0.32–10.73
TCE	6/3	2.0	.16	6/3	2.0	.16	8/3	2.7	.07	0.64–15.60
PCE	1/0	∞	.39	1/0	∞	.39	2/0	∞	.39	0.19–∞
MEK	5/3	1.7	.24	5/3	1.7	.24	9/3	3.0	.05	0.75–17.23
Spray paint	18/13	1.4	.19	18/8	2.2	.03	24/12	2.0	.02	0.96–4.39
Dyes-pigments	7/2	3.5	.06	6/2	3.0	.09	9/2	4.5	.03	0.93–42.8
Cutting oil	19/14	1.4	.19	18/15	1.2	.30	27/16	1.7	.05	0.88–3.35

of the respective control fathers were exposed to 1 or more of the 5 substances that we found to be significant fathers' occupational exposures. We do not find any significant associations for mothers' exposures to the specific substances about which we inquired. Few mothers had occupational exposure to the 5 substances in table 3, and few were employed in hydrocarbon-related jobs.

Home Exposures

Table 6 shows the ORs for home exposures that the mothers experienced during the pregnancy or nursing period and the fathers experienced during the pregnancy. We find the strongest association between leukemia and the use by either parent of household pesticides (OR=3.8, P=.004). The OR remains elevated after adjusting for all of the fathers' significant occupational exposures (OR=4.0, P=.004) and for home use of garden sprays (OR=2.4, P=.06) or incense (OR=3.2, P=.01). The risk associated with either parent using garden sprays (pesticides and herbicides) also remains elevated after adjusting for all of the fathers' significant occupational exposures (OR=5.6, P=.01) and use by either parent of household pesticides (OR=4.1, P=.04) or incense (OR=6.0, P=.01).

We find a statistically significant elevation in risk of leukemia for children whose parents burned incense in the home before pregnancy or during the nursing period (OR=2.7, P=.007). The risk increases if the parents burned incense more than once per week (OR=3.7, P=.009). The risk for burning incense remains after adjusting for the 5 significant fathers' occupational exposures (OR=2.6, P=.01) and either parent's use of garden sprays (OR=2.3, P=.02) or household pesticides (OR=2.0, P=.05).

The OR for fathers' exposure to chlorinated solvents after the birth of the child remains statistically significant after adjusting for parents' home use of household or garden pesticides and burning incense.

The OR for mothers who used paint during pregnancy (OR=1.8, P=.03) is significantly elevated. The risk is reduced for those mothers who used paints more than once per week (OR=1.3, P=.30), suggesting that the elevation in risk of leukemia is a chance finding.

Personal Habits and Childhood Exposures

Adjusting for parents' smoking, drinking, and dietary habits and the mothers' medication usage during pregnancy does not significantly alter the above findings, nor does adjusting for the child's exposure to ultrasound or x-rays. These findings will be reported in more detail in a later publication.

For each of the major risk factors identified here, we examined risk by histologic type of leukemia; however, these analyses were restricted somewhat by the relatively

TABLE 4.—*Average frequency of fathers' exposure to chlorinated solvents by period of exposure*

Subjects	Time period of exposure related to pregnancy		
	One year before pregnancy, days/person/month	During pregnancy, days/person/month	One year after pregnancy, days/person/month
Cases	7.8 (n=9)	9.7 (n=9)	9.0 (n=12)[a]
Controls	1.8 (n=4)	1.8 (n=4)	1.8 (n=4)

[a] Of the 14 case fathers in table 3, 2 were exposed after the child's 1st yr of life. One father was exposed when the child was age 5; the other was exposed when the child was age 1. Both exposures were 2 yr before the diagnosis of leukemia.

TABLE 5.—*Frequency of fathers' exposure to chemicals after the birth of the child and risk of childhood leukemia*

Exposure	Frequency of use			*P* of trend[a] (one-sided)
	Never	Low (<50/yr) OR	High (≥50/yr) OR	
Chlorinated solvents	1.0	1.7	8.0	.03
Spray paint	1.0	1.8	2.5	.01
Cutting oil	1.0	1.0	1.5	.02
MEK	1.0	1.0	7.0	.03
Dyes or pigment	1.0	2 cases/0 controls	3.5	.04

[a] Trend of categorical variables: never, low, and high.

TABLE 6.—*Home exposures of mothers during pregnancy and nursing and fathers during pregnancy of the index child and risk of childhood leukemia*

Exposure	Either parent				Mother			Father		
	Discordant pairs	OR	*P*-value	Confidence limits	Discordant pairs	OR	*P*-value	Discordant pairs	OR	*P*-value
Household, ≥once/wk	19/5	3.8	0.004	1.37–13.02	13/4	3.2	0.02	12/3	4.0	0.02
Garden pesticides or herbicides, ≥once/mo	13/2	6.5	0.007	1.47–59.33	9/1	9.0	0.02	5/1	5.0	0.07
Burned incense during pregnancy, ≥once/wk	22/8	2.7	0.007	1.18–7.14	11/3	3.7	0.02	15/6	2.5	0.03
	15/4	3.7	0.009	1.20–15.52	13/1	13.0	0.007	12/4	3.0	0.03
Paint, lacquer during pregnancy, ≥once/wk	30/21	1.4	0.10	0.79–2.63	27/15	1.8	0.03	19/16	1.2	0.31
	6/4	1.5	0.26	0.36–7.23	4/3	1.3	0.30	2/2	1.0	0.50
Petroleum products during pregnancy, ≥once/wk	31/27	1.1	0.26	0.66–2.00	14/7	2.0	0.07	33/31	1.1	0.40
	24/34	0.7	0.10	0.40–1.23	13/16	0.8	0.27	23/29	0.8	0.20

small number of cases with ANLL. In general, the same risk factors appear to be important for ALL and ANLL. We examined the effect on the ORs of age at diagnosis (<4 yr vs. ≥4 yr), whether the mother breast fed the child, and source of the control (friend vs. random-digit dial); however, none of these factors significantly alters the ORs for any of the exposures studied. We also analyzed separately those case-control pairs in which both mother and father responded; again, the risk estimates are consistent with those reported here.

DISCUSSION

Our study has the advantage that both parents were interviewed regarding occupational exposure to specific substances 1 year prior to conception, during the index pregnancy, and after the child was born. Most previous studies concerning childhood cancer and parents' occupations have either focused on a narrower period of potential exposure or have used occupational title as stated on birth or death certificates or in interviews to infer exposures. Our study did not attempt to confirm the stated exposures from the employers.

Systematic recall bias is a potential concern in studies relying on interview data, but such bias seems an unlikely explanation for the findings in this study because we could not document a general tendency toward elevated ORs for chemical exposure and because we found no significantly elevated ORs for mothers' exposures. Recall bias for industry or occupation is less likely, and in this study, risks associated with industries tended to confirm the results of inquiries about specific exposures. More control mothers than case mothers supplied occupational histories for the fathers, and they may not have known the specific substances to which the fathers were exposed. However, eliminating the pairs in which there was a surrogate interview from the analysis did not materially change the risks.

We reduced confounding by matching controls to cases. Friend controls may have over-matched for occupation of the parents, thus reducing the chances of finding significantly elevated OR.

After controlling for the fathers' exposure to chlorinated solvents, the fathers' exposure to spray paint, dyes or pigments, MEK, and cutting oil does not remain statistically significant; however, the ORs remain elevated. The small number of case-control pairs in the study may limit the ability to detect independent risks due to these substances because fathers who are exposed to one of these substances are more likely to be exposed to the others.

We were unable to assess the intensity of the exposures and, therefore, used frequency to estimate dose. Of the case and control fathers who reported exposure to chlorinated solvents, case fathers were exposed more frequently than control fathers regardless of exposure period, thus suggesting a dose-response relationship. The increase in the risk associated with increase in frequency of use seen for all of the 5 significant substances to which the fathers were exposed also lends support to independent effects of the 5 substances.

Our findings of significantly elevated risk of childhood leukemia associated with fathers' exposure to chlorinated solvents, MEK, spray paint, dyes or pigments, and cutting oils are consistent with previous investigations that have demonstrated elevated risks for leukemia in children whose fathers are employed in occupations where exposure to hydrocarbons may occur (*1, 4, 9*). These occupations include painters and machinists, who are likely to be exposed to spray paint and cutting oils and possibly to chlorinated solvents, MEK, or dyes. Motor vehicle drivers studied by Vianna et al. (*9*) may be exposed to these substances if they are involved in vehicle maintenance. As in other studies, we do not find statistically significantly elevated risks associated with hydrocarbon-related occupations of the fathers (*3, 12–16*). A likely explanation is that job titles misclassify particular exposures because persons with the same job title may have different exposures.

There is evidence in the literature that 4 of the 5 implicated exposures of the father in this study are carcinogenic in adult humans or in animals. Chlorinated solvents, including TCE, PCE, and CCl_4, have been found to cause cancer in laboratory animals (*21, 22*). It has been suggested that dry cleaners exposed primarily to PCE but also to TCE, CCl_4, and petroleum solvents may have higher mortality rates due to lung and cervical cancers and a slight excess of mortality due to leukemia

(*23*). Data regarding the carcinogenicity of TCE, CCl_4, and PCE are inadequate to determine carcinogenicity in humans (*22*), although fathers of children with brain tumors are more likely to be exposed to chlorinated hydrocarbon solvents than controls (*6*). It has been suggested that painters in the construction industry (*24–26*), artistic painters (*27*), and lacquer workers in the paints and coatings industry (*28*) have elevated mortality due to leukemia. There is evidence that many dyes are human carcinogens (*29–31*), and Van Steensel-Moll et al. (*12*) demonstrated a relative risk of 2.0 (95% confidence interval, 0.4–11.0) for children whose fathers worked with pigments (50% paints) (*12*). Workers exposed to cutting oils may have elevated risks for cancer (*32–34*). MEK is not known to be carcinogenic in animals or humans (*35*), although it was associated with childhood brain tumors in our previous study.

Previous studies have suggested an elevated risk of childhood cancer associated with fathers who work in the aircraft industry or the Air Force (*5, 6, 8, 9*). Our study demonstrates a significantly elevated risk for children whose fathers worked in the transportation equipment-manufacturing industry, most of whom worked in aircraft manufacturing. Most of this risk can be explained by exposure of the fathers to the 5 significant substances already discussed if unclassified degreasing solvents are included among chlorinated solvents.

Our study demonstrates an elevation in risk for leukemia in children whose mothers worked in personal service industries, which may be explained by exposures of the fathers. We are unable to demonstrate an elevated risk due to exposures of the mothers to specific substances. We are unable to confirm previous findings of elevated risk associated with mothers who worked as bakers, as pharmacists, or in hydrocarbon-related occupations (*4, 12*), but there were few mothers in these occupations. We are also unable to confirm elevated risk due to mothers' exposure to solvents (*12*). We actually find an OR less than 1 for mothers exposed to any solvents at work, and an insufficient number of mothers were exposed to any one type of solvent to allow for meaningful analysis. We find an elevated risk of childhood leukemia if the mother used paint or lacquer at home during the index pregnancy, in agreement with Van Steensel-Moll et al. (*12*). We are unable to demonstrate a dose-response relationship, as the risk is reduced for mothers who used paints more than once per week and the risk is not elevated for exposures during the nursing period, suggesting that this is due to chance.

We find elevated risks for children whose parents used pesticides in the home or garden and for those whose parents burned incense at home during the pregnancy or while nursing the child. We find that the mothers' use of these substances is associated with a higher risk than the fathers' use of the same substances at home. This may indicate that the pregnancy is an important time period for exposures associated with leukemia. It is unfortunate that we did not ask about the use of these substances after the delivery of the child for the mothers who did not nurse and after the nursing period for those who did nurse, in light of the higher risks due to occupational exposure after the birth of the child in this study. It seems reasonable, however, to assume that patterns of use of these substances are similar after the delivery of the child and that indeed this could be the time of greatest risk. We plan to re-interview these families to gain more insight into the relationships between these exposures and leukemia. We do not find an elevated risk for the children whose parents were exposed to pesticides at work, perhaps because direct exposure to the child is likely to be lower than if the pesticides are used in the home.

It has been suggested that pesticides can cause leukemia, neuroblastoma, brain tumors, and hematologic abnormalities in children (*36–39*). Farmers, who may be exposed to pesticides and herbicides, have been shown to have elevated risks of leukemia, lymphoma, and other cancers (*40*).

A study of childhood brain tumors also showed a significantly elevated risk for children whose parents burned incense in the home (*41*). Burning incense releases benzo[*a*]pyrene, several other polycyclic aromatic hydrocarbons, and sinapaldehyde (*42, 43*). Derivatives of sinapaldehyde and related aldehydes may cause nasal cancer in rats (*44*) and nasopharyngeal cancer in furniture workers and in inhabitants of Kenya exposed to these compounds in angiospermous wood (*45*).

All but 2 fathers exposed to chlorinated solvents after delivery were exposed during the child's 1st year of life. The occupational exposure after delivery and during pregnancy often overlapped; 9 case fathers and all of the control fathers were exposed during all 3 periods. Therefore, the separate effect of exposure *only* after delivery could not be assessed. The age of the children at the reference date did not differ between the children whose fathers were exposed and those who were not exposed to chlorinated solvents after delivery of the child. Fathers may have better recall of the specific substances to which they are more recently exposed, biasing toward the null the results of questions about specific exposures in the more distant past. Our results are consistent, however, with the experimental literature that suggests that mice are more likely to develop leukemia if administered carcinogenic compounds soon after birth rather than in utero or as adults (*46–48*).

Children may be exposed to the substances with which their parents work because the parents bring home these substances on their skin or clothes or in their exhaled air. Chlorinated solvents have been demonstrated in the exhaled air of workers for many hours after exposure (*49, 50*). Mothers may expose the children through breast milk. PCE has been detected in the breast milk and blood of a mother who visited her husband daily at a dry cleaning establishment (*51*). Her 6-week-old breast-fed infant developed obstructive jaundice and hepatomegaly not explained on the basis of other causes. We are unable to demonstrate a significant difference between the responses of the cases and controls with regard to questions about inhaling chemicals or getting them on their skin or clothes; however, most

case and control fathers brought their clothes home from work. We investigated the hypothesis that mothers who nursed may expose their children in this manner. Not controlling for breast feeding (≈50% of mothers) did not significantly affect the ORs.

Further study is warranted to investigate the role of chlorinated solvents, spray paint, dyes and pigments, cutting oil, MEK, pesticides, and incense in the etiology of childhood leukemia. In addition, verification of reported exposures is important to accomplish. Special attention should be paid to the time at which exposure to the parents occurs with relation to the index pregnancy, in order to shed light on possible mechanisms of carcinogenesis.

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