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Cancer Risk and Parental Pesticide Application in Children of Agricultural Health Study Participants

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Abbreviations

AHS	Agricultural Health Study
CI	Confidence interval
OR	Odds ratio
SEER	Surveillance, Epidemiology, and End Results
DDVP	Dichlorvos
EPTC	Ethyl dipropylthiocarbamate

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Abstract

Parental exposure to pesticides may contribute to childhood cancer risk. Through the Agricultural Health Study (AHS), a prospective study of pesticide applicators in Iowa and North Carolina, we examined childhood cancer risk and associations with parental pesticide application. Identifying information for 17,357 children of Iowa pesticide applicators was provided by parents via questionnaires (1993-1997) and matched against the Iowa Cancer Registry. Fifty incident childhood cancers were identified (1975-1998). Risk of all childhood cancers combined was increased (standardized incidence ratio (SIR)=1.36; 95% CI=1.03, 1.79). Risk of all lymphomas combined was also increased (SIR=2.18; 95% CI=1.13, 4.19), as was risk of Hodgkin's lymphoma (SIR=2.56; 95% CI=1.06, 6.14). Logistic regression was used to explore associations between self-reported parental pesticide application practices and childhood cancer risk. No association was detected between frequency of parental pesticide application and childhood cancer risk. An increased risk of cancer was detected among children whose fathers did not use chemically resistant gloves (OR=1.98; 95% CI=1.05, 3.76) compared with children whose fathers used gloves. Of sixteen specific pesticides used by fathers prenatally, ORs were increased for aldrin (OR=2.66), DDVP (OR= 2.06), and ETPC (OR=1.91). However, these results were based on small numbers and not supported by prior biologic evidence. Identification of excess lymphoma risk suggests that farm exposures including pesticides may play a role in the etiology of childhood lymphoma.

Introduction

Despite advances in treatment, cancer remains a leading cause of childhood mortality (Ries et al. 1999), and its etiology remains poorly understood (Chow et al. 1996). Exposure to pesticides has been implicated as a possible contributing factor in the pathogenesis of childhood cancer (Daniels et al. 1997; Zahm and Ward 1998), and several pesticides are carcinogenic in bioassays (IARC 1986). In two reviews (Daniels et al. 1997; Zahm and Ward 1998), parental pesticide use was fairly consistently associated with acute lymphocytic leukemia and central nervous system tumors, the two most common childhood cancers, and less consistently with Wilms' tumor, Ewing's sarcoma, and soft tissue sarcomas.

Associations between parental pesticide use and childhood cancer risk have been linked to either the mother or father. Evidence from animal models suggests that exposure of the father during the preconceptional time period may be especially important (Buckley 1994). Although not well investigated, critical time windows for childhood carcinogenesis may include the preconceptional, intrauterine, and postnatal periods (Anderson et al. 2000; Olshan et al. 2000). Several previous studies have examined the relationship of paternal pesticide exposure to childhood cancer by using paternal occupation in farming as a proxy for pesticide use (Gold et al. 1982; Hemminki et al. 1981; Kristensen et al. 1996; Magnani et al. 1990; Roman et al. 1993). However, inferring pesticide exposure from paternal occupation can be an imprecise means of exposure assessment (Gold and Sever 1994). Most previous studies of pesticides and childhood cancer lack detailed information on the frequency of specific pesticide exposures, on the nature of job tasks involving pesticides, and on the possible effect of pesticide protection practices (Daniels et al. 1997; Olshan and Daniels 2000).

The Agricultural Health Study (AHS), a large, prospective cohort of licensed pesticide applicators and their families in Iowa and North Carolina, was designed to examine the relationship of pesticide exposure to adult chronic diseases and has assembled detailed information on pesticide use by farmers and their spouses (Alavanja et al. 1996). In this report we examine cancer risk among children of pesticide applicators, and draw upon the detailed pesticide exposure data provided by AHS participants to explore the relationship of childhood cancer risk to parental pesticide application practices, including specific chemical use, frequency of exposure, and protective practices employed.

Methods

The AHS is a collaborative effort of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the United States Environmental Protection Agency. The design of the AHS is discussed in detail elsewhere (Alavanja et al. 1996). Briefly, it is a large prospective study of certified pesticide applicators and their spouses in Iowa and North Carolina. Persons applying for pesticide application licenses between 1993 and 1997 in North Carolina and Iowa were asked to participate in the study. Both private pesticide applicators (largely farmers) and commercial pesticide applicators (Iowa only) were enrolled. These analyses are limited to private pesticide applicators (farmers) because information about children was collected only from private applicators' spouses. Approximately 82% of eligible private pesticide applicators (N=52,395) were enrolled (Gladen et al. 1998). At enrollment, pesticide applicators were asked to complete a questionnaire providing information on pesticide application practices and health-related behaviors and additional details on pesticide use and work practices were obtained in

take-home questionnaires. Spouses were enrolled through a questionnaire brought home by the licensed applicator or by telephone. Females (applicators and spouses; N=20,625) were also asked to complete a questionnaire on female and family health that collected information on children born during or after 1975, including names, dates of birth, and social security numbers. A total of 21,375 children born during or after 1975 were enumerated by their mothers. Of these children, 17,357 (81%) resided in Iowa and 4,018 (19%) resided in North Carolina. A subsequent linkage of mothers and fathers to Iowa birth certificates indicated that the enumeration of children via questionnaires was accurate, as 95% of these children were verified through birth certificate linkage (Romitti P, personal communication).

We used a hybrid study design, in which the prospective cohort of pesticide applicators was formed between 1993 and 1997, and cancer cases among their children were both retrospectively and prospectively identified following parental enrollment. Identifying information for children in Iowa was matched against the Iowa Cancer Registry to identify cases of childhood cancer arising between 1975 and 1998. Childhood cancer was defined as cancer diagnosed from 0-19 years of age, which conformed with the standard SEER childhood cancer classification (Ries et al. 1999). Through this linkage, 50 cancers in children of AHS participants aged 0-19 years were identified; 37 cases were a perfect match and the remaining 13 cases were matched on name and birth date and verified using birth certificate and drivers' license databases.

A similar linkage was performed with the North Carolina Central Cancer Registry for the period 1990 to 1998. The starting point was later in North Carolina because the cancer registry was not fully operational until 1990. A matching algorithm based on names, dates of birth, and social security numbers initially identified 6 cancer cases among North Carolina children

between 0 and 19 years of age. Two of these cases were subsequently excluded since they were not invasive malignancies; the remaining four were leukemia, brain tumors, and bone tumors. Due to the small number of North Carolina cases, subsequent analyses were restricted to Iowa children.

A standardized incidence ratio (SIR) was generated to compare the observed number of childhood cancer cases identified among children of AHS participants to the expected number. The expected number of cancer cases was generated by applying age, sex, race, and time period-specific childhood cancer rates from Iowa SEER data to the person-years contributed by eligible children in the sample, according to the method of Breslow and Day (1987).

Pesticide exposure data were obtained from self-reports by applicators and spouses. The questionnaires are available in electronic format (Agricultural Health Study Data Working Group 2002). We focused on parental pesticide mixing and application, because these tasks are associated with potentially high exposure. General questions included whether applicators personally mixed and applied pesticides (ever/never), frequency of pesticide mixing and application (days per year), and whether they personally mixed and applied pesticides more than 50% of the time when pesticides were used or required mixing (yes/no). Information on ever use of 50 specific pesticides was obtained via the enrollment questionnaire. Detailed exposure information (decade of first use, and frequency and duration of use) was solicited for 22 pesticides in the initial questionnaire, and for 28 additional pesticides in the take-home questionnaire. Applicators' responses regarding decade of first use and duration of use were used to create dichotomized exposure variables that indicated whether each specific pesticide had been used prior to the child's birth. Children for whom timing of use was missing were excluded from this analysis. Individual pesticides were treated as separate exposure variables in the

analysis when there were 5 or more exposed cases. Individual pesticides were also grouped into classes (organophosphates, organochlorines, carbamates, chlorphenoxy compounds, and pyrethroids) to create exposure variables based on potentially similar mechanisms of pesticide action. Applicators were also asked to indicate whether they generally used protective equipment, such as chemically resistant gloves during pesticide application.

Though fathers were the primary licensed applicators in most households, mothers were also asked about mixing and application of pesticides (ever/never), and frequency and duration of pesticide mixing and application. Mothers were asked about mixing and application of 50 different individual pesticides, but they were not asked to provide information about timing, frequency, or duration of use for individual pesticides. For 17,280 children, the father was the primary licensed pesticide applicator. For seventy-six children, including one cancer case, the mother was the licensed pesticide applicator. Therefore, when the mother was the applicator, her data were more detailed than that of the remaining mothers, whereas the father's data was less detailed than that of the majority of fathers who were the applicator. This made it difficult to combine data for children whose mother was the applicator with that for children whose father was the applicator. The seventy-six children whose mothers were the licensed applicators were therefore eliminated from analyses of specific parental exposures. Although mothers who were applicators had potentially higher levels of exposure, there were too few of them for a stand-alone analysis.

Logistic regression analyses were used to compute odds ratios (OR) and 95% confidence intervals (CI), using SAS® version 8 software (SAS Institute 2001. Cary, NC) to examine the association between pesticide exposure variables and childhood cancer. Multiple logistic regression models were also created to examine potential confounders of cancer risk. Parental

age at child's birth, child's gender, child's birth weight, history of parental smoking (ever/never), paternal history of cancer, and maternal history of miscarriage were explored as potential additional confounders in bivariate analyses but were not significant and were excluded from final models. Race of child was not explored as a potential confounder because the sample included very few nonwhite children. Child's age at parent's enrollment in the study was related to cancer risk (beta coefficient=0.06; p=0.02) and was included in final models.

The Agricultural Health Study and linking of AHS data with the Iowa and North Carolina Cancer Registries was approved by the Institutional Review Boards of the National Cancer Institute, the National Institute of Environmental Health Sciences, the University of Iowa, and Battelle.

Results

Children of AHS participants were predominantly white, with slightly fewer females than males (**Table 1)**. In Iowa, the majority of farms on which children reside produce grains and livestock, with field corn as the most common farm product. Most children were between 5 and 19 years of age at the time of study enrollment. Mean maternal and paternal age at enrollment was 39 and 41 years, respectively.

Standardized incidence ratios (SIRs) were generated only for Iowa (n=50) due to the small number of cases in North Carolina (n=4). The expected total number of cancer cases in Iowa was 37, yielding a standardized incidence ratio of 1.36 (95% CI=1.03, 1.79). When tumor-specific SIRs were generated, more lymphoma cases were observed (n=9) than expected (SIR=2.18, 95% CI=1.13, 4.19). More cases were also observed than expected for brain tumors

(SIR 1.60; 95% CI=0.89, 2.89), neuroblastoma (1.26; 95% CI=0.40, 3.89), retinoblastoma (SIR=1.63; 95% CI=0.41, 6.53), Wilms' tumor (SIR=1.56; 95% CI=0.50, 4.84), and bone tumors (SIR=2.19, 95% CI=0.82, 5.84), but there were small numbers of these tumors.

SIRs for individual lymphoma subtypes were also examined. An increased incidence of Hodgkin's lymphoma was observed (SIR=2.56; 95% CI=1.06, 6.14). Increased incidences of Burkitt's lymphoma (SIR=2.67; 95% CI=0.37, 19.0) and non-Hodgkin's lymphoma (SIR=1.18; 95% CI=0.29, 4.70) were observed, but few cases of these tumor types were present **(Table 2)**.

Due to the small number of cancer cases identified, results of exposure analyses are presented only for factors involving five or more exposed cases (**Table 3).** All fathers reported applying pesticides, 72% reported mixing them personally more than 50% of the time, and 77% reported applying pesticides personally more than 50% of the time that they were used on the farm. No difference in cancer risk was observed for children whose fathers personally mix pesticides more than 50% of the time, compared with those whose fathers personally mix less than 50% of the time (OR=1.02; 95% CI=0.51, 2.06). Cancer risk was similar for children whose fathers personally apply pesticides more than 50% of the time, compared with children whose fathers apply pesticides less than 50% of the time (OR=0.74; 95% CI=0.37, 1.51). No relationship was detected between paternal frequency of application and childhood cancer (p trend=0.12). When use of protective equipment was examined, children of fathers who reported that they generally did not wear chemically resistant gloves (16%) had a twofold excess of childhood cancer risk (OR=1.98; 95% CI=1.05, 3.76). Of the 49 children who developed cancer, 47 had fathers who initiated pesticide application prior to the child's cancer diagnosis date; data on date of initial pesticide application was missing for the remaining 2 children's fathers.

Though the male spouse was the primary applicator, 58% of the mothers also reported ever mixing or applying pesticides **(Table 4).** No difference in cancer risk was observed for children whose mothers ever mixed or applied pesticides compared with those whose mothers did not (OR=0.73; 95% CI=0.41, 1.29). Children whose mothers applied pesticides fewer than 5 days per year had a lower risk of cancer than children whose mothers reporting never mixing or applying pesticides (OR=0.30; 95% CI=0.10, 0.86). For children whose mothers mixed or applied pesticides between 5 and 19 days per year (OR=0.90; 95% CI=0.42, 1.95), or greater than 19 days per year (OR=1.41; 0.42, 4.72), cancer risk was similar to children whose mothers never mixed or applied pesticides (referent).

No significant associations were observed between maternal application of specific pesticides and childhood cancer risk **(Table 5).** For fathers, a statistically significant increase in cancer risk was associated with exposure to aldrin prior to conception (OR=2.66; 95% CI=1.08, 6.59). The six childhood cancer cases which followed paternal prenatal aldrin exposure varied in site and morphology (data not shown). Excess risks that were not statistically significant were observed for dichlorvos (DDVP) and ethyl dipropylthiocarbamate (EPTC). Odds ratios for exposure to specific pesticide classes were each near 1.0.

We also examined associations between lymphoma and animal exposures. We observed a suggestive association with raising any farm animals (OR=2.38; 95% CI=0.30, 19.0; 8 exposed cases) and with raising cattle specifically (OR=4.13; 95% CI=0.86, 19.9; 7 exposed cases); however, there were too few exposed cases to evaluate further.

Discussion

The Agricultural Health Study provides a unique opportunity to examine cancer risk among children of farmer pesticide applicators whose pesticide exposure has been well characterized. This study detected a modest increase in childhood cancer risk among children of Iowa participants in the AHS. When specific cancer types were examined, risk of childhood lymphoma was twofold higher among children of AHS participants compared with the general population. The risk of Hodgkin's lymphoma specifically was increased. We did not detect an association between cancer risk and either paternal or maternal frequency of exposure. Father's lack of use of chemically resistant gloves was associated with increased childhood cancer risk. Although based on small numbers, it is possible that this finding may identify a high-risk application practice.

Our study is one of several to suggest that children of parents who are occupationally exposed to pesticides incur an increased risk of childhood cancer (Buckley et al. 1989; Daniels et al. 1997; Kristensen et al. 1996; Shu et al. 1988; Zahm and Ward 1998). Previous studies have most consistently implicated pesticide exposure in leukemia (Buckley et al. 1989) and central nervous system tumors (Daniels et al. 1997; Zahm 1999) and more recently neuroblastoma (Daniels et al. 2001). Our study did not detect an increased risk of these tumor types, but did suggest an increase for childhood lymphoma.

Few studies have previously examined risk of childhood lymphoma in association with pesticide exposure (Kristensen et al. 1996; Leiss and Savitz 1995; Schwartzbaum et al. 1991). Increased risk of non-Hodgkin's lymphoma in association with paternal or maternal pesticide exposure was previously reported (Kristensen et al. 1996; Leiss and Savitz 1995), but associations have not been reported for Hodgkin's disease (Kristensen et al. 1996; Schwartzbaum et al. 1991). In adult studies, pesticide exposure has been more frequently

implicated in non-Hodgkin's lymphoma (Dich et al. 1997; Persson 1996), though a few studies have also suggested an association with Hodgkin's lymphoma (Hardell et al. 1981; Persson et al. 1989; Persson et al. 1993). Adult epidemiologic studies have specifically implicated organochlorines (Hardell et al. 2001; IARC 1991), organophosphorus compounds (Cantor et al. 1992; Zahm et al. 1990), and phenoxy herbicides (Hoar et al. 1986; Zahm and Blair 1992; Zahm et al. 1990) in excess lymphoma risk. A recent study of children of pesticide applicators in Sweden also described an increased risk of Hodgkin's lymphoma (SIR=1.36; 95%CI=0.44, 3.17), though numbers of cases were too small to be conclusive and levels of pesticide exposure were not reported (Rodvall et al. 2003). This and other recent reports of increased lymphoma risk in relation to pesticide exposure (De Roos et al. 2003) strengthen the biologic plausibility of an association between pesticide exposure and lymphoma. It is also possible that the excess lymphoma incidence identified in our cohort represents exposure to a risk factor that we were unable to examine, such as Epstein-Barr virus infection (McCunney 1999).

Despite finding an overall increase in childhood cancer risk among children of pesticide applicators, we did not detect an increase in childhood cancer risk with increasing maternal or paternal frequency of pesticide exposure. The small numbers of cases and limited statistical power may have prevented us from detecting associations between frequency of pesticide use and childhood cancer risk. Our findings on mothers are limited because we lacked data on timing of exposures in relation to the child's birth. Additionally, our assessment of fathers' prenatal exposure was based on the decade of first use of pesticides and duration of use, which constitutes a broad time window. Therefore, we are unable to state whether pesticide exposure occurred only in the immediate prenatal or preconceptional time periods, or within a broader time window before the child's birth. Since farmers are reasonably accurate in supplying decade

of first use and duration of use of pesticides, (Blair et al. 2002; Hoppin et al. 2002), we are reasonably confident that prenatal paternal exposures were classified accurately. Further, pesticide exposure does appear to have preceded children's cancer diagnosis date in all cases for which timing of initial paternal pesticide application was available, strengthening the case that pesticide application temporally preceded childhood cancer. Finally, the increased childhood cancer risk in the cohort could actually reflect a factor other than pesticide exposure that we were not able to examine. The possibility that increased cancer risk within the cohort is unrelated to pesticide exposure must be considered, since we explored associations between many individual pesticides and detected few associations with cancer risk, and we did not detect a dose-response relationship between parental pesticide exposure and cancer risk.

Though power was limited for many detailed exposure analyses, we did detect an association between paternal prenatal exposure to aldrin and childhood cancer. This could be a chance finding, because recent reviews have suggested that aldrin is unlikely to have significant carcinogenic potential (IARC 1987; Sielken et al. 1999; Stevenson et al. 1999). This finding should be interpreted with caution given the lack of evidence of carcinogenicity, and lack of associations between other specific pesticide exposures and childhood cancer in our study.

The finding of an increased risk of childhood cancer associated with lack of chemically resistant glove use by the father deserves attention. Lack of glove use could reflect direct exposure to pesticides to the applicator (Rutz and Krieger 1992) and indirectly to children. Alternatively, lack of glove use could be a marker for less meticulous chemical practices in general, which could increase the opportunity for exposure to children on the farm. Such behavior has been associated with an increased risk of high pesticide exposure events (Alavanja et al. 2001) and thus may also be an indicator of less cautious handling of pesticides.

In conclusion, our study detected a small increase in risk of all childhood cancers combined, and lymphomas specifically, in a pesticide-exposed agricultural population. Our data suggest a modest increase in cancer risk among children of men who apply pesticides but do not use chemically resistant gloves, and among children of men who use aldrin prior to conception. The finding of increased lymphoma risk warrants further exploration in future studies, with improved ascertainment of pesticide exposure during critical time periods, and attention to exposure to specific chemical classes and other farm exposures.

References

Agricultural Health Study Data Working Group 2002. Agricultural Health Study Questionnaires. Bethesda, MD: National Institutes of Health. Available: http://www.aghealth.org/questionnaires.html [accessed 4 August 2003].

Alavanja MCR, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. 1996. The Agricultural Health Study. Environ Health Perspect 104:362-369.

Alavanja MCR, Sprince NL, Oliver E, Whitten P, Lynch CF, Gillette PP, et al. 2001. A nested case-control analysis of high pesticide exposure events from the Agricultural Health Study. Am J Ind Med 39:557-563.

Anderson L, Diwan BA, Fear NT, Roman E. 2000. Critical windows of exposure for children's health: Cancer in human epidemiological studies and neoplasms in experimental models. Environ Health Perspect 108:573-594.

Blair A, Tarone R, Sandler DP, Lynch CF, Rowland AS, Wintersteen W, et al. 2002. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13:94-99.

Breslow NE, Day NE. 1987. The design and analysis of cohort studies. IARC Sci Publ 82:178-229.

Buckley J. 1994. Male-mediated developmental toxicity: Paternal exposures and childhood cancer. In: Methods and Concepts in Detecting Abnormal Reproductive Outcomes of Paternal Origin (Olshan AF, Mattison DR, eds). New York:Plenum Press;169-175.

Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, et al. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Children's Cancer Study Group. Cancer Res 49:4030-4037.

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, et al. 1992. Pesticides and other agricultural risk factors for non-Hodgkins lymphoma among men in Iowa and Minnesota. Cancer Res 52:2447-2455.

Chow W, Linet MS, Liff JM, Greenberg RS. 1996. Cancers in children. In: Cancer Epidemiology and Prevention (Schottenfeld D, Fraumeni JF, eds). New York:Oxford University Press;1331-1363.

Daniels JL, Olshan AF, Savitz DA. 1997. Pesticides and childhood cancers. Environ Health Perspect 105:1068-1077.

Daniels JL, Olshan AF, Teschke K, Hertz-Picciotto I, Savitz DA, Blatt J, et al. 2001. Residential pesticide exposure and neuroblastoma. Epidemiology 12:4-6.

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, et al. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 60:e11.

Dich J, Zahm SH, Hanberg A, Adami H-O. 1997. Pesticides and cancer. Cancer Causes Control 8:420-443.

Gladen BC, Sandler DP, Zahm SH, Kamel F, Rowland AS, Alavanja MCR. 1998. Exposure opportunities of families of farmer pesticide applicators. Am J Ind Med 34:581-587.

Gold EB, Diener MD, Szklo M. 1982. Parental occupations and cancer in children: a case-control study and review of the methodologic issues. J Occup Med 24:578-584.

Gold EB, Sever LE. 1994. Childhood cancers associated with parental occupational exposures. Occup Med 9:495-539.

Hardell E, Eriksson M, Lindstrom G, Van Bavel B, Linde A, Carlbert M, et al. 2001. Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. Leuk Lymphoma 42:619-629.

Hardell L, Eriksson M, Lenner P, Lundgren E. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acid: a case-control study. British Journal of Cancer 43:169-176.

Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H. 1981. Childhood cancer and parental occupation in Finland. J Epidemiol Community Health 35:11-15.

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, et al. 1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256:1141-1147.

Hoppin JA, Yucel F, Dosemeci M, Sandler DP. 2002. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol 12:313-318.

IARC. 1986. Some Halogenated Hydrocarbons and Pesticide Exposures. IARC Monogr Eval Carcinog Risk Chem Hum 41:1-407.

IARC. 1987. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. IARC Monogr Eval Carcinog Risks Hum Suppl. 7:1-440.

IARC. 1991. Occupational Exposures in Insecticide Application, and Some Pesticides. IARC Monogr Eval Carcinog Risks Hum 53:5-586.

Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. 1996. Cancer in offspring of parents engaged in agricultural activities in Norway: Incidence and risk factors in the farm environment. Int J Cancer 65:39-50.

Leiss JK, Savitz DA. 1995. Home pesticide use and childhood cancer: A case-control study. Am J Public Health 85:249-252.

Magnani C, Pastore G, Luzatto L, Terracini B. 1990. Parental occupational and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. Tumori 76:413-419.

McCunney RJ. 1999. Hodgkin's disease, work and the environment. A review. J Occup Environ Med 41:36-46.

Olshan AF, Anderson L, Roman E, Fear N, Wolff M, Whyatt R, et al. 2000. Workshop to identify critical windows of exposure for children's health: Cancer work group summary. Environ Health Perspect 108:595-597.

Olshan AF, Daniels JL. 2000. Invited commentary: Pesticides and childhood cancer. Am J Epidemiol 151:647-649.

Persson B. 1996. Occupational exposure and malignant lymphoma. Int J Occup Med Environ Health 9:309-321.

Persson B, Dahlander AM, Fredriksson M, Brage HN, Ohnson CG, Axelson O. 1989. Malignant lymphomas and occupational exposures. Br J Ind Med 46:516-520.

Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. 1993. Some occupational exposures as risk factors for malignant lymphomas. Cancer 72:1773-1778.

Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al., eds. 1999. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. Bethesda, MD:National Cancer Institute, SEER Program.

Rodvall Y, Dich J, Wiklund K. 2003. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup Environ Med 60:798-801.

Roman E, Watson A, Beral V, Buckle S, Bull D, Baker K, et al. 1993. Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 living in West Berkshire and North Hampshire health districts. Br Med J 306:615-621.

Rutz R, Krieger RI. 1992. Exposure to pesticide mixer/loaders and applicators in California. Rev Environ Contam Toxicol 129:121-139.

Schwartzbaum JA, George SL, Pratt CB, Davis B. 1991. An exploratory study of environmental and medical factors potentially related to childhood cancer. Med Pediatr Oncol 19:115-121.

Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W, et al. 1988. A population-based case-control study of childhood leukemia in Shanghai. Cancer 62:635-644.

Sielken RLJ, Bretzlaff RS, Valdez-Flores C, Stevenson DE, de Jong G. 1999. Cancer dose-response modeling of epidemiological data on worker exposures to aldrin and dieldrin. Risk Anal 19:1101-1111.

Stevenson DE, Walborg EFJ, North DW, Sielken RLJ, Ross CE, Wright AS, et al. 1999. Monograph: reassessment of human cancer risk of aldrin/dieldrin. Toxicol Lett 109:123-186.

Zahm SH. 1999. Childhood leukemia and pesticides. Epidemiology 10:473-475.

Zahm SH, Blair A. 1992. Pesticides and non-Hodgkins lymphoma. Cancer Res 52(Supplement):5485-5488.

Zahm SH, Ward MH. 1998. Pesticides and childhood cancer. Environ Health Perspect 106:893-908.

Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, et al. 1990. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dicholorophenoxyacetic acid(2,4-D) in eastern Nebraska. Epidemiology 1:349-356.

Table 1. Demographic characteristics of 17,357 children[a] of Iowa participants in the Agricultural Health Study

		No.	Percent
Sex			
	Female	8082	48%
	Male	8659	52%
Race			
	White	16439	96%
	Nonwhite	769	4%
Child's age at enrollment[b]			
	<5 years	3182	19%
	5-9 years	3796	22%
	10-14 years	4568	26%
	15-19 years	3795	22%
	>19 years	1929	11%
Major farm crops/livestock[c]			
	Field corn	15811	92%
	Soybeans	14416	84%
	Hogs	9528	55%
	Beef	7791	45%
	Hay	6700	39%
	Alfalfa	5977	35%
	Oats	5364	31%

[a]Children born during/after 1975. Columns may sum to <17,357 due to missing data.

[b]Child's age at parent's enrollment in 1993-1997

[c]Farm type by crop product. Total >100% because most farms produce multiple products

Table 2. Standardized incidence ratios (SIR)[a] for cancers diagnosed at age 0-19 years among 17,357 children of Iowa participants in the Agricultural Health Study, 1975-1998

	Observed no. cancer cases	Expected no. cancer cases	SIR	95% CI
Total[b]	**50**	**36.87**	**1.36**	**1.03, 1.79**
Leukemia[c]	**9**	**9.88**	**0.91**	**0.47, 1.75**
Lymphoma	**9**	**4.13**	**2.18**	**1.13, 4.19**
Hodgkin's	5	1.96	2.56	1.06, 6.14
Non-Hodgkin's	2	1.70	1.18	0.29, 4.70
Burkitt's	2	0.37	2.67	0.37, 19.0
Brain tumors[d]	**11**	**6.87**	**1.60**	**0.89, 2.89**
Neuroblastoma	**3**	**2.39**	**1.26**	**0.40, 3.89**
Retinoblastoma	**2**	**1.22**	**1.63**	**0.41, 6.53**
Wilms' tumor	**3**	**1.92**	**1.56**	**0.50, 4.84**
Bone tumors	**4**	**1.82**	**2.19**	**0.82, 5.84**
Soft tissue tumors	**3**	**2.57**	**1.17**	**0.38, 3.62**
Germ cell tumors	**5**	**1.71**	**2.34**	**0.88, 6.24**

[a]Cancer rates for Iowa 1975-1998 were used as reference standard in calculation of standardized incidence ratios

[b]Cancers sum to <50 because one cancer belonged to type other than those listed

[c]Includes 8 acute lymphocytic leukemia cases

[d]Includes 6 astrocytoma cases; other brain tumor subtypes comprised 5 cases

Table 3. Paternal pesticide mixing and application characteristics and risk of childhood cancer (1975-1998) among 17,280 children of Iowa participants in the Agricultural Health Study

	# exposed[a]	% exposed	# exposed cases[b]	OR[c]	95% CI
Mix pesticides personally					
<50% of time	3680	21%	10	Referent	
>50% of time	12522	72%	37	1.02	(0.51, 2.06)
Apply pesticides personally					
<50% of time	2887	17%	10	Referent	
>50% of time	13279	77%	37	0.74	(0.37, 1.51)
Frequency of mixing/application					
<5 days/year	2102	12%	8	Referent	
5-19 days/year	9655	56%	29	0.74	(0.33, 1.64)
>19 days/year	4494	26%	10	0.62	(0.24, 1.57)
Generally use chemically resistant gloves					
Yes	14544	84%	36	Referent	
No	2732	16%	13	1.98	(1.05, 3.76)

[a]Totals sum to <17,280 children due to missing exposure data

[b]Totals sum to <49 exposed cancer cases due to missing exposure data

[c]Adjusted for child's age at enrollment

Table 4. Maternal pesticide mixing and application characteristics and risk of childhood cancer (1975-1998) among 17,280 children of Iowa participants in the Agricultural Health Study

	# exposed[a]	% exposed	# exposed cases[b]	OR[c]	95% CI
Mix/apply pesticides personally					
No	6591	38%	22	Referent	
Yes	9974	58%	26	0.73	(0.41, 1.29)
Frequency of mixing/application					
None	6591	38%	22	Referent	
<5 days/year	3799	22%	4	0.30	(0.10, 0.86)
5-19 days/year	2761	16%	9	0.90	(0.42, 1.95)
>19 days/year	587	3%	3	1.41	(0.42, 4.72)

[a]Totals sum to <17,280 children due to missing exposure data

[b]Totals sum to <49 exposed cancer cases due to missing exposure data

[c]Adjusted for child's age at enrollment

Table 5. Parental use of specific pesticides[a] and subsequent childhood cancer risk among 17,280 children of Iowa participants in the Agricultural Health Study

	# exposed	% exposed	# exposed cases	OR[b]	95% CI
Maternal use[c] (ever)					
Chlorphenoxy herbicides[d]	3189	19%	7	0.67	(0.30, 1.49)
Organophosphate insecticides[e]	4259	25%	14	1.10	(0.59, 2.07)
2,4 D	3009	17%	7	0.72	(0.32, 1.60)
Glyphosate	6075	35%	13	0.61	(0.32, 1.16)
Malathion	3273	19%	11	1.12	(0.57, 2.20)
Paternal use[f] (prenatal)					
Chlorphenoxy herbicides[d]	9713	56%	28	1.26	(0.62, 2.58)
Organochlorine insecticides[g]	1840	11%	7	1.28	(0.55, 2.97)
Organophosphate insecticides[e]	7219	42%	16	0.75	(0.36, 1.58)
Alachlor	4762	28%	10	0.78	(0.38, 1.60)
Aldrin	818	5%	6	2.66	(1.08, 6.59)
Atrazine	7799	45%	23	1.27	(0.70, 2.30)
Chlorpyrifos	2082	12%	5	0.76	(0.44, 3.11)
Cyanazine	4165	24%	10	0.95	(0.47, 2.02)
2,4 D	8769	51%	26	1.29	(0.71, 2.35)
DDVP	1218	7%	6	2.06	(0.86, 4.90)

Dicamba	4942	29%	9	0.69	(0.32, 1.48)
EPTC	1600	9%	6	1.91	(0.78, 4.70)
Glyphosate	3231	19%	6	0.84	(0.35, 2.34)
Malathion	3343	19%	8	0.78	(0.34, 1.79)
Metolachlor	3032	18%	5	0.69	(0.26, 1.84)
Metribuzin	2147	12%	5	0.86	(0.32, 2.32)
Phorate	1889	11%	5	0.89	(0.34, 2.34)
Trifluralin	6000	35%	17	1.14	(0.61, 2.11)
Terbufos	2761	16%	5	0.72	(0.28, 1.89)

[a]Individual pesticides and pesticide classes displayed where # exposed cases >=5

[b]Adjusted for child's age at enrollment

[c]Ever use of chemical by mother

[d]Includes 2,4-dichlorophenoxyacetic acid (2,4-D); 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); dicamba

[e]Includes chlorpyrifos, coumaphos, diazinon, dichlorvis, fonofos, malathion, parathion, phorate, terbufos, trichlorfon

[f]Use of chemical by father before child's birth

[g]Includes aldrin, dichlorodiphenyltrichloroethane (DDT), dieldrin, heptachlor, chlordane, lindane, toxaphene