



Parental Occupational Exposure to Pesticides and Childhood Brain Cancer

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The authors examined the risk of childhood brain cancer in relation to parental exposure to classes of pesticides among 154 children diagnosed with astrocytoma and 158 children diagnosed with primitive neuroectodermal tumors (PNET) in the United States and Canada between 1986 and 1989. Controls were selected by random digit dialing and were individually matched to cases by race, age, and geographic area. Each job in the fathers' work history and the usual occupation of mothers were assigned a probability, intensity, and frequency of exposure to insecticides, herbicides, and agricultural and nonagricultural fungicides. Elevated risks of astrocytoma were found for paternal exposure (ever vs. never) to all four classes of pesticides (odds ratio (OR) = 1.4–1.6). An increased risk of PNET was observed for only herbicides (OR = 1.5). For mothers, odds ratios for astrocytoma were elevated for insecticides, herbicides, and nonagricultural fungicides (OR = 1.3–1.6) but not agricultural fungicides (OR = 1.0). No indication was found of an increased risk for PNET. There was little indication for an association with cumulative and average parental exposure. Most risk estimates were around unity, and exposure-response patterns were absent. Overall, it seems unlikely that parental exposure to pesticides plays an important role in the etiology of childhood brain cancer.

brain neoplasms; case-control studies; child; occupational exposure; pesticides

Abbreviations: OR, odds ratio; PNET, primitive neuroectodermal tumors.

Although central nervous system malignancies are the second most common cancer in children, no modifiable risk factors have been identified that might prevent a considerable proportion of such tumors (1, 2). Paternal occupational exposure has received considerable attention as a potential risk factor for childhood brain cancer over the past few decades (3, 4), and exposure to pesticides has remained one of the more suggestive associations (5–7). In previous studies, this association was based mostly on exposure being defined simply as employment in agriculture (ever vs. never). However, job titles are generally poor proxies for identifying and quantifying specific exposures (8). Interpretation of previous studies also has been hampered by imprecise risk estimates due to a small study population and a low prevalence of exposure.

This community-based case-control study evaluated the association between parental occupational exposure to pesti-

cides (i.e., insecticides, herbicides, and fungicides) and the occurrence of brain cancer in their children.

MATERIALS AND METHODS

Study population

Selection of cases and controls has been described previously (9) and is summarized here. Cases of astrocytoma and primitive neuroectodermal tumors (PNET) were identified between 1986 and 1989 through the Children's Cancer Group. Eligible cases were those children diagnosed before 6 years of age with a tumor in the brain (i.e., *International Classification of Diseases for Oncology* code 191). Additionally, the patient's primary physician must have given permission to contact the parents of the case, and the biologic mother must have been available for interview and

able to speak English. Of the 394 eligible cases, interviews were conducted for 322 (82 percent).

Controls were selected by random digit dialing (10, 11) and were individually matched to cases by race, date of birth (within 1 year), and area code and the next five digits of the telephone number. Enough information to determine eligibility was obtained from 89 percent of the residences called. Of the total number of eligible controls ($n = 436$), 321 (74 percent) participated. Of the 321 controls, 236 were the first control identified. The second control identified was used in 65 instances; the third control in 15 instances; and the fourth, fifth, or sixth control in five instances. In 14 instances, one of the matching criteria had to be relaxed to find a control. For one case, a control could not be located. The final study population included 321 matched pairs: 155 astrocytoma and 166 PNET pairs. Demographic characteristics of cases and controls were similar (9).

Data collection

The mothers of cases and controls were interviewed by telephone about potential gestational, dietary, household, and familial risk factors. A complete occupational history of jobs held for 6 months or more since leaving high school was obtained from fathers. Mothers provided a proxy interview for 27 (18 percent) fathers of astrocytoma cases, 50 (32 percent) fathers of astrocytoma controls, 22 (14 percent) fathers of PNET cases, and 51 (32 percent) fathers of PNET controls. Mothers were asked about their "usual" occupation before the pregnancy and about all of their jobs during the pregnancy. No information on occupational history was obtained for nine parents, resulting in 312 case-control pairs for both fathers and mothers.

Occupational data were collected by using a branching questionnaire structure developed previously (12), which directed the interviewer to use questionnaires designed by industrial hygienists for certain jobs, including agricultural workers, printers, machinists, electricians, nurses/physicians, metal workers, office workers in industry, painters, carpenters, janitors, chemists, welders, and laboratory technicians. First, for each job, information about the type of business, the job title, the job tasks, and the general work environment was obtained from the general questionnaire. Subsequently, if a job-specific questionnaire was available for the particular job, additional questions were asked to identify various sources of exposure. Farmers were asked about the kind of livestock raised and/or crops grown on the farm and the use of pesticides (i.e., insecticides and herbicides) and fertilizers, but none of the other job modules contained questions specifically directed toward pesticide use.

Exposure assessment

Occupation and industry were coded by using the 1980 US Bureau of the Census classification system of jobs and industries (13). For the job title analysis, "occupational groups" were created by using a scheme previously developed by Schnitzer et al. (14) to aggregate workers based on similar job tasks and potential exposures among occupation/

industry combinations. We evaluated ever worked as a farm worker, as defined by Schnitzer et al., by using all other groups as the reference category. Their definition of farm manager and worker includes jobs such as farm managers, farmers, and farm workers in agriculture and horticulture; nursery workers, groundskeepers, and gardeners (except farm); animal caretakers (except farm); and graders, sorters, and inspectors of agricultural products. The coding system was not used to assess pesticides, however.

Four broad classes of pesticides (i.e., insecticides, herbicides, and agricultural and nonagricultural fungicides) were evaluated. "Nonagricultural fungicides" is the term used for disinfectants, germicides, and other chemicals used to control bacteria and other organisms. Evaluation of specific chemicals or chemical structures was not feasible. The first author (E. vW.; referred to as "first rater" in the remainder of this paper) reviewed each job blinded to case-control status. For mothers, only the usual occupation was evaluated because there was little, if any, variation between the usual occupation and the jobs held during pregnancy (about 80 percent agreement).

The first rater reviewed the jobs and, for each, classified the probability and intensity of exposure based on an extensive industrial hygiene literature review of determinants and levels of pesticide exposure and a job-exposure matrix created previously (15). The industrial hygiene literature review estimated the probability, the average pesticide exposure level (g/hour), and the confidence in these estimates for 41 industry/job combinations. Average pesticide exposure was calculated for these combinations from individual measurements reported in the industrial hygiene literature. For the other industry/job combinations not evaluated in this review, the probability, intensity, and confidence levels were assigned by using the original job-exposure matrix (15). Probability, defined as the percentage of workers in a particular industry exposed to either insecticides, herbicides, or agricultural or nonagricultural fungicides, was assigned to one of four arbitrary categories: <10 percent, 10–49 percent, 50–89 percent, and ≥ 90 percent. Exposure intensity was also assigned to one of four levels on an arbitrarily chosen scale ranging from 1 to 4. These weights roughly corresponded to pesticide levels of 5,000, 25,000, 75,000, and 150,000 $\mu\text{g}/\text{hour}$, respectively, which were then given a weight of 1, 5, 15, or 30 to reflect the exposure differences among the four intensity levels for the calculation of cumulative exposure.

Assessment of intensity was restricted to dermal exposure, because approximately 95 percent of total exposure to pesticides is from deposition on the skin (16). Because the major route of exposure to pesticides is deposition, physical parameters, such as vapor pressure, are less important; therefore, these weights were thought to be applicable to all pesticides received dermally. Use of personal protective equipment was not considered, because the impact on intensity of exposure is not well understood. Furthermore, information on personal protective equipment was not collected for all jobs. Therefore, modification of intensity estimates based on personal protective equipment would have been inconsistent across the jobs. Finally, an overall confidence was developed for each job on a scale of 1 (lowest) to 4 (highest) as a means of interpreting the potential for misclassification.

For fathers, duration of exposure in a given job (in days) was estimated as the difference between the start date and the end date multiplied by the proportion of all hours spent at work (50 workweeks \times hours per workweek \div 52 weeks \times 168 hours per week). If the number of hours per workweek employed was not reported, a 40-hour workweek was assumed. No information on duration of exposure was obtained for four fathers. Consequently, these observations were removed, leaving 308 case-control pairs (151 for astrocytoma, 157 for PNET) for the analyses of fathers.

For mothers, duration of exposure in the usual occupation was estimated as the reported number of years worked in the job (see above) multiplied by the proportion of all hours spent at work. Mothers reported full-time or part-time work; a 40-hour and a 20-hour workweek, respectively, were assumed. No information on number of years worked was available for 27 mothers. Thus, the final cumulative exposure analyses comprised 296 case-control pairs (147 for astrocytoma, 149 for PNET) for mothers.

Reliability assessment

An industrial hygienist (P. A. S.; referred to as "second rater" in the remainder of the paper) performed an independent exposure assessment for a subgroup of fathers in the study population to determine the reliability of the exposure assessment and the influence of potential exposure misclassification on the results of the epidemiologic analyses. The second rater was blinded to the case-control status of the study subjects and to the exposure values assigned by the first rater. Subjects were selected for review on the basis of their probability of exposure as assessed by the first rater. Jobs were stratified by probability level, and 5 percent of the jobs assigned to each category were selected. Subsequently, the entire work history for the fathers associated with this sample of jobs was evaluated. In total, 545 jobs (23 percent) were evaluated for pesticide exposure in the reliability assessment. The interrater agreement for probability was assessed with the kappa (for any vs. no exposure) and weighted kappa (for multiple levels of exposure) coefficient (17).

Statistical analysis

For each subject, the exposure assessments and job history were used to estimate cumulative exposure (expressed as exposure score-days) to each substance, which was calculated as the sum of the product of the intensity-level weight (1, 5, 15, 30) and the duration of exposure across jobs. For mothers, cumulative exposure was calculated based on jobs with any probability of exposure. For fathers, the exposure probability of each job was taken into account in calculating cumulative exposure levels (18). First, analyses were conducted by strata of exposure probability. In addition, an estimate of cumulative exposure was calculated by considering jobs with any probability of exposure or a probability of >10 percent but with an overall confidence level of medium-low or higher (≥ 2) only. Two other measures of exposure were also considered: average exposure (i.e., cumulative exposure divided by duration of exposure) and

cumulative exposure based on jobs with the highest intensity level only. Results of the epidemiologic analyses for these two exposures were comparable to those observed for the other measures of cumulative exposure. Therefore, average exposure and cumulative exposure based on maximum intensity are not discussed further in this paper. Total exposure was assessed as cumulative exposure across all jobs held up to the reference date. The reference date was determined as follows: for a case diagnosed at age X_{dx} , the reference age X_{ref} and the reference date were 12 months before the date of diagnosis. For the matched control, we assigned the same reference age X_{ref} and calculated the reference date as the date on which the control was age X_{ref} .

Cumulative exposure among fathers was examined during four time intervals in relation to pregnancy and birth: throughout the work history prior to the reference date, within 2 years prior to pregnancy, during pregnancy, and after birth. For mothers, only career cumulative exposure was evaluated based on the usual occupation. For both parents, career cumulative exposure was classified into three categories (low, medium, high) based on the 50th (medium) and 75th (high) percentiles of exposure among exposed controls. Cumulative exposure in the other time windows of exposure was classified into two categories based on the 50th percentile of exposure among exposed controls. The referent group always consisted of persons considered unexposed in all jobs.

Conditional logistic regression was used to estimate the odds ratio and 95 percent confidence interval for matched data by using the PHREG procedure in SAS software for PC version 8.1 (SAS Institute, Inc., Cary, North Carolina). The analyses were performed separately for PNET and astrocytoma to evaluate etiologic heterogeneity. Potential confounding factors included mother's education (high school or less, some college), household income (categories of $< \$25,000$, $\$25,000$ – $< \$35,000$, and $\geq \$35,000$ based on the distribution among controls), and maternal age at time of birth (< 24 , 24 – < 31 , and ≥ 31 years based on the 25th and 75th percentiles of age distribution among controls). This limited set of variables was chosen to capture potential confounding effects broadly related to socioeconomic status. In addition, there are few established risk factors for childhood brain cancer (2), which were unlikely to act as confounders in the present analysis. The effect of each class of pesticide was also assessed with adjustment for the effects of the other two classes of pesticides. Effect measure modification by proxy reporting status was considered in the analysis of paternal occupation.

RESULTS

Exposure assessment

About 23 percent (552 of 2,390 jobs) of paternal occupations involved potential exposure to insecticides, 11 percent involved potential exposure to herbicides, and 31 percent involved potential exposure to fungicides. For mothers, these respective proportions were 26 percent (162 of 624 usual occupations), 5 percent, and 30 percent. Farm workers were the predominant group of exposed workers among

TABLE 1. Most prevalent occupations held by fathers, by probability and intensity level of exposure to insecticides, herbicides, and fungicides, United States and Canada, 1986–1989

| Category and level of exposure | Probability of exposure | | Intensity level of exposure | |
|--------------------------------|-------------------------|---|-----------------------------|--|
| | No.* | Two main jobs† (%‡) | No. | Two main jobs (%) |
| Insecticides | | | | |
| 0 | 1,838 | Salesman (9), manager (8) | 1,838 | Salesman (9), manager (8) |
| 1 | 285 | Food service worker (34), food processor (15) | 176 | Janitor (17), salesman§ (14) |
| 2 | 141 | Janitor (18), farm worker (13) | 280 | Food service worker (34), food processor (13) |
| 3 | 88 | Farm worker (73), logger (7) | 93 | Farm worker (82), logger (2) |
| 4 | 38 | Farm worker (74), janitor (5) | 3 | Farm worker (100) |
| Herbicides | | | | |
| 0 | 2,135 | Salesman (9), manager (7) | 2,135 | Salesman (9), manager (7) |
| 1 | 76 | Farm worker (16), janitor (14) | 88 | Salesman§ (27), janitor (25) |
| 2 | 72 | Salesman§ (24), farm worker (18) | 73 | Farm worker (38), armed forces§ (10) |
| 3 | 64 | Farm worker (78), logger (8) | 94 | Farm worker (81), railway transport worker (2) |
| 4 | 43 | Farm worker (72), engineer (5) | 0 | |
| Fungicides | | | | |
| 0 | 1,643 | Salesman (12), manager (9) | 1,643 | Salesman (12), manager (9) |
| 1 | 123 | Farm worker (12), vehicle mechanic§ (11) | 524 | Food service worker (18), metal worker§ (10) |
| 2 | 458 | Food service worker (19), farm worker (19) | 169 | Farm worker (59), painter§ (5) |
| 3 | 160 | Carpenter§ (23), painter§ (19) | 54 | Carpenter§ (65), construction worker§ (15) |
| 4 | 6 | Janitor (33), farm worker (33) | 0 | |

* Total number of jobs in that category.

† Definition according to Schnitzer et al. (14); farm worker includes jobs such as farm managers and workers in agriculture and horticulture; nursery workers, groundskeepers, and gardeners (except farm); animal caretakers (except farm); and graders, sorters, and inspectors of agricultural products.

‡ Percentage of the total number of jobs in that category.

§ Potential source of exposure: fungicides in water-based machining oils (metal worker, vehicle mechanic), fungicides in paints (painter, construction worker), fungicides as wood preservatives (carpenters, construction workers), herbicide exposure during the Vietnam War (armed forces), and handling cans containing pesticides (hardware sales workers).

fathers for all three pesticide classes, whereas a large proportion of pesticide exposure among mothers was due to being employed as food service workers (insecticides and nonagricultural fungicides). Table 1 presents the most prevalent occupations that fathers held by probability and intensity level of exposure to insecticides, herbicides, and fungicides.

Reliability assessment

Overall, most of the jobs considered unexposed by the second rater were considered unexposed by the first rater. About 92 percent and 95 percent of jobs considered unexposed to insecticides and herbicides, respectively, by the second rater were also considered unexposed by the first rater. Compared with the first rater, the second rater classified 1 percent more jobs as exposed to fungicides. The interrater agreement for the assignment of any versus no exposure was moderate, with a kappa coefficient of 0.6 for each of the three classes of pesticides. After all levels of probability were taken into consideration, the agreement between the two raters was moderate for each of the three classes of pesticides (weighted kappa = 0.6 for insecticides and herbicides; weighted kappa = 0.5 for fungicides).

Epidemiologic analysis

No indication of an increased risk was found for either fathers or mothers who worked as a farm manager or farm worker, although the risk estimates for mothers were very imprecise (table 2). No difference in risk was evident between the two brain tumor subtypes. For fathers, elevated risks of astrocytoma were found for all four classes of pesticides (odds ratio (OR) = 1.4–1.6), whereas some indication of an increased risk of PNET was observed only for herbicides (OR = 1.5). For mothers, odds ratios for astrocytoma were elevated for insecticides (OR = 1.9), herbicides (OR = 1.3), and nonagricultural fungicides (OR = 1.6) but not agricultural fungicides (OR = 1.0). There was no indication of an increased risk for PNET; the odds ratios for herbicides and fungicides were below unity.

Little indication was found of an association between cumulative parental exposure and astrocytoma or PNET (table 3). Although sporadic increases in risk were found, most risk estimates were around unity, and exposure-response gradient patterns were absent. Odds ratios for the histology subtypes were generally similar in magnitude, but more odds ratios below the null value (OR = 1.0) were observed for PNET. Consideration of different estimates of

TABLE 2. Adjusted odds ratios and 95 percent confidence intervals from conditional logistic regression for any potential exposure to pesticides during work history in relation to risk of childhood brain cancer, United States and Canada, 1986–1989

| Exposure | Astrocytoma | | | | PNET* | | | |
|-----------------|-------------|----------------|-------|-----------|-------------|----------------|-----|----------|
| | Cases (no.) | Controls (no.) | OR*,† | 95% CI* | Cases (no.) | Controls (no.) | OR† | 95% CI |
| Fathers | | | | | | | | |
| Farm worker‡ | 21 | 19 | 1.1 | 0.5, 2.3 | 28 | 30 | 0.9 | 0.5, 1.7 |
| Insecticide | 82 | 70 | 1.5 | 0.9, 2.4 | 81 | 78 | 1.1 | 0.7, 1.7 |
| Herbicide | 51 | 37 | 1.6 | 1.0, 2.7 | 51 | 42 | 1.5 | 0.9, 2.6 |
| Fungicide | 99 | 85 | 1.6 | 1.0, 2.6 | 99 | 96 | 1.1 | 0.7, 1.8 |
| Agricultural | 28 | 22 | 1.4 | 0.7, 1.7 | 33 | 33 | 1.0 | 0.6, 1.8 |
| Nonagricultural | 87 | 72 | 1.5 | 0.9, 2.4 | 82 | 81 | 1.0 | 0.6, 1.6 |
| Mothers | | | | | | | | |
| Farm worker | 1 | 1 | 1.0 | 0.1, 16 | 1 | 2 | 0.6 | 0.1, 7.0 |
| Insecticide | 53 | 35 | 1.9 | 1.1, 3.3 | 37 | 37 | 1.0 | 0.6, 1.7 |
| Herbicide | 9 | 8 | 1.3 | 0.5, 3.7 | 6 | 11 | 0.5 | 0.2, 1.5 |
| Fungicide | 56 | 42 | 1.6 | 0.9, 2.7 | 39 | 50 | 0.7 | 0.4, 1.2 |
| Agricultural | 1 | 1 | 1.0 | 0.1, 18.8 | 2 | 4 | 0.6 | 0.1, 3.2 |
| Nonagricultural | 55 | 41 | 1.6 | 0.9, 2.7 | 37 | 46 | 0.7 | 0.4, 1.2 |

* PNET, primitive neuroectodermal tumors; OR, odds ratio; CI, confidence interval.

† For ever vs. never exposed; adjusted for maternal age, household income, and maternal education.

‡ Definition according to Schnitzer et al. (14); farm worker includes jobs such as farm managers and workers in agriculture and horticulture; nursery workers, groundskeepers, and gardeners (except farm); animal caretakers (except farm); and graders, sorters, and inspectors of agricultural products.

cumulative exposure based on probability or confidence did not greatly affect the patterns and magnitude of the risk estimates across exposure categories. For all four classes of pesticides, similar results were observed for the three time windows in relation to pregnancy and birth (data not shown).

Excluding from the analyses fathers for whom a proxy interview was obtained did not greatly affect the results reported above (data not shown). In an attempt to separate the effects of each class of pesticide from the others, we evaluated the risk estimates for each class individually after adjustment for the effects of the two classes (table 4). Because the risk estimates for the histologic subtypes were very imprecise, the discussion in this paper is limited to the analysis for the subtypes combined. No association with childhood brain cancer was found for paternal exposure to pesticides, with the possible exception of herbicides. For mothers, an exposure-response trend was suggested for insecticides, whereas no evidence was found for an increased risk associated with exposure to herbicides and fungicides.

DISCUSSION

Several studies of childhood brain cancer have reported associations with paternal employment in agriculture (19–22). Additionally, a Swedish cohort study (23) reported an increased risk for pesticide exposure (relative risk = 2.4). However, other studies found only a weakly increased brain tumor risk (19–21). Our study found no evidence for an

increased risk associated with paternal or maternal employment as a farm manager or farm worker. Interestingly, a previous evaluation of this study population found an association between PNET and farm residence of the mother during pregnancy and of the child for at least a year (9).

Many previous studies used job title or industry, which are generally poor proxies for identifying and quantifying specific exposures (8) and may be strongly associated with socioeconomic status and lifestyle factors. In the current study, each job that a subject held was evaluated for exposure to insecticides, herbicides, and fungicides after thoroughly reviewing the industrial hygiene literature, using a pesticide job-exposure matrix used previously (15), and obtaining information on each person's work history from generic and job-specific questionnaires. Our method of exposure assessment attempted to take into account exposure variability within jobs due to specific tasks, processes, and technology.

The highest exposure to pesticides can be found among workers involved in manufacturing, formulation, and application in either the agricultural or public health sectors (24), but these jobs are rare. However, the prevalence of pesticide exposure in a community-based case-control study may not be limited to agricultural work only (table 1). Hence, we found a relatively high prevalence of exposure potential in our study population.

If the time window for assessing exposure is overly broad, both etiologically relevant and irrelevant exposures will be incorporated. Consequently, this form of exposure misclassi-

TABLE 3. Adjusted odds ratios and 95% confidence intervals from conditional logistic regression for career cumulative exposure to pesticides in relation to risk of childhood brain cancer, by percentile of exposed controls, United States and Canada, 1986–1989

| Exposure level* | Astrocytoma | | | | | | PNET† | | | | | |
|-------------------|-------------|-----------|--------|----------|-----|----------|--------|----------|--------|----------|-----|----------|
| | >0–<50‡ | | 50–<75 | | ≥75 | | >0–<50 | | 50–<75 | | ≥75 | |
| | OR†,§ | 95% CI† | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| <i>Fathers</i> | | | | | | | | | | | | |
| Insecticides | | | | | | | | | | | | |
| Any probability | 1.4 | 0.8, 2.5 | 1.8 | 0.9, 3.8 | 0.9 | 0.4, 2.3 | 1.3 | 0.8, 2.3 | 1.0 | 0.5, 2.0 | 0.7 | 0.3, 1.6 |
| Probability ≥50% | 1.7 | 0.7, 4.6 | 0.9 | 0.2, 3.7 | 2.0 | 0.4, 9.6 | 2.0 | 0.9, 4.3 | 0.5 | 0.1, 2.2 | 0.8 | 0.2, 3.1 |
| Confidence ≥2 | 1.9 | 1.0, 3.4 | 1.3 | 0.6, 3.2 | 1.0 | 0.4, 2.5 | 1.3 | 0.8, 2.3 | 1.0 | 0.4, 2.2 | 0.6 | 0.2, 1.4 |
| Herbicides | | | | | | | | | | | | |
| Any probability | 2.0 | 1.0, 3.7 | 0.8 | 0.3, 2.7 | 1.4 | 0.5, 4.0 | 1.7 | 0.9, 3.3 | 1.2 | 0.5, 3.3 | 1.3 | 0.5, 3.3 |
| Probability ≥50% | 1.6 | 0.5, 5.0 | 0.8 | 0.2, 3.9 | 2.0 | 0.4, 9.5 | 1.3 | 0.5, 3.2 | 1.6 | 0.6, 4.6 | 0.4 | 0.1, 2.3 |
| Confidence ≥2 | 1.8 | 0.9, 3.8 | 0.4 | 0.1, 1.9 | 1.5 | 0.5, 4.3 | 1.6 | 0.8, 3.1 | 1.3 | 0.5, 3.4 | 0.5 | 0.2, 1.9 |
| Fungicides | | | | | | | | | | | | |
| Any probability | 1.3 | 0.7, 2.4 | 2.7 | 1.3, 5.4 | 1.1 | 0.5, 2.3 | 1.3 | 0.8, 2.3 | 1.1 | 0.5, 2.1 | 0.6 | 0.3, 1.4 |
| Agricultural | 1.5 | 0.6, 3.4 | 0.8 | 0.2, 3.4 | 1.9 | 0.5, 7.2 | 1.3 | 0.6, 2.6 | 0.6 | 0.2, 1.8 | 1.1 | 0.4, 3.0 |
| Nonagricultural | 1.3 | 0.8, 2.4 | 2.1 | 1.0, 4.4 | 1.2 | 0.5, 2.6 | 1.2 | 0.7, 2.0 | 1.0 | 0.5, 2.1 | 0.5 | 0.2, 1.2 |
| Probability ≥50%¶ | 1.0 | 0.4, 2.4 | 2.1 | 0.8, 5.2 | 0.9 | 0.3, 2.8 | 0.9 | 0.4, 1.9 | 0.4 | 0.1, 1.7 | 0.5 | 0.1, 1.5 |
| Confidence ≥2¶ | 1.2 | 0.6, 2.3 | 1.1 | 0.4, 3.2 | 1.5 | 0.6, 4.0 | 0.9 | 0.5, 1.7 | 1.4 | 0.6, 3.2 | 1.0 | 0.4, 2.1 |
| <i>Mothers</i> | | | | | | | | | | | | |
| Insecticides | 1.7 | 0.8, 3.6 | 1.7 | 0.9, 3.4 | | | 1.0 | 0.5, 2.0 | 0.9 | 0.4, 1.7 | | |
| Herbicides | 2.6 | 0.4, 15.9 | 0.9 | 0.2, 3.3 | | | 0.8 | 0.2, 3.2 | 0.2 | 0.0, 1.8 | | |
| Fungicides¶ | 2.0 | 0.9, 4.2 | 1.2 | 0.6, 2.2 | | | 0.7 | 0.4, 1.4 | 0.5 | 0.3, 1.1 | | |

* Any probability, cumulative exposure based on jobs with any probability of exposure; probability ≥50%, cumulative exposure based on jobs with a probability of medium-high or higher; confidence ≥2, cumulative exposure based on jobs with any probability of exposure but with an overall confidence level of medium-low or higher.

† PNET, primitive neuroectodermal tumors; OR, odds ratio; CI, confidence interval.

‡ Percentiles of the distribution of exposure (in units of exposure score-days) among exposed controls.

§ Odds ratios were adjusted for the effects of maternal age, household income, and maternal education.

¶ Agricultural and nonagricultural fungicides were combined.

fication would dilute the resulting effect estimates. In this study, similar patterns of risk were observed across three specific time periods relative to pregnancy and birth. However, the high correlation of exposure across time intervals (about 70 percent of persons exposed in one time window were also exposed in the other two time windows) limited our ability to disentangle the time period of relevance. For mothers, only the usual occupation was evaluated because there was little variation between the usual occupation and the jobs held during pregnancy.

Different classes of brain tumors are derived from distinct cells and may have different etiologies (25). Real effects may be masked when diseases with different etiologies are studied as one disease (26). We found some indication of an elevated risk among astrocytoma cases (OR = 1.6) in relation to parental occupational exposure to all three classes of pesticides based on a dichotomous exposure measure (table 2), but little evidence for an increased risk was found for the PNET subtype. On the other hand, analyses of cumulative exposure provided little evidence for an association between parental pesticide exposure and childhood brain cancer, although elevated risks for astrocytoma were sporadically

found. An increased risk of astrocytoma and “other glial” tumors with paternal employment in agriculture has been reported previously (27). In contrast, another study found little indication of an elevated risk with paternal or maternal employment in agriculture for any brain tumor subtype (28), similar to our findings.

The results of this study must be interpreted by recognizing several limitations. First, selection bias can be a major issue in the design and interpretation of case-control studies. This bias may depend on the nature of the control group and factors determining participation of both cases and controls. In our study, controls were matched by area of residence, which may have introduced matching by socioeconomic status and overmatching for exposures that relate to socioeconomic status or geographic area (2). Second, controls were selected on the basis of random digit dialing. Although this procedure generates sets of telephone numbers without relying on a directory that would not contain new or unpublished numbers (10), difficulties in defining the source population of the controls and in determining the degree of nonresponse are limitations of this control selection procedure (10). In our study, 26 percent of first eligible controls

TABLE 4. Odds ratios and 95% confidence intervals from conditional logistic regression for career cumulative exposure in relation to risk of childhood brain cancer (histology subtypes combined), adjusted for the effects of the other classes of pesticides, United States and Canada, 1986–1989

| Exposure* | Unexposed | | >0–<50† | | | | ≥50 | | | | |
|------------------|-----------------------------|-----------------------------|----------|----------|----------|----------|-----------------------------|----------|----------|----------|----------|
| | Cases/ controls (no.) | Cases/ controls (no.) | Model 1‡ | | Model 2§ | | Cases/ controls (no.) | Model 1‡ | | Model 2§ | |
| | | | OR | 95% CI¶ | OR | 95% CI | | OR | 95% CI | OR | 95% CI |
| <i>Fathers</i> | | | | | | | | | | | |
| Any probability | | | | | | | | | | | |
| Insecticides | 145/160 | 101/74 | 1.5 | 1.0, 2.1 | 1.1 | 0.7, 1.8 | 62/74 | 1.0 | 0.6, 1.4 | 0.7 | 0.4, 1.2 |
| Herbicides | 206/229 | 64/39 | 1.8 | 1.1, 2.7 | 1.6 | 1.0, 2.7 | 38/40 | 1.2 | 0.7, 2.0 | 1.6 | 0.7, 3.3 |
| Fungicides | 110/127 | 104/90 | 1.4 | 0.9, 2.0 | 1.2 | 0.8, 1.9 | 94/91 | 1.2 | 0.8, 1.9 | 1.1 | 0.7, 1.8 |
| Probability ≥10% | | | | | | | | | | | |
| Insecticides | 145/160 | 50/41 | 1.3 | 0.8, 2.0 | 1.0 | 0.6, 1.9 | 44/41 | 1.2 | 0.7, 2.0 | 1.0 | 0.5, 2.4 |
| Herbicides | 206/229 | 41/31 | 1.4 | 0.9, 2.3 | 1.4 | 0.7, 2.8 | 33/31 | 1.2 | 0.7, 2.2 | 1.4 | 0.5, 3.7 |
| Fungicides | 110/127 | 96/82 | 1.3 | 0.9, 1.9 | 1.2 | 0.8, 1.8 | 79/83 | 1.0 | 0.7, 1.6 | 0.9 | 0.6, 1.4 |
| Probability ≥50% | | | | | | | | | | | |
| Insecticides | 145/160 | 35/21 | 1.7 | 1.0, 3.1 | 2.2 | 0.8, 5.9 | 18/22 | 0.9 | 0.5, 1.9 | 0.7 | 0.2, 2.8 |
| Herbicides | 206/229 | 24/20 | 1.3 | 0.6, 2.6 | 0.7 | 0.2, 2.1 | 21/20 | 1.2 | 0.6, 2.3 | 1.6 | 0.4, 6.3 |
| Fungicides | 110/127 | 34/33 | 1.0 | 0.6, 1.8 | 1.0 | 0.6, 1.8 | 23/33 | 0.7 | 0.4, 1.3 | 0.7 | 0.4, 1.3 |
| Confidence ≥2 | | | | | | | | | | | |
| Insecticides | 175/190 | 76/57 | 1.5 | 1.0, 2.2 | 1.4 | 0.8, 2.3 | 50/57 | 1.0 | 0.6, 1.5 | 0.9 | 0.5, 1.6 |
| Herbicides | 228/243 | 46/32 | 1.5 | 0.9, 2.4 | 1.3 | 0.7, 2.2 | 30/32 | 1.1 | 0.6, 1.9 | 1.2 | 0.6, 2.5 |
| Fungicides | 170/185 | 51/53 | 1.0 | 0.6, 1.5 | 0.8 | 0.5, 1.4 | 61/54 | 1.3 | 0.8, 2.0 | 1.2 | 0.7, 1.9 |
| <i>Mothers</i> | | | | | | | | | | | |
| Insecticides | 215/225 | 45/36 | 1.3 | 0.8, 2.2 | 1.6 | 0.8, 2.9 | 40/36 | 1.2 | 0.7, 1.9 | 1.9 | 1.0, 3.8 |
| Herbicides | 285/278 | 10/9 | 1.3 | 0.5, 3.6 | 1.0 | 0.3, 3.0 | 3/6 | 0.5 | 0.1, 2.2 | 0.5 | 0.1, 2.2 |
| Fungicides | 210/205 | 47/40 | 1.1 | 0.7, 1.8 | 0.8 | 0.5, 1.4 | 43/52 | 0.8 | 0.5, 1.3 | 0.6 | 0.3, 1.0 |

* Any probability, cumulative exposure based on jobs with any probability of exposure; probability ≥10%, cumulative exposure based on jobs with a probability of medium-low or higher; probability ≥50%, cumulative exposure based on jobs with a probability of medium-high or higher; confidence ≥2, cumulative exposure based on jobs with any probability of exposure but with an overall confidence level of medium-low or higher.

† Percentiles of the distribution of exposure (in units of exposure score-days) among exposed controls.

‡ Odds ratios (ORs) were adjusted for the effects of maternal age, household income, and maternal education.

§ The three classes of pesticides (insecticides, herbicides, and all fungicides combined) were evaluated in one statistical model for each cumulative exposure measure; odds ratios were additionally adjusted for the effects of maternal age, household income, and maternal education.

¶ CI, confidence interval.

did not participate for unknown reasons, and non-Whites were less likely to participate than Whites. Although cases and controls were matched by race and matched analyses were performed, the nonrepresentativeness of either cases or controls within racial groups could have resulted in spurious negative or positive findings (25).

Furthermore, recall bias is always of concern in community-based case-control studies. To evaluate the possibility of recall bias, one might compare the number of jobs reported for fathers of cases and controls. If recall bias occurred, one would expect more complete reporting by fathers of cases, which may be reflected by a larger number of jobs reported by fathers of cases compared with fathers of controls. In our study, fathers of cases held a total of 1,218 jobs (average, 3.9 jobs per person), while fathers of controls held 1,172 jobs (average, 3.8 jobs per person). Therefore, recall bias for jobs appears not to have been of much concern. However, for exposure assessment we relied on job characteristics reported by the study subjects, such as tasks performed and products used. If more detailed information

was obtained for fathers of cases than for father of controls, the potential for differential recall bias may have existed.

Considerable effort was made to ensure the quality of exposure assessment, but misclassification of exposure undoubtedly occurred. Therefore, two raters evaluated a subset of jobs separately to assess the reliability of the exposure assessment and its influence on the reported risk estimates. Interrater agreement was moderate (kappa = 0.5–0.6), thereby indicating that some potential for exposure misclassification existed. Interrater agreement was slightly lower for fungicides, possibly because little information on fungicide use was available from the literature. The two raters may have used different industrial hygiene information to arrive at their estimates, in particular for jobs not included in the industrial hygiene review, which could explain the somewhat low agreement between raters. However, interrater agreements similar to the ones reported here have been found in studies assessing the reliability of industrial hygiene panel ratings, with kappa coefficients generally ranging from 0.4 to 0.7 (29–32). Although these findings are somewhat

reassuring, it should be kept in mind that kappa coefficients compare the job-level agreement but that odds ratios are affected by agreement on the group level.

Another limitation is the large proportion of mothers who provided a proxy interview for fathers. More proxy interviews were conducted for controls than for cases. Previous studies have shown that proxy respondents are less likely to recall or report detailed work history information accurately (33, 34). Nevertheless, analyses restricted to fathers for whom an in-person interview was conducted showed patterns and magnitudes of the associations similar to those in the analyses including all fathers. The effect of proxy status on the risk estimates was also investigated indirectly by taking into account the confidence we had in our assignment of probability and intensity. For example, for all four classes of pesticides, a slightly higher proportion (2–4 percent) of jobs were assigned a low confidence when reported by proxy respondents. Nevertheless, excluding from the analysis jobs with low confidence did not change our interpretation of the results.

It was difficult to interpret the results for each class of pesticide individually because of the high degree of correlation between exposures to these substances. For example, 55 percent and 84 percent of fathers ever exposed to insecticides were also exposed to herbicides and fungicides, respectively. To address this correlation, we also assessed the effect of each pesticide after adjusting for the effects of the other two pesticides. On the basis of these analyses, little evidence of an increased risk was found for paternal exposure to any class of pesticide. Nevertheless, there was some indication for an association with maternal exposure to insecticides.

In conclusion, these data did not support the association of paternal employment in agriculture with pesticide exposure, although the potential for a small elevated risk was present. It should be noted, however, that although pesticides were separated into four distinct classes, a large variety of chemicals and chemical structures may be found within these classes. Evaluation of broad classes of pesticides may have resulted in diluting the effect, if any, of a specific pesticide within the class.

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