Pesticides and Childhood Cancers

Julie L. Daniels, Andrew F. Olshen, and David A. Savitz

Department of Epidemiology, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC 27599 USA

To evaluate the possible association between pesticides and the risk of childhood cancers, epidemiologic studies published between 1970 and 1996 were critically reviewed. Thirty-one studies investigated whether occupational or residential exposure to pesticides by either parents or children was related to increased risk of childhood cancer. In general, the reported relative risk estimates were modest. Risk estimates appeared to be stronger when pesticide exposure was measured in more detail. Frequent occupational exposure to pesticides or home pesticide use was more strongly associated with both childhood leukemia and brain cancer than either professional exterminations or the use of garden pesticides. Occupational pesticide exposure was also associated with increased risk of Wilms’ tumor, Ewing’s sarcoma, and germ cell tumors. Residence on a farm, a proxy for pesticide exposure, was associated with increased risk of a number of childhood cancers. Although increased risk of some childhood cancers in association with pesticide exposure is suggested by multiple studies, methodological limitations common to many studies restrict conclusions; these include indirect exposure classification, small sample size, and potential biases in control selection. Opportunities for methodologic improvement in future studies of pesticides and childhood cancers are described. Key words: agriculture, case–control methods, childhood cancer, environment, neoplasms, occupation, pesticides, review.

Methods and Overview

This review included published literature that assessed the risk of cancer in children associated with exposure to pesticides through parental occupation or by residential use. We included all studies identified through Medline published in English between 1970 and 1996. For each study, Table 1 lists the study design; time period studied with regard to pregnancy; source of cases, controls, and exposure information; and factors adjusted for in either the study’s design or analysis. We used relative risk estimates when presented; otherwise we calculated odds ratios and confidence intervals from the data provided. In this paper, we will refer to relative risk estimates >1.5 as suggestive of a positive association. Risk estimates associated with occupational and residential pesticide exposure prior to conception and during pregnancy and childhood are presented in Tables 2–4 by cancer type.

Table 1 presents the key characteristics of all the studies reviewed. Because of the relative rarity of childhood cancers, most epidemiologic investigations have been case–control studies. Childhood cancer cases have been primarily identified through population-based or hospital tumor registries. Controls have been derived from a variety of sources including census records, telephone random-digit dialing, birth certificates, friends of cases, and children with other cancers or illnesses. Nearly all of the occupational studies retrospectively inferred exposure based on job title and industry rather than by direct measurement of pesticide exposure. Job title information has been obtained through interviews with parents, as well as from birth and death records. Residential exposure, which refers to pesticide use in the home and in the garden, has been assessed solely by recall of parents. Because pesticide exposure was the primary interest in only a few studies, information about both occupational and residential exposure was limited. Although some studies reported the association between pesticides and all childhood cancers combined, most studies evaluated the

Address correspondence to J.L. Daniels, Department of Epidemiology, CB #7400, School of Public Health, University of North Carolina, Chapel Hill, NC 27599 USA.

The authors acknowledge Kay Teschke for her constructive review of the manuscript.

Received 15 April 1997; accepted 10 July 1997.
| Setting and study period | Case group | Upper age bound (years) | Case (n) | Case source | Control source | Data source; period of interest | Design: adjusted variables\(^a\) | Reference |
|--------------------------|------------|-------------------------|----------|-------------|----------------|-------------------------------|---------------------------------|-----------|
| Baltimore, MD, Res 1965–1975 | Brain | 19 | 84 | H | BC,C | Interview; PG, CH, BC, PG | Age, race, sex NA | (37) |
| Finland, Occ 1950–1975 | Brain, leukemia | 14 | 948 | T | BC | Interview; PG, CH | Age: NA | (31) |
| Baltimore, MD, Occ 1965–1969–1974 | Brain, leukemia | 19 | 7,043 | T,DC | BC,C | Interview; PG, CH | Age, race, sex, Dx date: NA | (30) |
| Los Angeles, CA, Occ 1972–1977 | Brain | 24 | 209 | T | F | Interview; PG, CH | NA | (32) |
| Ohio, Occ 1969–1978 | Brain, deaths | 19 | 481 | DC | BC | Interview; PG, CH | Age, race, sex: pat age, birth order, birth wt, percent county farmed, sex, age | (29) |
| Michigan, Occ 1977–1983 | Brain | 19 | 74 | H | PR | Interview; PG, CH | Age, sex, region: Dx age | (28) |
| Ohio, Occ 1975–1982 | Brain and CNS | 19 | 110 | H | RD | Interview; PG, CH | Age, race, sex, region: NA | (27) |
| Pennsylvania, Delaware, New Jersey, Occ 1980–1986 | Brain, AG | 14 | 163 | H | RD | Interview; PG, CH | Age, race, region: NA | (26) |
| Missouri, Res 1985–1989 | Brain | 10 | 45 | T | F,C | Interview; PG, CH | Age, sex: smoke, income, pat education, time from Dx to interview | (36) |
| United States, Canada, Res 1996–1989 | Brain, AG, PNET | 5 | 321 | CCG | RD | Interview; PG, CH | Age, race, region: income | (33) |
| Denver, CO, Res 1976–1983 | Brain, leukemia, lymphoma, sarcoma | 14 | 252 | T | RD | Interview; PG, CH | Age, sex, region: Dx age, income, mat age, mat race, mat smoke, pat education, EMF | (34) |
| Norway, Res\(^b\) 1965–1991 | Leukemia | 39 | 182 | T | NA | Agricultural registry; CH | NA: age, calendar year, birth year | (38) |
| Finland, Occ 1973–1980 | Leukemia Other | 14 | 519 | T | PR | Mail questionnaires; PG,CH | Age, sex, region: age, sex | (42) |
| Los Angeles, CA, Occ 1980–1984 | Leukemia | 10 | 123 | T | F,RDD | Interview; PG, CH | Age, race, sex, ethnicity: NA | (44) |
| China, Occ 1985–1986 | Leukemia | 14 | 309 | T | PR | Interview; PG | Age, sex, age, sex, birth order, rural residence, mat X rays | (40) |
| France, Occ 1977–1982 | Leukemia NA | 201 | NA | I | Interview; NA | Age, sex: NA | (46) |
| United States, Canada, Occ 1980–1984 | ANLL | 17 | 204 | CCG | RDD | Interview; PG, CH | Age, race, region: NA | (39) |
| Italy, Occ 1981–1984 | Leukemia, lymphoma | 14 | 128 | T | PR | Interview; PG, CH | Age, sex, region: NA | (41) |
| Canada, Occ 1983–1985 | Leukemia, lymphoma | 14 | 128 | T | PR | Interview; PG | Age, sex, region: NA | (41) |
| Tennessee, Res 1979–1986 | ALL | 74 | 522 | H | C | Interview; CH | NA: age, birth year, race, med education, pat occupation | (43) |
| Texas, Occ 1964–1978 | Neuroblastoma | 14 | 157 | DC | BC | Interview; PG | Age: NA | (51) |
| Delaware, Occ 1979–1985 | Neuroblastoma | 14 | 157 | DC | BC | Interview; PG | Age, race, region: NA | (52) |
| North Carolina, Occ 1967–1976 | Rhabdomyosarcoma | 14 | 33 | T | BC | Interview; CH | Age, race, sex: NA | (57) |
| San Francisco, CA, Occ 1976–1986 | Ewing's sarcoma | 31 | 43 | T,H | RD | Interview; PC, PG, CH | Age, sex, region: income, birth year, medication, region | (48) |
| United States, Canada, Occ 1982–1989 | Germ cell | 14 | 105 | CCG | RD | Mail questionnaires; PG, CH | NA: age, sex, five births, gestation age, mat smoke, med education | (43) |
| Ohio, Occ 1950–1981 | Wilms' tumor NA | 105 | T | BC | Interview; PG | Age, sex, race, region: NA | (50) |
| United States, Canada, Occ 1984–1986 | Wilms' tumor | 15 | 200 | CCG | RD | Mail questionnaires; CH | Age, region: income, education | (56) |
| Brazil, Occ 1987–1989 | Wilms' tumor | 109 | H | H | Interview; PC, PG | Age, sex, hospital, region, trimester admitted: age, sex, hospital, region, income, education | (49) |
| Quebec, Occ 1965–1970 | Cancer, death | 4 | 386 | H | BC | BC, PG | NA | (53) |

(Table 1 continued, next page)
effects of pesticides on one specific type of cancer. Because much of the research has focused on childhood brain tumors and leukemia, this review reports these studies separately from those of other cancers.

Cancers of the Brain and Central Nervous System

Both of the interview studies that evaluated paternal occupational exposure to pesticides prior to conception reported increased risks of childhood brain cancer; odds ratios (ORs) = 1.8 (27) and 2.7 (28) (Table 2). Paternal occupational exposure during pregnancy was also positively associated with childhood brain cancer risk in most studies; this was not seen for exposure during childhood (27–31). The results in all these occupational studies were imprecise, often dependent on a few exposed cases, and pesticide exposure was inferred by employment in agriculture and not explicitly measured. In fact, two of the five studies classified exposure based on birth certificate information (29,31). No studies were found that evaluated maternal occupational pesticide exposure and childhood brain cancer risk.

Childhood brain cancer risk associated with residential pesticide use varied by the type of pesticide application. Most studies found the households of brain cancer cases to be no different that those of controls in their use of professional extermination (32–34) or garden pesticides (34,35). The exception is the study of Davis et al. (36), which reported two- to threefold increases in risk of childhood brain cancer when pesticides were separated by type—insecticides, herbicides, or extermination of termites. Multiple studies found that parents’ use of other home pesticides during pregnancy or after delivery was associated with an increased risk of brain cancer in their children (32–34,36,37). Both studies that evaluated exposure to no-pest strips during pregnancy or childhood reported an increased risk of brain cancer (34,36).

Davis et al. (36) also reported strong relative risks associated with the use of pesticide bombs during pregnancy, childhood use of lice shampoos, and childhood contact with pesticides used on pets. This study of 45 cases was the only one to evaluate the association between residential pesticide exposure and brain cancer as the primary hypothesis (36). The remaining studies collected and utilized less specific information, initially evaluating residential exposure as a confounder or covariate for other primary hypotheses (32,33,35–37). In general, studies reporting positive effects of residential pesticide exposure were those with greater detail on the timing, frequency, and form of pesticide use (33,34,36).

Farm residence during pregnancy or childhood was also shown to increase risk for childhood brain cancer including primitive neuroectodermal and nonastrocytic neuroepithelial tumors, but not astrocytic gliomas (33,37,38). Farm residence may serve as a proxy measure for both occupational and residential pesticide exposures, but it does not indicate direct exposure to an individual. The study of farm residence by Kristensen et al. (38) used information on the type of crop, the amount of pesticides purchased, and the use of pesticide equipment, as recorded on 5-year agricultural census reports to classify the farm’s possible pesticide exposure levels. Because the exposure information was collected for 5-year periods, this study could not isolate the time of exposure with respect to pregnancy and childhood; yet, it suggested that the risk of childhood brain cancer increased relative to the increase in the level of pesticides purchased (ORs = 2.0, 2.9, and 3.3) (38). Opportunities for exposure misclassification were high in these studies, but were probably nondifferential with respect to case status (33,37,38).

Leukemia

Although some studies classified leukemia as either acute nonlymphocytic leukemia (ANLL) (39) or acute lymphocytic leukemia (ALL) (40–43), most studies did not separately analyze these two forms of the disease. However, results from studies that made this distinction did not indicate differences in the risk of different types of leukemia associated with pesticide exposure. Because ALL is the most common form of childhood leukemia (5), studies that group all types of leukemias generally reflect ALL.

Five of the nine studies that evaluated occupational exposures and the risk of childhood leukemia suggested a positive association (Table 3). When studies specifically considered the use of pesticides by either parent during pregnancy rather than general employment in agriculture, the magnitude of the association with the child’s risk of leukemia greatly increased (39–41) except in the Dutch study of ALL, which did not report positive results from a mailed questionnaire (42). For both parents, Buckley et al. (39) found an increased risk of ANLL with pesticide exposure prior to conception, as well as with prolonged pesticide exposure spanning the period 1 year before birth to diagnosis. No excess risk was found when either parent had been exposed to pesticides for less than 1,000 days; however, seven case mothers had more than 1,000 days of cumulative exposure to pesticides prior to delivery, compared to none of the control mothers (p = 0.008). Paternal exposure to pesticides for more than 1,000 days nearly tripled the risk of childhood ANLL (39). With one exception (42), studies of occupational exposure after the child’s birth also suggested an increased risk of childhood leukemia (30,39,44,45).

Five studies evaluated residential exposure to pesticides. In general, no increased relative risks were associated with farm residence (38), garden pesticide use (34,43), or home extermination (34). However, taking into account the frequency of exposure, Lowengart et al. (46) reported increased risk

| Setting and study period | Case group | Upper age bound years | Case (n) | Case source | Control source | Data source; period of interest | Design: adjusted variables | Reference |
|--------------------------|------------|-----------------------|---------|-------------|----------------|-------------------------------|--------------------------|-----------|
| England, Octb 1959-1962  | Cancer, death | 14 | 4,385 | DC | NA | DC, CH | NA | (54) |
| Denmark, Oct 1968-1984   | Cancer, general | 14 | 1,747 | T | PR | Employment registry; FC | NA/ age, sex | (55) |

All studies reviewed were case–control studies except where indicated.

Abbreviations: Res, residential; Occ, occupational; AG, astrocytic glioma; PNET, primitive neuroectodermal tumor; ANLL, acute nonlymphocytic leukemia; ALL, acute lymphocytic leukemia; H, hospitals; T, tumor registry; BC, birth certificate or registry; DC, death certificate; F, friend or neighborhood; RDD, random digit dial; CCG, Children’s Cancer Study Group; PR, population registry; PC, pericranial; PG, pregnancy, CH, childhood; Dx, diagnosis; NA, information not available or not applicable to the study design; mat, maternal; pat, paternal; CNS, central nervous system; EMF, electromagnetic fields.

* Variables used in control selection are noted as design variables; variables controlled for in analyses are noted as adjusted variables.

** Study reviewed was not a case–control study.
with frequent exposure to pesticides in either the home (OR = 3.8) or garden (OR = 6.5) during pregnancy and Buckley et al. (39) reported a dose–response gradient with the frequency of home pesticide exposure during childhood (ORs = 1.8, 2.0, and 3.5), although these results were imprecise. Leiss and Savitz (34) reported a strong association between leukemia and the use of no-pest strips in the home during either pregnancy or childhood. The two studies of leukemia that considered cumulative exposure to either occupational or household pesticides showed stronger positive associations than those classifying exposure as ever versus never (39, 46). In general, results from leukemia studies suggest that no-pest strips and frequent use of pesticides in the home may be strongly associated with childhood leukemia (34, 39, 46), but even using either professional exterminations or garden pesticides did not greatly impact risk (34, 43).

Other Childhood Cancers

Among other childhood cancers (Table 4), parental occupational pesticide exposure during pregnancy was associated with an elevated risk for germ cell tumors (47) and Ewing’s sarcoma (48); however, these studies were small. In a recent study of Wilms’ tumor, Sharpe et al. (49) also reported increased risks associated with occupational pesticides, as determined through parental interview. This study also reported that the magnitude of risk for Wilms’ tumor increased slightly with increased frequency of pesticide exposure during pregnancy and varied by the child’s sex and age at diagnosis; male children and children who were diagnosed when they were over 2 years of age were more likely to have had either a mother or father who was occupationally exposed (49). This study contrasted the negative results of an earlier Wilms’ tumor study that had used birth certificates to crudely determine the father’s occupational pesticide exposure (50). Another birth certificate study reported no increased risk for neuroblastoma associated with employment in agriculture during pregnancy (51). A later study of neuroblastoma that used information from parental interviews supported these negative results for exposure during pregnancy, but reported increased risk for paternal employment in agriculture prior to conception, although results were imprecise (52). Studies that evaluated childhood cancers of all types collectively reported no increased risk with occupational pesticide exposure. These studies were limited to determining exposure status from birth certificates (31, 53), death certificates (54), and employment registries (55). Collectively studying different cancers would not have allowed researchers to distin-

guish whether certain cancers had a different association with occupational pesticide exposure than others.

In a study of farm residence, Kristensen et al. (38) reported elevated rate ratios for Wilms’ tumor, neuroblastoma, retinoblastoma, and non-Hodgkin’s lymphoma in Norway; however, as previously noted, this study was unable to address the timing of exposure with regard to pregnancy or whether parents were individually exposed. Leiss and Savitz (34) reported no association between garden pesticide use during pregnancy and either lymphoma or soft tissue sarcoma, but soft tissue sarcoma risk was increased fourfold with garden pesticide use during childhood. Schwartzbaum et al. (43) also evaluated garden pesticides. This study compared the exposures of children with various types of cancer to those of children with rhabdomyosarcoma and found only the risk of osteosarcoma to be elevated with garden pesticide use. However, the use of ill children as a comparison group may be problematic (see Discussion). Finally, studies evaluating home extermination reported no increased risk for sarcomas (34, 48), but they did report increased risk of Wilms’ tumor (56) and lymphoma (34) associated with childhood exposure. Exposure during pregnancy was not associated with elevated risk of these tumors (34, 48). It is likely that the small size of these studies of rare tumors may have contributed to their imprecise results.

Discussion

Collectively, these studies suggest an increase in risk of brain cancer, leukemia, Wilms’ tumor, Ewing’s sarcoma, and germ cell tumors associated with paternal occupational exposure to pesticides prior to and during pregnancy. Maternal occupational exposure during pregnancy was studied less frequently, but was also associated with leukemia, Wilms’ tumor, and germ cell tumors. Most of these cancers were only evaluated in one or two studies, and the number of exposed cases was often small. Childhood brain cancer and leukemia were the most studied, with fairly consistent, moderate increases in risk (27–31, 39–42, 44–46). Farm residence was associated with brain cancers, neuroblastoma, retinoblastoma, non-Hodgkin’s lymphoma, and Wilms’ tumor to varying degrees. However, inference of individual-level exposure from the aggregate pesticide exposure for all farm residents limits conclusions about risk from these studies (33, 37, 38). Few studies have evaluated no-pest strips or pesticides used on pets (34, 36); however, those studies, as well as studies of pesticide use in the home, have reported fairly consistent associations for exposure during childhood and the risk of brain cancer and leukemia, despite their small size (32–34, 36, 39, 46). It remains unclear whether a specific time window of exposure may be of greater importance in studying the effects of home pesticide use. In general, professional extermination and use of garden pesticides were less likely to show positive effects than the use of other home pesticides for most childhood cancers (32–37, 43, 46, 48); however, the risk of Wilms’ tumor (56) and lymphoma (34) was elevated with professional extermination use during childhood and brain cancer was elevated with termite extermination during pregnancy (36).

Few studies distinguished between herbicides, insecticides, fungicides, or other types of pesticides, which are not always mutually exclusive categories (36, 41). It is possible that differences in the chemical properties of various pesticides, the methods of application, and consequently the exposure pathways (dermal, ingestion, or inhalation) may be partially responsible for the reported differences in risk of childhood cancer associated with pesticide exposure. The magnitude of the relative risks reported in these studies also appears to vary by the timing and frequency of exposure, as well as by the heterogeneity of study groups and other aspects of study design. Drawing conclusions from these studies requires careful consideration of possible methodological limitations. Exposure misclassification, insufficient sample size, biases in control selection, and uncontrolled confounding are among the primary limitations of case–control studies of pesticides and childhood cancers.

The measure of exposure in all these studies was indirect, based on parents’ self-report of job titles, industry, and residential pesticide use. Information collected about home and occupational pesticide exposure has often been limited to a few general questions in an interview or questionnaire, which was rarely designed to collect detailed information about pesticide exposure. Several studies collected exposure information from birth or death certificates, which may not accurately represent the actual job, exposure, or time period of interest (29, 31, 50, 51, 53, 54). Thus, most studies dichotomized exposure into ever versus never exposed, without regard to the frequency or duration of exposure or the specific type of pesticide (27–31, 34–37, 40–45, 47, 48, 50–55, 57). The studies showing a positive relationship between pesticides and childhood cancers tended to be those that had a priori interest in pesticides and ascertained exposure in more detail with respect to timing, intensity, or pesticide type (33, 34, 36, 38, 39, 46, 49, 56). By employing industrial hygienists to aid in
Table 2. Case–control studies evaluating the risk of childhood brain cancer associated with parental occupational and residential exposure and residential exposure to pesticides prior to conception, during pregnancy, and during childhood.

| Exposure type and frequency | Occupation (Father) | Farm residence | Garden | Home extermination | Pesticide (general) | Reference |
|-----------------------------|--------------------|----------------|-------|-------------------|---------------------|-----------|
| Cancer type                 | Exposure period    | Cancer type    | OR    | OR                | OR                  | Cl or p-value | |
| Agriculture                 | 2.4                | 1.2–4.9        |       |                   |                     | (29)       |
| Agriculture                 | 1.6                | 0.4–6.1        |       |                   |                     | (27)       |
| Agriculture                 | 2.7b               | 0.8–8.1        |       |                   |                     | (27)       |
| Agriculture                 | 1.8a               | 0.6–6.0        |       |                   |                     | (28)       |
| Agriculture                 | 1.0                | 0.2–4.3        |       |                   |                     | (28)       |
| Farmer                     | (1/0)b             | Unspec         | 1.3   | 0.7–6.3           |                     | (29)       |
| Farmer                     | (1/2)a            | Unspec         | (1/0)b |                  |                     | (30)       |
| Farm, unspecified           | 1.2                |               |       |                   |                     | (31)       |
| Horticulture                | 1.3                | 0.9–1.8        |       |                   |                     | (30)       |
| Pesticide c                 | 1.4                | 1.0–1.9        |       |                   |                     | (30)       |
| Grain farm                 | 1.3                | 1.0–1.8        |       |                   |                     | (26)       |
| Horticulture               | NAG                | 0.9–2.7        |       |                   |                     | (30)       |
| Grain farm                | NAG                | 1.1–2.8        |       |                   |                     | (30)       |
| Pest purchase-low          | NAG                | 0.9–4.7        |       |                   |                     | (30)       |
| Pest purchase-medium       | NAG                | 1.5–1.6        |       |                   |                     | (30)       |
| Pest purchase-high         | NAG                | 1.4–7.8        |       |                   |                     | (30)       |
| Farm, unspecified           | Unspec             | 4.5            |       |                   |                     | (37)       |
| Farm, unspecified           | Unspec             | 1.0b           |       |                   |                     | (37)       |
| Farm, unspecified           | AG                 | 0.5            |       |                   |                     | (33)       |
| Farm > 1 year              | PNET               | 0.8–23.9       |       |                   |                     | (33)       |
| Garden                      | 0.6                | 0.3–1.1        |       |                   |                     | (24)       |
| Pesticide                  | 1.5                | 0.6–3.9        |       |                   |                     | (36)       |
| Insecticide                | 1.2c               | 0.5–3.0        |       |                   |                     | (36)       |
| Insecticide                | 1.1                | 0.5–2.5        |       |                   |                     | (36)       |
| Herbicide                  | 1.0c               | 0.4–2.4        |       |                   |                     | (36)       |
| Herbicide                  | 1.1                | 0.7–3.3        |       |                   |                     | (36)       |
| Herbicide                  | 1.0c               | 0.7–3.3        |       |                   |                     | (36)       |
| Herbicide                  | Pre-Dx             | 0.9            |       |                   |                     | (36)       |
| Home extermination          | 1.3                | 0.7–2.1        |       |                   |                     | (34)       |
| Ever                        | 1.0                | 0.4–1.4        |       |                   |                     | (32)       |
| Ever                        | PNET               | 0.6–1.9        |       |                   |                     | (32)       |
| Insecticides                | Unspec             | 2.3            |       |                   |                     | (37)       |
| Insecticides                | Unspec             | 1.2b           |       |                   |                     | (37)       |
| Termites, father           | 2.9                | 1.3–7.1        |       |                   |                     | (36)       |
| Chlordane, father          | 1.5                | 0.5–4.9        |       |                   |                     | (36)       |
| Pesticide (general)         | Ever               | 1.8            | 0.8–4.0 |                   |                     | (39)       |
| Ever                        | 1.2c               | 0.5–2.9        |       |                   |                     | (36)       |
| Ever                        | AG                 | 0.8–2.7        |       |                   |                     | (39)       |
| Ever                        | PNET               | 0.6–1.4        |       |                   |                     | (39)       |
| Ever                        | 1.5                | 0.5–8.3        |       |                   |                     | (39)       |
| Ever                        | 6.2c               | 1.4–28.4       |       |                   |                     | (39)       |
| Ever                        | 1.5                | 0.9–2.4        |       |                   |                     | (34)       |
| Ever                        | 5.2                | 1.2–22.2       |       |                   |                     | (36)       |
| Ever                        | 1.9d               | 0.6–5.9        |       |                   |                     | (36)       |
| Ever                        | 0.6                | 0.2–1.5        |       |                   |                     | (36)       |
| Ever                        | 0.8                | 0.2–1.5        |       |                   |                     | (36)       |
| Ever                        | 7 months–Dx        | 1.1            |       |                   |                     | (36)       |
| Ever                        | 6.2c               | 1.4–28.4       |       |                   |                     | (39)       |
| Ever                        | 1.5                | 0.9–2.4        |       |                   |                     | (34)       |
| Ever                        | 5.2                | 1.2–22.2       |       |                   |                     | (36)       |
| Ever                        | 1.9d               | 0.6–5.9        |       |                   |                     | (36)       |
| Ever                        | 0.6                | 0.2–1.5        |       |                   |                     | (36)       |
| Ever                        | 7 months–Dx        | 1.1            |       |                   |                     | (36)       |
| Ever                        | 6.2c               | 1.4–28.4       |       |                   |                     | (39)       |

(Table 2 continued, next page)
the development and interpretation of
cstructed questionnaires with job-
and exposure-specific questions, the quality of
information obtained from interviews may
be substantially improved (33,49,58-61).
Questions on the type of crop and purpose
for pesticide use have been helpful in studies of
pesticides (58,62). Information from new
pesticide-exposure databases and reference
literature can also be incorporated with the
information from the questionnaires to
improve exposure classification (63,64). In
addition to improving interview questions,
biological exposure data may be utilized to
validate self-reported exposure information
in studies evaluating recent exposures.
Although the expense and logistics of collect-
ing biological samples may be prohibitive for
large-scale childhood cancer studies or stud-
ies of past exposures, smaller substudies may
accommodate such direct measurement of
pesticides. This information may give
researchers the ability to validate and refine
interview instruments to capture information
on exposure routes and timing for parents
and children (61,65).

Even when exposure assessment instru-
ments have been used in an attempt to collect
exposure information in sufficient detail, par-
ents probably had difficulty remembering
details about the frequency and timing of pes-
ticide use relative to conception, pregnancy,
and their child’s diagnosis, especially when
these time periods may have been up to 20
years earlier. Similarly, when both parents
were not interviewed, the accuracy of the
mothers’ report of paternal occupational
exposures is questionable (66). Despite inves-
tigators’ efforts to elicit accurate information
by parental recall, it is possible to markedly
improve the quality of the information
obtained. Recent studies have shown that the
manner in which the question is asked
(closed response options rather than open
questions), the specificity of the questions,
and provision of memory aids prompted
improved recall (58,59,62). For example,
Davis et al. (36) provided a list of pesticide
brands and chemical names as a memory aid
to help parents identify which pesticides were
used in or around their home. In general,
such aids are thought to improve exposure
classification by increasing the sensitivity of
reporting for both cases and controls; howev-
er, they are not thought to improve the speci-
ficity (67). Although many errors in exposure
assessment are likely to be nondifferential
with respect to disease status (61), differential
recall based on motivation of case parents
could result in an overestimate of effect,
particularly in studies of childhood disease
where case parents may be more motivated to find
a reason for their child’s illness (68). Highly
structured interviews with detailed questions
is one strategy for reducing recall bias
(60,61,67). Unfortunately, indirect exposure
assessment based on parental recall remains
one of the major limitations of case-control
studies, which is not easily corrected.
However, until reliable and affordable bi-
markers of direct pesticide exposure are de-
veloped to capture historical periods of interest,
edemiologic studies must continue to improve
indirect exposure assessment tools.

Analysis of the information collected on
pesticides may also be problematic. There
may be multiple sources of pesticide expo-
sure during the same time period, including
home, garden, and occupational exposures
by one or both parents. Most studies did not
evaluate pesticides separately by specific pes-
ticide, chemical class, frequency and dura-
tion of exposure, or account for multiple
exposures; these studies also did not specify
their rationale in selecting the time of inter-
est. Limited animal data on mechanisms of
perinatal carcinogenesis and consideration of
human development suggests that mechani-
isms would differ for exposures prior to
conception, in utero, and during childhood
(8). By not separately considering these
time windows with respect to either the timing
or the cumulative effects of exposure, studies
have assumed that risk is similar across all
exposure windows. Despite the lack of labo-
atory information to guide researchers in
determining which specific time periods
during development are more susceptible to
pesticide exposure, epidemiologic studies
should consider specific exposure windows
relative to conception, pregnancy, and child-
hood. Failure to consider interactive effects
or uncontrolled confounding of pesticide
exposure by multiple time periods and mul-
tiple types of exposure could bias study
results in either direction (61).

There was also variability in case and
control participation rates and study size.
The participation rates in these studies
ranged from 52 to 100%. Low participation
rates increase the potential for selection bias,
limiting the validity of study results and
conclusions. These studies were generally of
small sample size, forcing researchers to
choose between less precise results if they
attempted to control for confounding or
potentially less valid results if they did not.
Despite the rarity of childhood cancers, larg-
er studies with nearly complete case ascer-
tainment are necessary to increase the power
to detect real differences between cases and
controls and to allow evaluation of potential
confounders and effect modifiers. In recent
years, collaborative study groups including
multiple children’s hospitals have begun
addressing this need for larger epidemiologic
studies (3,33,39,43,56).

In principle, control selection may be the
easiest methodological issue to address. Some

Table 2. (continued)

| Exposure type and frequency | Cancer type | Exposure period | Pregnancy OR | CI or p-value | Childhood OR | CI or p-value | Reference |
|----------------------------|-------------|----------------|--------------|--------------|--------------|--------------|-----------|
| On pets, insects (continued) | Cancer type | Exposure period | Pregnancy OR | CI or p-value | Childhood OR | CI or p-value | Reference |
| Ever | Ever | 0.4* | 0.1-1.0 | 0-6 months | 1.8* | 1.8-6.6 | (36) |
| Pet collar, flea | Ever | 0.9 | 0.4-2.1 | 0-6 months | 5.5 | 1.5-20.0 | (36) |
| Shampoo, lice (Kwell) | Ever | 0.6* | 0.2-1.3 | 0-6 months | 4.4* | 1.4-14.3 | (36) |

Brain cancers were studied collectively unless specified. Abbreviations: AG, astrocytic glioma; NAG, non-astrocytic neuroepithelial tumor; PNET, primitive neuroectodermal tumor; Dx, diagnosis; Unspec, age of exposure during childhood was not specified in reviewed study; OR, odds ratio; CI, 95% confidence intervals.

*Exposure prior to conception.
†Unable to calculate OR; (r cases exposed/n controls exposed).
‡Cancer control group.
studies have used friends or neighborhood children for comparison. This raises concern that common parental occupational exposures, ecological exposures, and similarities in home and yard pesticide practices may overrepresent exposure in the controls and dilute potential associations. Similarly, comparison groups of children with other cancers or illnesses may attenuate effects of exposures because different childhood cancers may have some common etiologic factors. In this review, studies that compared cases to cancer controls often found no effects or inverse effects of pesticides and the cancer of interest (30,36,37,43). Using telephone number to randomly select controls (random digit dialing) from the same broad geographic region as the case may provide the most demographically similar control groups, without overmatching on exposures of interest (69).

Finally, childhood cancers are not etiologically homogeneous diseases. Studies of broadly defined disease are less likely to identify risks associated with pesticides and other risk factors when only subsets of cases are actually affected. A few studies evaluated ALL and ANLL separately, reporting little difference in their relationship with pesticide exposure (38-42). However, when Bunin et al. (33) evaluated histologic subgroups of

| Exposure type and frequency | Cancer type | OR  | CI or p-value | Exposure period | OR  | CI or p-value | Reference |
|----------------------------|-------------|-----|---------------|-----------------|-----|---------------|-----------|
| Occupation, parents (either) | Agriculture | 0.3 | 0.1-1.6       | 0-50            | 0.9 | 0.5-1.5       | (40)      |
|                             | Farmer      | 1.0 | 0.3-3.7       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
| Occupation (father)         | Agriculture | 1.0 | 0.6-1.7       | 0-50            | 0.9 | 0.5-1.5       | (40)      |
|                             | Pesticide   | 1.0 | 0.4-6.3       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
|                             | Pesticide 1-1,000 days | 1.0 | 0.4-6.3       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
|                             | Pesticide >1,000 days | 1.0 | 0.4-6.3       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
| Occupation (mother)         | Agriculture | 0.3 | 0.1-1.6       | 0-50            | 0.9 | 0.5-1.5       | (40)      |
|                             | Pesticide   | 1.0 | 0.4-6.3       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
|                             | Pesticide 1-1,000 days | 1.0 | 0.4-6.3       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
|                             | Pesticide >1,000 days | 1.0 | 0.4-6.3       | 0-50            | 0.6 | 0.3-1.4       | (40)      |
| Farm residence              | Agriculture | 0.3 | 0.1-1.6       | 0-50            | 0.9 | 0.5-1.5       | (40)      |
|                             | General pesticide | 0.3 | 0.1-1.6       | 0-50            | 0.9 | 0.5-1.5       | (40)      |

Abbreviations: ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia; Dx, diagnosis; Unspec, age of exposure during childhood was not specified in reviewed study; OR, odds ratio; CI, 95% confidence interval.

*Types of leukemia were studied collectively unless specified.

*Exposure prior to conception.

*Unable to calculate OR; (n cases exposed/n controls exposed).

*Cancer control group.
### Table 4. Case–control studies that evaluated the risk of other childhood cancers associated with parental occupational and residential exposure to pesticides prior to conception, during pregnancy, and during childhood

| Exposure type and frequency | Cancer type                | Exposure period | Age | OR   | CI or p-value | Reference |
|-----------------------------|----------------------------|-----------------|-----|------|---------------|-----------|
| Occupation (parents)        |                            |                 |     |      |               |           |
| Farmer                      | Cancer, general            |                 |     | 1.2  | p<0.05        | (31)      |
| Occupation (father)         |                            |                 |     |      |               |           |
| Farmer                      | Cancer, general            |                 |     | 0.7  | 0.4–1.2       | (52)      |
| Farmer                      | Cancer, general            |                 |     | 0.9  | 0.4–1.8       | (53)      |
| Farmer                      | Cancer, general            |                 |     | 1.1  |               | (54)      |
| Agriculture                 | Wilms'                     |                 |     | 0.6  |               | (50)      |
| Pesticide                   | Wilms'                     |                 |     | 0.3  |               | (50)      |
| Pesticide <10 times         | Wilms'                     |                 |     | 2.7  | 0.8–9.8       | (49)      |
| Pesticide >10 times         | Wilms'                     |                 |     | 3.2  | 1.2–9.0       | (49)      |
| Pesticide Wilms', male child|                             |                 |     | 8.6  | 2.1–35.1      | (49)      |
| Pesticide Wilms', female child|                          |                 |     | 1.3  | 0.4–4.1       | (49)      |
| Agriculture                 | Neuroblastoma              |                 |     | 0.6  | 0.2–1.4       | (51)      |
| Agriculture                 | Neuroblastoma              |                 |     | 0.7  | 0.1–5.8       | (52)      |
| Agriculture                 | Neuroblastoma              |                 |     | 3.5  | 0.7–34.6      | (52)      |
| Agriculture                 | Ewing’s sarcoma            |                 |     | 7.3  | 1.9–28.4      | (49)      |
| Pesticide                   | Ewing’s sarcoma            |                 |     | 8.8  | 1.7–21.9      | (49)      |
| Pesticide                   | Germ cell                  |                 |     | 1.8  | 0.7–5.0       | (47)      |
| Occupation (mother)         |                            |                 |     |      |               |           |
| Pesticide <10 times         | Wilms'                     |                 |     | 0.3  | 0.1–2.3       | (49)      |
| Pesticide >10 times         | Wilms'                     |                 |     | 12.86| 6.4–2869.0    | (49)      |
| Pesticide Wilms', male child|                             |                 |     | 4.6  | 0.8–26.4      | (49)      |
| Pesticide Wilms', female child|                          |                 |     | 2.0  | 0.5–8.9       | (49)      |
| Pesticide                   | Germ cell                  |                 |     | 2.4  | 0.9–6.9       | (47)      |
| Farm residence              |                            |                 |     |      |               |           |
| Orchards                    | Cancer, general            |                 |     | 1.9  | 1.2–2.9       | (30)      |
| Orchards                    | Wilms'                     |                 |     | 4.8  | 1.6–14.7      | (30)      |
| Orchard + pesticide         | Wilms'                     |                 |     | 8.9  | 2.7–29.5      | (30)      |
| Pesticide                   | Wilms'                     |                 |     | 2.5  | 1.0–6.6       | (30)      |
| Field vegetables            | Neuroblastoma              |                 |     | 2.5  | 1.0–6.1       | (30)      |
| Field vegetables + pesticides| Retinoblastoma             |                 |     | 3.2  | 0.9–10.9      | (30)      |
| Horticulture + pesticides   | NHL                        |                 |     | 2.1  | 1.0–4.3       | (30)      |
| Pesticide                   | Hodgkin’s                  |                 |     | 1.3  | 0.8–2.1       | (30)      |
| Pesticide                   | Soft tissue sarcoma        |                 |     | 1.3  | 0.5–2.9       | (30)      |
| Pesticide                   | Rhabdomyosarcoma           |                 |     | 1.0  | 0.2–5.2       | (57)      |
| Garden                      |                            |                 |     |      |               |           |
| Ever                        | Wilms'                     | 0–Dx            |     | 0.7b | p=0.30        | (43)      |
| Ever                        | Neuroblastoma              | 0–Dx            |     | 1.1b | p=0.78        | (43)      |
| Ever                        | NHL                        | 0–Dx            |     | 1.3b |               | (43)      |
| Ever                        | Hodgkin’s                  | 0–Dx            |     | 1.4b |               | (43)      |
| Ever                        | Lymphoma                   | 0.5             |     | 0.2–1.2| 0–2 years | 0.8 | 0.3–1.8 | (34) |
| Ever                        | Lymphoma                   | 2 years–Dx      |     | 0.6  | 0.4–1.0       | (34)      |
| Ever                        | Soft tissue sarcoma        | 0.8             |     | 0.5–1.3| 0–2 years | 4.1 | 1.0–16.9 | (34) |
| Ever                        | Ewing’s sarcoma            | 0–Dx            |     | 1.1b |               | (43)      |
| Ever                        | Osteosarcoma               | 0–Dx            |     | 2.6b | p=0.01        | (43)      |
| Home extermination          |                            |                 |     |      |               |           |
| Ever                        | Wilms'                     | 3 years Pre-Dx  |     | 2.4  | 1.1–5.1       | (56)      |
| Ever                        | Wilms'                     | 3 years Pre-Dx  |     | 2.2  | 1.3–3.8       | (56)      |
| Ever                        | Wilms'                     | 3 years Pre-Dx  |     | 2.2  | 0.9–5.1       | (56)      |
| Ever                        | Lymphoma                   | 1.2             |     | 0.4–3.9| 0–2 years | 1.8 | 1.1–2.9 | (34) |
| Ever                        | Lymphoma                   | 2 years–Dx      |     | 1.6  | 0.9–2.9       | (34)      |
| Ever                        | Soft tissue sarcoma        | 0.3             |     | 0.0–1.8| 0–2 years | 0.5 | 0.1–2.4 | (34) |
| Ever                        | Soft tissue sarcoma        | 2 years–Dx      |     | 0.7  | 0.1–5.3       | (34)      |
| Ever                        | Ewing’s sarcoma            | 0.3             |     | 0.0–2.1| Unspec      | 0.6 | 0.3–1.2 | (40) |
| General pesticide           |                            |                 |     |      |               |           |
| Ever                        | Rhabdomyosarcoma           |                 |     | Unspec|               | (57)      |
| No-pest strip               |                            |                 |     |      |               |           |
| Ever                        | Lymphoma                   | 1.4             |     | 0.7–2.5| 0–2 years | 1.3 | 0.4–2.7 | (34) |
| Ever                        | Lymphoma                   | 2 years–Dx      |     | 1.1  | 0.6–1.9       | (34)      |
| Ever                        | Sarcoma                    | 0.6             |     | 0.1–2.6| 0–2 years | 0.5 | 0.1–2.3 | (34) |

Abbreviations: NHL, Non-Hodgkin’s lymphoma; Dx, diagnosis; Unspec, age of exposure during childhood was not specified in reviewed study; OR, odds ratio; CI, 95% confidence interval.

*Exposure prior to conception.

*Cancer control group.
brain cancer, they reported different effects of pesticide exposure on astrocytic glioma and primitive neuroectodermal tumor (33). A study of Wilm’s tumor has also suggested that risk may vary by the age of diagnosis and the sex of the child as well (49). In order to better understand cancer etiology, studies have recently begun to evaluate environmental risk factors for childhood cancers using cases more narrowly defined by characteristics such as histopathology, age, and biological markers (3).

Although many of these studies suggest an association between certain exposures and certain cancers, an etiologic relationship between pesticide exposure and childhood cancer is far from proven. Future epidemiologic research should incorporate the methodologic improvements previously noted in order to confirm and further define any association between pesticides and specific childhood cancers. Specifically, studies should carefully classify exposure with regard to chemical type and timing and more narrowly define cancer type based on histology. Laboratory investigations are also needed to provide the critical data for understanding these mechanistic relationships.

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