Pesticides and Childhood Cancer

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Children are exposed to potentially carcinogenic pesticides from use in homes, schools, other buildings, lawns and gardens, through food and contaminated drinking water, from agricultural application drift, overspray, or off-gassing, and from carry-home exposures of parents occupationally exposed to pesticides. Parental exposure during the child’s gestation or even preconception may also be important. Malignancies linked to pesticides in case reports or case–control studies include leukemia, neuroblastoma, Wilms’ tumor, soft-tissue sarcoma, Ewing’s sarcoma, non-Hodgkin’s lymphoma, and cancers of the brain, colorectum, and testes. Although these studies have been limited by nonspecific pesticide exposure information, small numbers of exposed subjects, and the potential for case–response bias, it is noteworthy that many of the reported increased risks are of greater magnitude than those observed in studies of pesticide-exposed adults, suggesting that children may be particularly sensitive to the carcinogenic effects of pesticides. Future research should include improved exposure assessment, evaluation of risk by age at exposure, and investigation of possible genetic–environment interactions. There is potential to prevent at least some childhood cancer by reducing or eliminating pesticide exposure.

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Introduction

Pesticides are agents designed to kill insects, weeds, fungi, rodents, and other unwanted animals and plant life. Many are carcinogenic in animal bioassays and some are known or suspected to be human carcinogens. Of 51 pesticides evaluated by the U.S. National Cancer Institute and the U.S. National Toxicology Program as of 1990, 24 demonstrated carcinogenicity in chronic bioassays (1). As of 1997, the International Agency for Research on Cancer had classified 26 pesticides as having sufficient evidence of carcinogenicity in animals and 19 as having limited evidence in animals (2,3). Of these, 8 and 15 pesticides, respectively, are still registered for use in the United States (4,5) (Table 1). Furthermore, many compounds banned or severely restricted in the United States, notably many organochlorine insecticides, are still in use in other countries.

Sources of Pesticide Exposure

The majority of pesticide use in this country is related to agriculture. Children living on or near treated croplands can be exposed through agricultural application drift, overspray, or off-gassing (6,7). Pesticide-laden dust is tracked into homes on shoes and on pets (8,9) and is a major source of exposure within the home (9,10). Farmers and other occupationally exposed parents may bring pesticides into the home on their clothing and equipment (11). Young children, who are likely to spend a large proportion of their time on the floor or ground and who frequently put hands and objects in their mouths (10), may be at particularly high risk of exposure.

Contamination of ground and surface water from agricultural runoff can also result in the exposure of children to pesticides. The U.S. Department of Agriculture estimates that 50 million people in the United States obtain their drinking water from groundwater that is potentially contaminated by pesticides and other agricultural chemicals (12). The U.S. Environmental Protection Agency (U.S. EPA) National Pesticide Survey of drinking water wells found one or more pesticides or pesticide degradates in 10.4% of community water systems and 4.2% of rural domestic wells (13). Conventional drinking water treatment techniques do not remove the pesticide contaminants. A 1994 study of tests for five herbicides in 20,000 samples of tap water and drinking water sources found that 14.1 million people routinely drink water contaminated with atrazine, cyanazine, simazine, alachlor, and metolachlor (14). Many samples contained two or more herbicides. In 1995 another survey by the same environmental organization also found widespread contamination of tap water by herbicides, frequently at levels exceeding the U.S. EPA lifetime health advisory level (15). Again, multiple pesticides were found simultaneously in approximately two-thirds of the cities. Pesticides can persist in the groundwater even after use has been curtailed. For example, dibromochloropropane, a soil fumigant banned in California in 1977, is still found in sufficient concentrations in California groundwater (16,17) to “pose a significant health risk in agricultural areas” (17).

A recent report found increased concentrations of triazone and acetanilide herbicides in rainfall during the late spring and summer in the United States (18). The highest concentrations were observed in Midwest Corn Belt states following herbicide applications to cropland.

Food can become contaminated by pesticides, particularly insecticides, as a result of treatments in the field, during storage, or in the home (7). Although diet does not appear to be a major route of exposure for most pesticides (19), concerns exist over the occasional single food item that may have extremely high residues (e.g., one potato had lethal levels of aldicarb) (20) and the effects on children, who typically eat more fruits per unit of body weight than adults and who may be particularly sensitive to toxic effects because of immature metabolism and other factors (21). One report estimated that one out of every four times a child 5 years of age or under eats a peach, he or she is exposed to an unsafe level of organophosphate insecticides (22). A 1995 survey of 76 jars of baby food from grocery stores found 16 pesticides in eight...
Table 1. Pesticides with limited or sufficient evidence of carcinogenicity in animals [International Agency for Research on Cancer (2)].

| Pesticide                  | Animal evidence of carcinogenicity | Currently registered in the United Statesa |
|----------------------------|-----------------------------------|---------------------------------------------|
| Herbicides                 |                                   |                                             |
| Amitrole                   | Sufficient                        | Y                                           |
| Atrazine                   | Limited                           | Y                                           |
| Dieldrate                  | Limited                           | Y                                           |
| Monuron                    | Limited                           | Y                                           |
| Nitrofen                   | Sufficient                        | N                                           |
| Picloram                   | Limited                           | Y                                           |
| Sulfate                    | Sufficient                        | N                                           |
| Trifluran                   | Limited                           | Y                                           |
| Insecticides               |                                   |                                             |
| Aldrin                     | Limited                           | N                                           |
| Aramite                    | Sufficient                        | N                                           |
| Arsenic and arsenical compounds | Limited                 | Nb                                          |
| Chlordane/heptachlor       | Sufficient                        | N                                           |
| Chlordecone                | Sufficient                        | N                                           |
| Chlorbenzilate             | Limited                           | N                                           |
| DDT                        | Sufficient                        | N                                           |
| Dichlorvos                 | Sufficient                        | Y                                           |
| Dicofol                    | Limited                           | Y                                           |
| Dieldrin                   | Limited                           | N                                           |
| HCH, α-HCH                 | Sufficient                        | N                                           |
| β-HCH, γ-HCH (lindane)     | Limited                           | Y                                           |
| Methyl parathion           | Limited                           | Y                                           |
| Mirex                      | Sufficient                        | N                                           |
| Tetraclorvinphos           | Limited                           | Y                                           |
| toxaphene                  | Sufficient                        | N                                           |
| Nonarsenical insecticides  | Limited                           | Y                                           |
| Fungicides                 |                                   |                                             |
| Captorf                    | Sufficient                        | N                                           |
| Captain                    |                                   |                                             |
| Chlorothalonil             | Limited                           | Y                                           |
| Ethylene thiourea          | Sufficient                        | Yc                                          |
| Formaldehyde               | Sufficient                        | Y                                           |
| Hexachlorobenzene          | Sufficient                        | N                                           |
| Pentachloronitrobenzene    | Limited                           | Y                                           |
| Pentachlorophenol          | Sufficient                        | Y                                           |
| ortho-phenyl phenol        | Sufficient                        | N                                           |
| Sodium ortho-phenyl phenate| Sufficient                        | N                                           |
| 2,4,6-Trichlorophenol      | Sufficient                        | Y                                           |
| Ziram                      | Limited                           | Y                                           |
| Other                      |                                   |                                             |
| Crescote                   | Sufficient                        | Y                                           |
| 1,2-Dibromo-3-chloropropane| Sufficient                        | N                                           |
| 1,3-Dichloropropene        | Sufficient                        | Yb                                          |
| Dimethylcarbamoyl chloride | Sufficient                        | –                                           |
| 1,1-Dimethyl hydrazine     | Sufficient                        | –                                           |
| Ethylene dibromide         | Sufficient                        | N                                           |
| Methyl bromide             | Limited                           | Y                                           |
| Methylmercury chloride     | Sufficient                        | N                                           |

Abbreviations: –, could not be determined; HCH, hexachlorocyclohexane; N, no; Y, yes. *Data from IARC (2,3) and the U.S. EPA (4,5). **Severely restricted. *Contaminant or metabolite of a registered product.

brand-name products (23). The pesticides detected included three probable human carcinogens and five possible human carcinogens, as classified by the U.S. EPA. Infants can also be exposed to pesticides and pesticide metabolites in breast milk and via placental transfer (24,25).

Exposure may occur from leaks, spills, and accidents during the manufacture, distribution, and application of pesticides and from routine pollution from manufacturing and disposal sites. For example, 20% of Arkansas children who lived near an herbicide manufacturing plant had residues of 2,4-dichlorophenoxacetic acid (2,4-D) in their urine (26).

The majority of most children's exposure to pesticides, however, is from home, lawn, and garden use of pesticides (27). The National Home and Garden Pesticide Use Survey conducted by the U.S. EPA found that 82% of U.S. households used pesticides with an average of three to four different pesticide products per home (28). Sixty-six percent of households treated their home's primary living area one or more times per year (28). Thirty-seven percent of households reported insecticide treatments when there was no major insect problem (28). These data were consistent with the earlier National Household Pesticide Usage Study (29), which reported that 84% of households used pesticides inside the home. In data from a childhood cancer case–control study, Leiss and Savitz (30) reported that 26% of control households had a history of home extermination and 27% reported use of pest strips. Use of termiticides outside and beneath a home can also result in indoor pesticide exposure (7). There are also case reports of extreme pesticide use, such as the report of a child whose mattress was sprayed twice per week for most of his life with DDVP-Baygon (Bayer, Leverkusen, Germany), a combination of an organophosphate and a carbamate insecticide (31).

Pesticide use on gardens and lawns may also result in exposure to children either during application or if engaging in activities on the lawn within one day of application (32,33). The National Home and Garden Pesticide Survey (28) found that 2% of households used herbicides on the yard or garden annually. Similar frequencies of use ranging from 21 to 33% have been reported in other surveys (7,29,34). The use of lawn care pesticides is increasing 5 to 8% annually (35). Use of lawn chemicals at any time (ever) was reported to be 63% (30) and 68% (36) in the control populations of two cancer case–control studies. The amount of pesticides per treated acre of household land is almost five times the application rate for treated agricultural lands (37). A biomonitoring study of dogs found that animals having contact with lawns treated with 2,4-D had measurable levels in their urine for several days after application (38). Thus, incidental contact with lawn care pesticides may lead to exposures. Public lands such as school yards, parks, and golf courses are often treated with pesticides and may result in exposure to children.

Both indoor and outdoor pesticide use can result in household contamination, particularly in carpets (7,9,39), that can persist for years because of the lack of sun, rain, and other factors that speed pesticide degradation outdoors (40–43). The number and
concentration of pesticides found in household dust are greater than those found in air, soil, or food (41,43). These residues are of great concern for children. In one study of a broadcast flea treatment, the household residues had a vertical (floor to ceiling) concentration gradient so the resulting respiratory dose estimated for a child was 4 to 6 times greater than that for an adult; dermal dose estimates were 30 times greater (44). Children’s toys can also serve as a reservoir for pesticides (45). The organophosphate insecticide chlorpyrifos accumulates on plastic and in plush toys through a two-stage process whereby the pesticide was deposited on surfaces during application, then released as a vapor, redeposited, and sorbed by furniture and toys for at least 2 weeks postapplication (45).

Children may be exposed to pesticides through pet products and through use of insecticidal shampoos for lice infestations, sometimes with a large number of applications per child.

**Epidemiologic Studies**

**Study Designs**

The evidence that pesticide exposure may be associated with childhood cancer comes from case reports and several types of epidemiologic studies. Case reports are observations of unusual cancer–exposure combinations in one or more individuals. Reports involving several cases are often called clusters. Case reports may reflect a causal relationship or may be due to chance. The specific pesticide exposures are often clearly identified in case reports, much more so than in larger studies, and often demonstrate excessive use of pesticides around children [e.g., a child’s mattress sprayed with propoxur twice weekly for most of the child’s life (31)]. Case reports can stimulate further investigation using more rigorous research techniques. Cross-sectional, or ecologic, studies evaluate the correlation between rates of cancer and exposure based on population-level data (e.g., county pesticide use and county cancer incidence rates). Typically, they are not based on data on the individual level, have little information on potential confounders, do not take disease latency into account, and do not account for migration into or out of the geographic area under investigation. They can, however, provide clues to cancer etiology, usually at low cost. The most rigorous study designs are the case–control and cohort approaches. In case–control studies, past pesticide exposures of cases and controls are compared. Using the cohort approach, study groups are selected on the basis of exposure status (e.g., pesticide-exposed group vs unexposed group) and disease rates in the two groups are compared. The advantages and limitations of each approach are described by Grufferman (46).

Most of the data on childhood cancer and pesticides are from case–control studies. There have been few case reports for most of the childhood cancers and only one relevant cohort study, an investigation of cancer among children of Norwegian farmers (47,48). Most of the research has focused on leukemia and brain cancer, with little attention given to other childhood malignancies. This is probably a reflection of the rarity of these other cancers, which makes them difficult to study.

The studies are reviewed by cancer type, identifying the study design, the number of cases, the exposure (e.g., occupational exposure to pesticides, household use of pesticides, specific chemicals), the person exposed (e.g., mother, father, child), the amount, the timing of exposure (e.g., preconception, during pregnancy, at birth, during childhood), the number of exposed cases, risk estimate, and confidence intervals (CI), when available. Some studies investigated more than one cancer type and appear in multiple tables in this paper. Studies that presented data only for all childhood cancers combined are not included.

**Leukemia**

Beginning in the late 1970s, there were several case reports of leukemia among children exposed to pesticides (Table 2). The termiticide chlor dane, the organophosphate insecticide dichlorvos, and the carbamate propoxur were linked to leukemia among children (31,49,50). A cluster of cancers including leukemia was noted among children in the farm community of McFarland, California (51). These excess cancer rates remain controversial and under investigation almost 10 years after the initial report.

This review of 17 case–control studies and one cohort study supports a possible role for pesticides in childhood leukemia (30,48,52–67). Most, but not all, of the studies report elevated risks among children whose parents were occupationally exposed to pesticides or who used pesticides in the home or garden. Parental use of pesticides in the home or garden during pregnancy (father or mother) or nursing (mother only) was associated with 3- to 9-fold increases in childhood leukemia in a case–control study in Los Angeles County, California (55). Maternal employment in agricultural occupations (odds ratio [OR] 1.8) or reported exposure to pesticides during pregnancy (OR 3.5) was associated with acute lymphocytic leukemia (ALL) in a case–control study in China (57). Occupational exposure to pesticides by either parent and use of pesticides in the home or garden during childhood was linked to acute myeloid leukemia (AML) in U.S. children (58). Some of the studies report excesses that are not statistically significant, possibly because of the extremely small numbers of exposed subjects.

Many of the studies evaluated parental occupations obtained from birth certificates or other records, assuming that employment as a farmer or in other agricultural occupations implied pesticide exposures. Buckley et al. (58) obtained lifetime occupational histories and calculated the number of days of pesticide exposure. The ORs increased to 2.7 among children whose fathers were exposed for more than 1000 days. Seven cases and no controls had mothers with more than 1000 days of pesticide exposure.

Some studies evaluated risk of leukemia according to reports of pesticide use in the home or garden and, in some, analyzed separately for parental exposure and for the child’s exposure. Household pesticide use might be assumed to be insecticides only, whereas garden and lawn pesticides include both insecticides and herbicides. Leiss and Savitz (30) evaluated pesticide products and found significant excesses of leukemia associated with use of pest strips, but not for household extermination or yard pesticide treatments. Only one study analyzed levels of pesticides or their metabolites in biologic specimens. Scheele et al. (63) found no significant differences in levels of DDT, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethylene, hexachlorobenzene, hexachlorocyclohexane, or dieldrin in the bone marrow of childhood leukemia cases at diagnosis when compared to controls. When all studies were reviewed, no clear patterns of risk by which parent was exposed, by timing of exposure, or by histologic type of leukemia were apparent.

Exposure–response gradients were seen in the two studies that assessed levels of the child’s direct exposure to pesticides. Children who were exposed to pesticides less than once per week, one to two times per week, or most days of their lives had ORs of 1.8, 2.0, and 3.5, respectively, in a study of acute nonlymphocytic leukemia by Buckley et al. (58). Mulder et al. (66)
### Table 2. Summary of studies on pesticides and childhood leukemia.

| Study design | Reference | Cancer | Total cases, no. | Exposure | Timing of exposure | Exposed cases, no. | Risk estimate/ comment |
|--------------|-----------|--------|-----------------|----------|-------------------|-------------------|------------------------|
| Case report  | Infante et al., 1978 (49) | Acute stem cell | 1 | Chlordane | Annual house treatment | 1 | Age 9, included 1 year removal of floor boards with heavy treatment |
| Case report  | Reeves et al., 1981 (50) | ALL | 1 | Dichlorvos Propoxur | Used in home 30 times | 1 | Age 11, diagnosed 16 weeks after last use |
| Case report  | Reeves, 1982 (37) | CML, ALL | 13 | Propoxur, Dichlorvos, propoxur | Mattress sprayed 2 times/ week for most of life. One case: seven cans sprayed in house 2 weeks prior to diagnosis | 13 | |
| Case report  | Moses, 1989 (51) | Leukemia | NA | Residence in McFarland, CA, farm town | Prenatal and childhood | NA | |
| Case–control | Hemminki et al., 1981 (52) | Leukemia | 319 | Paternal occupation as farmer | Pregnancy | 156a | 1.3 (not significant) |
| Case–control | Gold et al., 1982 (53) | Leukemia | 43 | Paternal occupation as farmer | Before birth | 2a vs 0 controls | |
| Case–control | Van Steensel-Moll et al., 1985 (54) | Leukemia | 519 | Paternal occupation in agriculture | Pregnancy | 3 | 0.4 (0.1, 1.7) |
| Case–control | | | | Maternal pesticide exposure | Before birth | 2a vs 0 controls | |
| Case–control | | | | Paternal occupation in agriculture | Before birth | 3 | 0.4 (0.1, 1.3) |
| Case–control | | | | Maternal occupation in agriculture | Before birth | 4 | 0.7 (0.2, 2.5) |
| Case–control | Lowengart et al., 1987 (55) | Leukemia | 123 | Parental pesticide use in home: either | Pregnancy and (mother only) nursing | 19a | 3.8 (significant) |
| Case–control | | | | Maternal | Pregnancy | 13a | 3.2 (significant) |
| Case–control | | | | Paternal | Pregnancy | 12a | 4.0 (significant) |
| Case–control | | | | Parental pesticide use in garden: either | Maternal | 13a | 6.5 (significant) |
| Case–control | | | | | Paternal | 9a | 9.0 (significant) |
| Case–control | | | | | Parental | 9a | 5.0 (significant) |
| Case–control | Laval and Tuyns, 1988 (56) | Leukemia | 201 | Parental occupational exposure to pesticides | Ever | 12 | vs 3 controls |
| Case–control | Shu et al., 1988 (57) | Leukemia | 309 | Occupation in agriculture: Maternal | Pregnancy | 12 | 2.3 (0.9, 6.3) |
| Case–control | | | | Maternal | Pregnancy | 6 | 1.8 (0.6, 5.4) |
| Case–control | | | | Paternal | Pregnancy | 4 | 1.6 (0.4, 6.3) |
| Case–control | | | | Pesticide exposure: Maternal | Pregnancy | 2 | 0.3 (0.1, 1.6) |
| Case–control | Buckley et al., 1989 (58) | ANLL | 204 | Occupational pesticide exposure: Maternal | Ever (1000+ days) | 17 | 2.7 (1.0, 7.0) |
| Case–control | | | | | Before pregnancy | NA | 1.7 (not significant) |
| Case–control | | | | | During pregnancy | NA | 1.9 (not significant) |
| Case–control | | | | | After pregnancy | NA | 1.8 (not significant) |
| Case–control | | | | | Ever (1000+ days) | 7 | vs 0 controls |
| Case–control | | | | | Before pregnancy | NA | 3.0 (significant) |
| Case–control | | | | | During pregnancy | NA | 6.0 (significant) |
| Case–control | | | | | After pregnancy | NA | 7.0 (significant) |
| Case–control | | | | | | | 11.4 (significant) |
| Case–control | Gardner et al., 1990 (59) | Leukemia | 52 | Paternal occupation as farmer | Birth | 5 | 12.6 (0.8, 9.0) |

(Continued)
Table 2. Continued.

| Study design | Reference | Cancer* | Total cases, no. | Exposure | Timing of exposure | Exposed cases, no. | Risk estimate/comment |
|--------------|-----------|---------|------------------|----------|-------------------|-------------------|----------------------|
| Case-control | Magnani et al., 1990 (60) | ALL | 142 | Paternal occupation as farmer | Before birth | 4 | 1.8 (0.5, 6.5) |
|              |           | ANLL  | 22  | Maternal occupation in agriculture | Birth to diagnosis | 5 | 5.6 (1.3, 24.3) |
|              |           |       |     | Maternal insecticide exposure | NA | No association |
| Case-control | Infante-Rivard et al., 1991 (61) | ALL | 128 | Maternal occupation in agriculture | Pregnancy | 9* | 1.8 (0.6, 6.4) |
| Case-control | Schwartzbaum et al., 1991 (62) | ALL | 522 | Parental gardening with pesticides | Birth to diagnosis | NA | 1.3 (not significant) |
|              |           | ANLL  | 107 | Parental gardening with pesticides | NA | 0.9 (not significant) |
| Case-control | Scheele et al., 1992 (63) | ALL | 35  | Bone marrow levels of DDT/DDE, HCB, HCH, dieldrin | At diagnosis | 38 | No significant differences |
| Case-control | Deschamps and Band, 1993 (64) | Leukemia | 15 | Pesticides sprayed in nearby parks, mosquito control, census data | Childhood | 15 | No difference |
| Case-control | Roman et al., 1993 (65) | ALL | 39  | Paternal occupation in agriculture | Birth | 11 | 1.1 (0.1, 5.9) |
|              |           | Other leukemia | 11 | Maternal occupation in agriculture | At interview | 15 | 0.8 (0.1, 3.3) |
|              |           | Non-Hodgkin’s lymphoma | 6 | Paternal occupation in agriculture | NA | Results for leukemia and non-Hodgkin’s lymphoma combined |
| Case-control | Mulder et al., 1994 (66) | Leukemia, | 7 | Pesticide exposure: | | |
|              |           | lymphoma | 7 | Child | Ever | 2 | 1.3 (0.1, 11.4) |
|              |           |       |     | ≥ 3 hr/week | 2 | 6.0 (0.3, 368.3) |
|              |           | Combined | Paternal | Ever | 6 | 1.0 (0.2, 6.1) |
|              |           |       |     | ≥ 3 hr/week | 5 | 2.1 (0.4, 12.5) |
|              |           |       | Summary pesticide indicator | > 2 indicators | 5 | 0.8 (0.1, 4.4) |
|              |           |       |     | > 3 indicators | 4 | 1.7 (0.3, 10.5) |
|              |           |       |     | > 4 indicators | 3 | 3.1 (0.3, 28.3) |
| Case-control | Leiss and Savitz, 1995 (30) | Leukemia | NA | Pest strips | Last 3 months pregnancy | 21 | 3.0 (1.6, 5.7) |
|              |           |       |     | Last 2 years < dx | Birth-2 years < dx | 21 | 1.7 (1.2, 2.4) |
|              |           |       |     | > 2 years < dx to dx | 18 | 2.6 (1.7, 3.9) |
|              |           |       | House extermination | Last 3 months pregnancy | 4 | 0.4 (0.1, 1.2) |
|              |           |       |     | Last 2 years < dx | Birth-2 years < dx | 6 | 0.3 (0.1, 0.8) |
|              |           |       |     | 2 years < dx to dx | 2 years < dx to dx | 7 | 0.9 (0.5, 1.4) |
|              |           |       | Yard pesticide treatment | Last 3 months pregnancy | 27 | 1.1 (0.6, 1.9) |
|              |           |       |     | Birth-2 years < dx | Birth-2 years < dx | 36 | 0.9 (0.5, 1.8) |
|              |           |       |     | > 2 years < dx to dx | > 2 years < dx to dx | 33 | 1.1 (0.8, 1.5) |
| Case-control | Meinert et al., 1996 (67) | Leukemia | 173 | Farmer: paternal | 2 years < birth | 6 | 1.6 (not significant) |
|              |           |       | Maternal | Occupational exposure to pesticides: | | |
|              |           |       |       | Paternal | Ever | 9 | 1.2 |
|              |           |       |       | Year < pregnancy | Year < pregnancy | 9 | 1.8 |
|              |           |       |       | Pregnancy | Pregnancy | 5 | 1.3 |
|              |           |       |       | Childhood | Childhood | 9 | 1.2 |
|              |           |       | Maternal | Ever | 4 | 1.6 |
|              |           |       |       | Year < pregnancy | Year < pregnancy | 2 | — |
|              |           |       |       | Pregnancy | Pregnancy | 2 | — |
|              |           |       |       | Childhood | Childhood | 4 | 1.6 |
|              |           |       | Either parent | Ever | 12 | 1.5 |
|              |           |       |       | Year < pregnancy | Year < pregnancy | 11 | 2.2 |
|              |           |       |       | Pregnancy | Pregnancy | 7 | 2.0 |
|              |           |       |       | Childhood | Childhood | 12 | 1.5 |
|              |           |       | Pesticide use: any | Ever | 27 | 2.5 (1.1, 5.4) |
|              |           |       | Garden | 2 years < birth | 20 | 2.5 (1.0, 6.1) |
|              |           |       | Farm | to diagnosis | Farm to diagnosis | 7 | 1.6 |
|              |           |       | House extermination: any | Ever | 37 | 0.8 |
|              |           |       | By pest controller | 3 | 1.0 |
| Cohort       | Kristensen et al., 1996 (49) | Leukemia, | 323, 292 | Parental agricultural work, | Before birth | 113 | 1.0 (0.8, 1.2) |
|              |           | Acute | cohort | Census pesticide expenditures | Census pesticide expenditures | 52 | 1.1 (0.8, 1.5) |
|              |           | ALL |       | 29 | 1.2 (0.9, 1.7) |
|              |           | AML |       | 12 | 1.4 (0.6, 2.9) |
|              |           | Other |       | 11 | 0.9 (0.4, 1.9) |

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANLL, acute nonlymphocytic leukemia; CML, chronic myelogenous leukemia; dx, diagnosis; NA, not available in published report. *Number of discordant pairs with exposed cases.
reported that children with greater than two, greater than three, or greater than four indicators of pesticide exposure had ORs of 0.8, 1.7, and 3.1, respectively, in a study of leukemia and lymphoma combined.

**Brain Cancer**

The role of pesticides in the development of childhood brain cancer was evaluated in one case report, 16 case-control studies, and one cohort study (30,47,48,52,53,68-81) (Table 3). Significant elevations in brain cancer risk related to at least one measure of pesticide exposure were observed in nine studies (30,47,48,71,72,76-79,81). Nonsignificant elevations were observed in an additional five studies (52,53,70,74,75), with deficits or no association reported in three studies (69,73,80). The largest risk estimates, reported by Davis et al. (76), Cordier et al. (77), and Pagoda and Preston-Martin (81), were based on parent-reported use of pesticides in the home or garden or on pets, in contrast to the lower risks associated with parental employment in occupations or industries thought to involve pesticide exposure. Most (30,71,74-76,81), but not all (30,77,79), of the studies that evaluated timing of exposure found greater risks associated with prenatal exposure than for exposures sustained during childhood. Three studies (53,70,76) had both cancer and noncancer control series. In general, the ORs based on noncancer controls were higher than those based on cancer controls.

Exposure-response gradients, although based on crude measures of exposure, were evaluated in the studies of Bunin et al. (78), Kristensen et al. (48), and Pagoda and Preston-Martin (81). Maternal use of household insecticide sprays or other pesticides ever and on at least a weekly basis was associated with ORs of 1.5 and 2.2, respectively (78). Children of fathers engaged in agricultural work had rate ratios (RRs) of 2.0, 2.9, and 3.3 for nonastrocytic neuroepithelial tumors for levels 1, 2, and 3 of pesticide exposures, respectively (48). Pagoda and Preston-Martin (81) reported increasing risk of childhood brain cancer with the number of pets and the number of hours per day children spent with their pets, presumably a surrogate for increasing exposure to pesticides used on pets.

**Neuroblastoma**

Table 4 presents three case reports, four case-control studies, and one cohort study with information on pesticides and neuroblastoma (47,49,51,62,82-85). There is little evidence for a role of pesticides in the etiology of this tumor, with four comparisons showing decreased risks (83-85), two showing nonsignificant excesses of 1.1 and 3.5 (62,85), and only one study with a significant excess (47). Kristensen et al. (47) reported a RR of 2.5 (95% CI 1.0, 6.1), based on seven cases of neuroblastoma, among a cohort of children of Norwegian farmers who grew field vegetables.

Four of the five analytical studies, however, were based solely on potential pesticide exposure imputed from parental employment in agricultural occupations (47,83-85). One study assessed risk associated with parental gardening with pesticides (62). No studies evaluated detailed information on pesticides used in the home, specifically or during childhood.

**Non-Hodgkin's Lymphoma**

The relationship between pesticides and childhood non-Hodgkin's lymphoma was investigated in one case report, six case-control studies, and one cohort study (30,48,51,60,62,65,66,86) (Table 5). Two case-control studies, however, were based on leukemia and lymphoma cases combined with no data presented separately for each histologic type (65,66). Another case-control study was presented at a U.S. National Cancer Institute workshop but has not yet been published (86). Several of the reports did not include the number of total cases or the number of exposed cases (30,51,60,62,86). All appear to have very few exposed cases.

Despite these limited data, there are some notable findings concerning childhood non-Hodgkin's lymphoma and pesticides. Risk increased with level of pesticide expenditures (level 1: RR = 1.3; level 2: RR = 1.6; level 3: RR = 2.5) among a cohort of children of Norwegian farmers (48). Excess non-Hodgkin's lymphoma was observed among children whose homes had been exterminated or had pest strips, although the excesses were not statistically significant except for home extermination during the time period from birth to 2 years prior to diagnosis (30). Buckley (86) reported ORs of 1.0, 2.2, and 5.2 for childhood non-Hodgkin's lymphoma associated with maternal household insecticide use less than once per week, one to two times per week, and daily, respectively. Garden insecticide sprays and home extermination were also associated with excess childhood non-Hodgkin's lymphoma in the same study (86). The study by Mulder et al. (66), based on seven leukemia and seven non-Hodgkin's lymphoma cases combined, reported increased risk with increasing pesticide exposure of the child or father; however, results for non-Hodgkin's lymphoma alone were not presented.

**Wilms' Tumor**

The early case-control studies on Wilms' tumor did not report elevated risks associated with possible pesticide exposure, as determined by parental occupational titles only or imputed from occupational titles using job-exposure matrices (62,87,88) (Table 6). The later studies (89,90), which were based on subjects' reports of household or occupational use of pesticides, reported elevated risks. Olshan et al. (89) found that children whose homes had been exterminated had 2.2 times the risk of Wilms' tumor than children in untreated homes. The risk did not increase with the frequency of extermination, however. In a study of Wilms' tumor in Brazil (90), risk increased with frequency of parental agricultural use of pesticides. Children whose fathers or mothers used agricultural pesticides 10 times or more had ORs for Wilms' tumor of 3.2 (95% CI 1.2, 9.0) and 128.6 (95% CI 6.4, 2569), respectively. The risk associated with pesticide use particularly increased among children of parents with longer farming duration.

**Ewing's Sarcoma**

Reports related to pesticides and Ewing's sarcoma are presented in Table 7 (91-95). Paternal employment as a farmer or in other agricultural occupations was associated with an approximately 9-fold significantly increased risk of Ewing's sarcoma in two studies (93,94) and a nonsignificant 3-fold excess in a third study (95). Parental exposure to pesticides in any occupation was associated with a 6-fold increase of Ewing's sarcoma in children (94). More direct exposure of children to pesticides, either through household extermination, living on a farm or ranch, or through household pets, was associated with modest nonsignificantly elevated ORs less than 1.5 (95) or deficits (94).

**Other Malignancies**

Table 8 presents data on studies of childhood osteosarcoma (62), soft-tissue sarcoma (30,48,96), colorectal cancer (97-99), testicular cancer (48,100), other germ cell malignancies (101), Hodgkin's disease (48,62), and retinoblastoma (48,102). With three or fewer reports per cancer, little can be definitively concluded about the possible role of pesticides.
### Table 3. Summary of studies on pesticides and childhood brain cancer.

| Study design | Reference | Total cases, no. | Exposure | Timing of exposure | Exposed cases, no. | Risk estimate/comment |
|--------------|-----------|------------------|----------|-------------------|-------------------|----------------------|
| Case report  | Chadduck et al., 1987 (68) | 1 | Heptachlor | Pregnancy and nursing | 1 | Gliosarcoma diagnosed in an infant 7 weeks of age |
| Case-control | Fabia and Thuy, 1974 (69) | 101 | Paternal occupation as farmer | Birth | 6 | 0.6 (calculated) |
| Case-control | Gold et al., 1979 (70) | 84 | Household extermination | Before diagnosis | 16 | 2.3 (p = 0.10), noncancer controls |
| Case-control | Gold et al., 1982 (53) | 70 | Paternal occupation as farmer | Before birth | 1 | 0.8 (0.5, 1.4), cancer controls vs noncancer controls |
| Case-control | Hemminki et al., 1981 (57) | 282 | Paternal occupation as farmer | Pregnancy | 107 | 1.2 (not significant) |
| Case-control | Sinks, 1985 (71) | NA | Maternal aerosol pesticide use | Pregnancy | NA | 1.7 (significant) |
| Case-control | Wilkins and Koutras, 1988 (72) | 110 | Paternal occupation in agriculture | Birth | 30 | 1.8 (0.9, 3.5) |
| Case-control | Howe et al., 1989 (73) | 74 | Child exposed to herbicides or insecticides | Childhood | 19 | 0.9 (0.5, 1.9) |
| Case-control | Wilkins and Sinks, 1990 (74) | 110 | Paternal occupation in agriculture | Preconception | 6 | 2.7 (0.8, 9.1) |
| Case-control | Davis et al., 1993 (78) | 45 | Pesticides at home, Pest strips | Pregnancy | 8 | 5.2 (1.2, 22.2) |
| Case-control | Kuijten et al., 1992 (79) | 163 | Paternal agricultural industry | Preconception | 11 | 1.8 (0.6, 6.0) |
| Case-control | Davis et al., 1993 (78) | 45 | Termite control, Garden insecticides | 7 months to diagnosis | 38 | 3.4 (1.1, 10.6), friend controls |
| Case-control | Cordier et al., 1994 (77) | 75 | Farm residence | 7 months to diagnosis | 20 | 3.1 (1.0, 9.3) |

(Continued on next page)
### Table 3. Continued.

| Study design  | Reference                        | Total cases, no. | Exposure                                                                 | Timing of exposure | Exposed cases, no. | Risk estimate/ comment |
|---------------|----------------------------------|------------------|--------------------------------------------------------------------------|--------------------|---------------------|------------------------|
| Case–control  | Bunin et al., 1994 (78)          | 155<sup>b</sup>  | Maternal household insecticide sprays or pesticides: ever                | Pregnancy          | 34                  | 1.5 (0.8, 2.7)         |
|               |                                  |                  | At least weekly                                                          |                    | 8                   | 2.2 (0.6, 7.4)         |
|               |                                  |                  | Maternal household examination                                          | Pregnancy          | 24                  | 0.7 (0.4, 1.4)         |
|               |                                  |                  | Farm residence: maternal                                                | Pregnancy          | 5                   | 0.5 (0.1, 1.8)         |
|               |                                  |                  | Child                                                                    | ≥ 1 year childhood | 6                   | 0.4 (0.1, 1.6)         |
|               |                                  | 166<sup>c</sup>  | Maternal household insecticide sprays or pesticides: ever                | Pregnancy          | 31                  | 0.7 (0.4, 1.4)         |
|               |                                  |                  | At least weekly                                                          |                    | 5                   | 1.0 (0.2, 4.9)         |
|               |                                  |                  | Maternal household examination                                          | Pregnancy          | 34                  | 1.0 (0.6, 1.9)         |
|               |                                  |                  | Farm residence: maternal                                                | ≥ 1 year childhood | 14                  | 3.7 (0.8, 23.9)        |
|               |                                  |                  | Child                                                                    |                    | 14                  | 5.0 (1.1, 46.8)        |
| Case–control  | McCredie et al., 1994 (79)       | 82               | Maternal live or work on farm                                           | Pregnancy          | 5                   | 0.9 (0.3, 2.6)         |
|               |                                  |                  | House treatment with pesticides                                         |                    | 20                  | 2.0 (1.0, 3.9)         |
| Case–control  | McCredie et al., 1994 (80)       | 82               | Live or work on farm                                                    | Childhood          | 4                   | 0.6 (0.2, 1.9)         |
|               |                                  |                  | Regular contact with horses                                            |                    | 6                   | 0.7 (0.3, 1.8)         |
|               |                                  |                  | House pesticide treatment                                               | NA                 |                     | No association         |
| Case–control  | Leiss and Savitz, 1995 (30)      | NA               | Home extermination                                                      | Last 3 months pregnancy | 8               | 1.3 (0.7, 2.1)         |
|               |                                  |                  | Birth–2 years < dx                                                     | 12                 | 1.4 (0.6, 2.7)       |
|               |                                  |                  | 2 years < dx to dx                                                     | 5                  | 1.1 (0.4, 3.0)       |
|               |                                  |                  | Yard pesticide treatment                                               | Last 3 months pregnancy | 12           | 0.6 (0.3, 1.1)         |
|               |                                  |                  | Birth–2 years < dx                                                     | 17                 | 0.5 (0.2, 0.9)       |
|               |                                  |                  | 2 years < dx to dx                                                     | 16                 | 0.5 (0.4, 0.8)       |
|               |                                  |                  | Pest strips                                                             | Last 3 months pregnancy | 10           | 1.5 (0.9, 2.4)         |
|               |                                  |                  | Birth–2 years < dx                                                     | 13                 | 1.4 (0.7, 2.9)       |
|               |                                  |                  | 2 years < dx to dx                                                     | 9                  | 1.8 (1.2, 2.9)       |
| Case–control  | Pagoda and Preston-Martin, 1997 (81) | 224         | Flea and tick treatment                                                | Pregnancy          | 76                  | 1.7 (1.1, 2.6)         |
|               |                                  |                  | Diagnosed < 5 years                                                    | 29                 | 2.5 (1.2, 5.5)       |
|               |                                  |                  | Spray and foggers                                                      | Pregnancy          | 17                  | 10.8 (1.3, 89.1)       |
|               |                                  |                  | Termiteicides                                                           | Pregnancy          | 5                   | 2.7 (0.5, 14.2)        |
|               |                                  |                  | Nuisance pest pesticides, not otherwise specified                      | Childhood          | 23                  | 0.7 (0.4, 1.3)         |
|               |                                  |                  | Lice treatments                                                         | Pregnancy          | 106                 | 1.1 (0.8, 1.7)         |
|               |                                  |                  |                                                                      |                    | 150                 | 1.0 (0.6, 1.5)         |
|               |                                  |                  |                                                                      |                    |                     |                        |
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|               |                                  |                  |                                                                      |                    |                     |                        |
|               |                                  |                  |                                                                      |                    |                     |                        |
| Cohort        | Kristensen et al., 1995, 1996 (47,48) cohort | 323, 292        | Paternal agricultural work: pesticide expenditures<sup>d</sup>          | Before birth       | 31                  | 2.7 (1.6, 4.8)*        |
|               |                                  |                  |                                                                        |                    | 60                  | 1.4 (1.0, 1.9)*        |
|               |                                  |                  |                                                                        |                    | 7                   | 2.0 (0.8, 4.7)         |
|               |                                  |                  |                                                                        |                    | 17                  | 2.9 (1.5, 5.6)         |
|               |                                  |                  |                                                                        |                    | 7                   | 3.3 (1.4, 7.8)         |

<sup>a</sup>Number of discordant pairs with exposed cases. <sup>b</sup>Astrocytoma. <sup>c</sup>Primitive neuroectodermal tumor. <sup>d</sup>Expenditures—levels are levels of money spent. <sup>e</sup>Nonastrocytic gliomas. <sup>f</sup>Nonastrocytic neuroepithelioma tumor.
### Table 4. Summary of studies on pesticides and neuroblastoma.

| Study design | Reference | Total cases, no. | Exposure | Timing of exposure | Risk estimate/ comment |
|--------------|-----------|------------------|----------|-------------------|------------------------|
| Case report  | Infante and Newton, 1975 (82) | 1 | Maternal exposure to chlordane, spent 25–30 hr/week in basement with strong odor from household treatment | First trimester of pregnancy | 1 | Case diagnosed at 2 years, 8 months of age |
| Case report  | Infante et al., 1978 (49) | 14 | Chlordane | Pregnancy and childhood | 5 | — |
| Case report  | Moses, 1989 (51) | NA | Residence in McFarland, CA, farm town | Pregnancy and childhood | NA | — |
| Case–control | Spitz and Johnson, 1985 (83) | 157 | Paternal occupation in agriculture | Birth | 6 | 0.6 (0.2, 1.4) |
| Case–control | Wilkins and Hundleby, 1990 (84) | 101 | Paternal occupation in agriculture, forestry, or fishing Paternal industry in agriculture, forestry, or fishing | At birth | 7 | 0.9 (0.4, 2.2) |
| Case–control | Schwartzbaum et al., 1991 (82) | 104 | Paternal occupation as farmer | Preconception | 7 | 3.5 (0.7, 34.5) |
| Case–control | Schwartzbaum et al., 1991 (82) | 104 | Parental gardening with pesticides | Pregnancy | 2 | 0.7 (0.1, 5.8) |
| Cohort       | Kristensen et al., 1995 (47) | 323, 292 cohort | Parental agricultural work | Before birth | 7 | 2.5 (1.0, 6.1) |

*Number of discordant pairs with exposed cases.

### Table 5. Summary of studies on pesticides and childhood non-Hodgkin’s lymphoma.

| Study design | Reference | Total cases, no. | Exposure | Timing of exposure | Risk estimate/ comment |
|--------------|-----------|------------------|----------|-------------------|------------------------|
| Case report  | Moses, 1989 (51) | NA | Residence in McFarland, CA, farm town | Pregnancy and childhood | NA | — |
| Case–control | Magnani et al., 1990 (60) | 19 | Parental occupation as farmer | Pregnancy and childhood | NA | No association |
| Case–control | Schwartzbaum et al., 1991 (82) | 104 | Parental gardening with pesticides | Birth to diagnosis | NA | 1.3 (not significant) |
| Case–control | Buckley, 1991 (86) | NA | Maternal household insecticide use: < 1/week 1–2/week Daily Garden insecticide spraying: < 1/month ≥ 1/month Home extermination | Pregnancy | NA | — |
| Case–control | Roman et al., 1993 (65) | 39 | Paternal occupation in agriculture | Birth | 11 | Results are for leukemia and lymphoma combined |
| Case–control | Mulder et al., 1994 (69) | 7, 7 | Pesticide exposure: child Ever ≥ 3 hr/week Paternal ≥ 3 hr/week > 2 indicators > 3 indicators > 4 indicators Summary pesticide indicator | At interview | 15 | — |
| Case–control | Leiss and Savitz, 1995 (30) | NA | Home extermination Last 3 months of pregnancy Pregnancy–2 years < dx 2 years < dx Yard treatment Last 3 months of pregnancy Pregnancy–2 years < dx 2 years < dx Pest strips Last 3 months of pregnancy Pregnancy–2 years < dx 2 years < dx | | | |
| Cohort       | Kristensen et al., 1996 (48) | 323, 292 cohort | Parental agricultural work, census pesticide expenditures Level 1st Level 2nd Level 3rd Horticultural/pesticide products | Before birth | 11 | 2.1 (1.0, 4.3) |

*ALL. aOther leukemia. bNon-Hodgkin’s lymphoma. cLeukemia and lymphoma combined. dLevels of money spent.
### Table 6. Summary of studies on pesticides and Wilms' tumor.

| Study design | Reference | Total cases, no. | Exposure | Timing of exposure | Exposed cases, no. | Risk estimate/comment |
|--------------|-----------|------------------|----------|-------------------|--------------------|-----------------------|
| Case report  | Moses, 1989 (57) | NA | Residence in McFarland, CA, farm town | Pregnancy and childhood | NA | — |
| Case-control | Kantor et al., 1979 (67) | 149 | Paternal occupation as farmer | Birth | 1 vs 8/145 controls |
| Case-control | Wilkins and Sinks, 1984 (88) | 82 | Paternal occupational exposure: DDT, Ethylene dibromide, Endrin, Insecticides, not otherwise specified | At birth | 3, 0.4 (not significant) |
| Case-control | Schwartzbaum et al., 1991 (62) | 101 | Parental gardening with pesticides | Birth to diagnosis | NA, 0.7 (not significant) |
| Case-control | Olshan et al., 1995 (90) | 200 | Household insecticide extermination | Childhood: ever | 78, 2.2 (1.2, 3.8) |
| Case-control | Sharpe et al., 1995 (90) | 109 | Agricultural use of pesticides: Maternal, < 10 times ≤ 10 times ≥ 10 times | Before birth | 2, 0.3 (0.1, 2.3) |
| | | | Paternal: < 10 times ≥ 10 times | | 6, 128.6 (0.4, 2569) |
| | | | Paternal farmwork: Exposure | | 3, 0.6 (0.1, 2.4) |
| | | | ≤ 24 months: no exposure Exposed | | 5, 0.9 (0.2, 4.8) |
| | | | 25–48 months: no exposure Exposed | | 16, 2.9 (0.9, 9.0) |
| | | | 49–108 months: no exposure Exposed | | 6, 4.8 (1.0, 22.4) |
| | | | Maternal farmwork: Exposure | | 4, 1.0 (0.2, 4.3) |
| | | | ≤ 24 months: no exposure Exposed | | 10, 4.1 (1.0, 17.5) |
| | | | 25–48 months: no exposure Exposed | | 7, 1.3 (0.4, 4.4) |
| | | | 49–108 months: no exposure Exposed | | 2, 0.5 (0.0, 4.8) |
| | | | Maternal agricultural work, census pesticide expenditures Oranges or greenhouse Pesticide spraying Orchard or greenhouse and pesticide spraying | Before birth | 4, 8.9 (2.7, 29.5) |
| Cohort | Kristensen et al., 1995, 1996 (47,48) cohort | 323, 292 | Parental agricultural work, census pesticide expenditures Oranges or greenhouse Pesticide spraying Orchard or greenhouse and pesticide spraying | Before birth | 4, 8.9 (2.7, 29.5) |

*In general, risks were higher for boys than for girls.

### Table 7. Summary of studies on pesticides and Ewing's sarcoma.

| Study design | Reference | Total cases, no. | Exposure | Timing of exposure | Exposed cases, no. | Risk estimate/comment |
|--------------|-----------|------------------|----------|-------------------|--------------------|-----------------------|
| Case report  | Holman et al., 1983 (91) | 6 | Rural residents, exposure to farm animals and agricultural exposures | Childhood | 6 | Ages 12–34 |
| Case report  | Zamora et al., 1986 (92) | 2 | Paternal occupation in agriculture, contact with farm animals | Childhood | 2 | Two brothers diagnosed at 8 and 15 years of age |
| Case-control | Daigle, 1987 (83) | 98 | Paternal occupation in agriculture | At conception NA | 9.0 (significant) |
| Case-control | Schwartzbaum et al., 1991 (62) | 49 | Parental gardening with pesticides | Childhood NA | 1.1 (not significant) |
| Case-control | Holly et al., 1992 (94) | 43 | Paternal occupation in agriculture | 6 months ≤ conception to dx | 7 | 8.9 (1.8, 42.7) |
| | | | Paternal exposure to herbicides, pesticides, fertilizers Household extermination | | 7 | 6.1 (1.7, 21.9) |
| Case-control | Winn et al. 1992 (95) | 208 | Paternal occupation as farmer | Pregnancy Child | 1 | 0.3 (0.02, 2.1) |
| | | | Household extermination | | 15 | 0.6 (0.3, 1.2) |
| | | | Usual occupation | | 13 | 2.2 (0.7, 6.5) |
| | | | Occupations in agriculture | | 14 | 1.5 (0.5, 4.4) |
| | | | Living on farm or ranch | | 43 | 1.4 (0.8, 2.4) |
| | | | Household or greenhouse and pesticide spraying | | 160 | 1.5 (0.9, 2.4) |

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Table 8. Summary of studies on pesticides and childhood osteosarcoma, soft-tissue sarcoma, colorectal cancer, germ cell cancer, Hodgkin’s disease, and retinoblastoma.

| Study design | Reference | Cancer | Total cases, no. | Exposure | Timing of exposure | Risk estimate/ comment |
|--------------|-----------|--------|------------------|----------|--------------------|------------------------|
| Case–control | Schwartzbaum et al., 1991 (62) | Osteosarcoma | 78 | Parental gardening with pesticides | Birth to diagnosis | NA 2.6 (p=0.01) |
| Case–control | Magrini et al., 1998 (96) | Soft-tissue sarcoma | 52 | Maternal farming occupation | Ever before birth | 7.0 (1.5, 33.2) |
| Case–control | Leiss and Savitz, 1995 (30) | Soft-tissue sarcoma | NA | Yard pesticide treatment | Last 3 months of pregnancy | 0.8 (0.5, 1.3) |
| Cohort | Kristensen et al., 1996 (49) | Soft-tissue sarcoma | 323, 292 cohort | Parental agricultural work | Before birth | 0.9 (0.5, 1.5) |
| Case report | Pratt et al., 1997 (97) | Colorectal | 13 | Chemicals used in production of cotton and soybeans | Childhood | — |
| Case report | Pratt et al., 1987 (98) | Colorectal | 1 | Environmental dioxin in Missouri | Childhood | — |
| Case–control | Caldwell et al., 1981 (99) | Colorectal | 10 | Serum levels of DDT, dieldrin, chlordane, heptachlor | Diagnosis | 10 Generally, cases had higher levels than controls; cases were from rural area |
| Case–control | Mills et al., 1984 (102) | Germ cell (testes) | 347 | Farming occupation | Ever | 8.3 (1.8, 21.5) |
| Case–control | Shu et al., 1995 (101) | Germ cell (testes) | 105 | Insecticides or herbicides: Maternal Paternal | Ever | 2.4 (0.9, 6.9) |
| Cohort | Kristensen et al., 1996 (49) | Germ cell (testes) | 323, 292 cohort | Parental agricultural work: pesticides | Ever | 1.8 (0.7, 5.0) |
| Case–control | Schwartzbaum et al., 1991 (62) | Hodgkin’s disease | 133 | Parental gardening with pesticides | Before birth | 1.2 (1.0, 1.5) |
| Cohort | Kristensen et al., 1990 (48) | Hodgkin’s disease | 323, 292 cohort | Parental agricultural work: Pesticide use Pesticide spraying equipment | Before birth | 0.8 (0.4, 1.5) |
| Case–control | Bunin et al., 1990 (102) | Retinoblastoma | 182 | Maternal grandfather occupation: Farmer or farm worker | At mother’s birth | 1.0 (0.1, 7.5) |
| Cohort | Kristensen et al., 1996 (49) | Eye | 323, 282 cohort | Parental agricultural work: Ever Field work and pesticide purchases | Before birth | 0.8 (0.4, 1.6) |

*Number of discordant pairs with exposed cases.

Leiss et al. (30) found a 4-fold increased risk of soft-tissue sarcoma among children whose yards had been treated with pesticides during their childhood, but not if the treatment occurred prenatally. Kristensen et al. (48) found little evidence for an increased risk of soft-tissue sarcoma in children of Norwegian farmers. The farming status was ascertained before the children’s births, not at birth or during childhood, but little change probably occurred. Magnani et al. (96) found elevated risks of soft-tissue sarcoma among children whose mothers were farmers either before birth or between birth and diagnosis, but the numbers of exposed cases were extremely small.

Nine of 13 extremely rare cases of colorectal cancer among children had exposure to insecticides used in the production of cotton and soybeans (97). A case–control study of rural children with colorectal cancer found that cases had higher serum levels of DDT, dieldrin, chlordane, and heptachlor than controls (99).

Testicular cancer, with peak incidence at 20 to 39 years of age, is not typically considered a childhood cancer. The tumor, however, is likely to have been initiated during the prenatal or childhood period. Mills et al. (100) found a 6-fold excess of testicular cancer among men employed as farmers or farmworkers. Kristensen et al. (48), however, found no excess of testicular cancer among children whose parents were farmers. Parental exposures to pesticides were associated with nonsignificant...
excesses of other germ cell malignancies in a study by Shu et al. (101).

Two studies of Hodgkin's disease reported small nonsignificant excesses among children whose parents used pesticides occupationally or in the garden (48,62). A 10-fold risk of nonhereditary retinoblastoma was observed among children whose paternal grandfather was a farmer or farmworker at the time of the mother's birth (102). There was no excess risk observed for sporadic heritable retinoblastoma.

Methodologic Issues

Based on the research to date on the role of pesticides in the etiology of childhood cancers, little can be definitively concluded, particularly for specific pesticides. There are methodologic issues that limit the informativeness or affect the interpretation of most of the studies in this review.

Case Definition

Many types of childhood cancer are comprised of heterogeneous histologic subtypes. For example, childhood leukemia consists of ALL, AML, chronic lymphocytic leukemia, and other forms. Soft-tissue sarcoma includes rhabdomyosarcoma, fibrosarcoma, and other types. If these subtypes have different etiologies, grouping them may mask associations. If chronic lymphocytic leukemia is associated with pesticide use but ALL, which is far more common, is not, then studies of all childhood leukemia combined may not show any excess risk.

Similarly, there may be different exposures or different impact from the same exposure by age at diagnosis. Leukemia among infants under 1 year of age may be a different disease with different etiology than leukemia diagnosed at older ages. Buckley et al. (58) reported ORs of 1.7 to 7.0 for acute nonlymphocytic leukemia associated with parental pesticide use for all ages combined, but an OR of 11.4 for cases diagnosed under 6 years of age. The pesticide association was also stronger among brain cancer cases diagnosed under 5 years of age in the study by Pagoda and Preston-Martin (81). Larger studies with the ability to evaluate exposures by histology and other case characteristics may result in increased sensitivity and more informative studies.

Choice of Controls

The case–control studies of pesticides and childhood cancer have generally used one or more of four types of controls: general population controls, friends, siblings, or other cancer cases. General population controls have been criticized for introducing possible recall, or case–response, bias. Childhood cancer-case parents, who have probably anxiously pondered possible reasons for their child's disease, may report exposures that parents of healthy children, who have not been vigorously examining their past exposures, may fail to remember and report. False positive associations may be observed. Using friends of the cases as controls may result in overmatching on exposure status. Friends may have parents in similar occupations, may live in the same neighborhoods, attend the same school, and may play on the same pesticide-treated soccer fields. False negative results may be observed. Sibling controls would suffer even more from overmatching. Using other cancer cases as controls should minimize recall bias because the parents of both the case and the control children are equally motivated to recall and report their children's exposures. If pesticides are also associated with the other cancer with which the controls are diagnosed, however, false negative results may occur. For example, some childhood brain cancer studies had other childhood cancer cases for controls, which, given childhood cancer patterns, must have been almost entirely leukemia cases. If leukemia is associated with pesticide exposure, little elevation in risk would have been apparent among the brain cancer cases even if pesticides truly played a role.

More information on the extent of recall bias, if any, is needed and more objective methods of obtaining exposure information must be developed so we can use general population controls, which appear to maximize the sensitivity of childhood cancer studies.

Exposure Assessment

Most of the studies on childhood cancer and pesticides were based on crude exposure information with little specificity in pesticide type or amount. The most specific data were presented in case reports. The analytical epidemiologic studies were generally based on measures such as parental occupation, self-reported or imputed parental occupational exposure to pesticides (not otherwise specified), farm crop, type of livestock, broad pesticide class (e.g., insecticide), or pesticide product type (e.g., flea powder). The more crude and encompassing the exposure classifications are, the greater possibility that the increased risks from individual pesticides or chemical classes of pesticides will be diluted and go undetected. In addition, crude exposure measures may reflect a nonpesticide risk factor.

Examination of dose–exposure–response relationships can aid interpretation of causality. Evidence of an exposure–response gradient decreases the likelihood that an association is due to chance. Some childhood cancer studies of pesticides have used these surrogate measures for dose: duration in occupation with pesticide exposure, total number of average frequency of pesticide applications, number of pets, number of hours with pets, number of hours in treated homes, farming census data on pesticide expenditures, and biologic measures. Modifications of risk by protective practices, such as staying in the home after pesticide treatment, lack of delay in harvesting food after treatment, and failing to follow pesticide label application instructions were also used as crude indicators of exposure amount (81).

The studies by Scheele et al. (63) and Caldwell et al. (99) were based on measures of pesticides and their metabolites in biologic specimens. Biologic measures avoid the problems of recall bias and lack of specificity of pesticide type, but may be affected by disease or treatment and generally reflect only very recent exposures. Compounds for which biologic measures reflect lifetime exposures are limited generally to the persistent organochlorines. Biologic measures for lifetime exposure to pesticides that are more quickly metabolized and excreted are not available.

One ongoing study of childhood cancer is measuring potential household pesticide exposure by analyzing pesticide residues in carpet dust collected by high-volume surface sampler vacuums (103). Pesticide residues indoors are protected from degradation by the sun and microbial activity and therefore are more persistent than pesticide residues outdoors. This approach can give a picture of cumulative exposure to some of the more persistent pesticides such as organochlorine insecticides, but does not assess exposure to short-lived volatile chemicals.

Children living near agricultural lands treated with pesticides have higher levels of pesticides in their homes than children of nonfarm families living away from agricultural land (10). Pesticide levels in house dust were inversely correlated with the distance of the home from sprayed orchards. Pesticide detections in groundwater also have been associated with the proximity to sprayed crops (104). Methods have been developed to use remote sensing
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(i.e., satellite images) and geographic information systems to characterize the types of crops near the subjects' residences (105,106). By combining the crop pattern data and crop-specific pesticide use information with the proximity of residence to cropland, the probability of exposure to individual pesticides can be estimated (107). This technique was used to reconstruct exposure for a short and recent time frame in a study of pesticide exposure and low birth rate in Colorado (106) and for historical exposures from the 1980s using satellite imagery and historical U.S. Farm Service Administration records in a pilot study in Nebraska (107). These techniques have not yet been used in childhood cancer research, but may enhance future efforts.

Indirect measures of potential exposure may be less preferable than direct home or biologic measurements. Direct measures, however, are usually expensive and often difficult to obtain in large studies with hundreds or thousands of subjects. In addition, direct measures usually reflect recent exposures, whereas historical data, even if indirect, may be more important for diseases of long latency.

More studies with crude exposure assessments (e.g., pesticides, not otherwise specified) will not make major contributions to our understanding or to prevention strategies. To facilitate epidemiologic research on specific pesticides, improvements are needed to identify the type and amount of pesticide exposure, including validity and reliability studies. In addition, continued efforts should be made to make information available on the identity of the so-called inert ingredients in pesticide formulations. These ingredients, although not responsible for the pesticidal action of the formulations, are not biologically inert and can be extremely important when trying to correctly assess the carcinogenic potential of a pesticide.

Timing of Exposure

Some childhood cancer studies have evaluated pesticide exposure during critical time periods such as preconception (e.g., ever, 3 months prior to conception, and 6 months prior to conception), during pregnancy (e.g., ever, the first trimester, and the last trimester), and postnatally, including while nursing, during infancy, and at specified numbers of years prior to diagnosis.

Information on time periods of higher risk might provide insight into mechanism, such as whether there had been a germ line versus somatic mutation, or whether risks were related to age-dependent metabolic capabilities. Such information might also influence judgments concerning causality. Large numbers of subjects are needed, with variation in timing, to evaluate whether risks differ by time period. Most studies conducted to date, however, have a small number of subjects, with most subjects exposed preconception through diagnosis, offering little chance of identifying when pesticides might act to initiate the cancer under investigation.

Genetic–Environmental Interactions

Within the population there are subgroups of children who may differ in their susceptibility to cancer because of genetically determined metabolic polymorphisms or by mutations in major cancer genes. Among adults, genetics play a role in the ability to metabolize pesticides. At least a 15-fold difference in the ability to detoxify organophosphate insecticides has been observed (27). Metabolic polymorphisms important to pesticide carcinogenicity may also exist and should be investigated. A family history of cancer, a crude measure of genetic susceptibility, appeared to enhance the carcinogenic effects of pesticides in case–control studies of adults (108,109). Similar research among children should be conducted.

Statistical Power

The statistical power of existing studies on childhood cancer and pesticides is limited. Most studies have small numbers of cases, typically in the range of 50 to 200 subjects, with most comparisons based on less than 20, and usually less than 10, exposed cases. These numbers are insufficient to evaluate dose response, timing of exposure, multiple pesticide exposures, or genetic–environment interactions. Large national or international efforts will be needed to provide enough exposed cases to adequately address these issues. Studies of intermediate effects such as chromosomal aberrations and DNA adducts, which may be more prevalent than cancer, may be informative and should be considered.

Strength of Association

Most of the methodologic limitations noted for existing studies on childhood cancer and pesticides would cause studies to underestimate risk. For example, heterogeneity of disease, poor exposure assessment, and use of cancer controls would bias true positive associations toward the null. Despite these limitations and the almost certain underestimation of risks that is occurring, it is striking that many of the reported increased risks are of greater magnitude than those observed in studies of pesticide-exposed adults (110). For example, childhood studies have reported increases in risk as large as 4- to 9-fold for leukemia (55,58) and 6- to 7-fold for brain cancer (76,77), whereas studies of farmers and other exposed adults have rarely reported relative risks greater than 2 (110). Children may be particularly sensitive to possible carcinogenic effects of pesticides. This is of concern, given the children working on farms and the high prevalence of use of pesticides in the home in the general population.

Conclusions

Many of the cancers associated with pesticides among children, such as leukemia, brain cancer, non-Hodgkin's lymphoma, soft-tissue sarcoma, and Hodgkin's disease, are the same cancers that are repeatedly associated with pesticide exposure among adults (110), suggesting that a role among children is highly plausible. Furthermore, although the research has been limited by nonspecific pesticide exposure information, small numbers of exposed subjects, potential for recall bias, and a small number of studies for most cancers, the magnitude of the risks is often greater than among adults, indicating greater susceptibility.

There is a need to study and better quantify these exposures. Studies must entail sophisticated exposure assessment, such as that used in epidemiologic studies of occupational exposures and adult cancers, and consideration of possible genetic and environmental interactions.

Future research should incorporate, where appropriate, techniques such as prospectively collected parental use of pesticides in agriculture, more detailed occupational histories, environmental measures for pesticide residues, geographic information systems, and biologic measures of pesticides and their metabolites. Special heavily exposed populations such as children of migrant farmworkers should be studied (111,112).

Although research is underway to characterize the risks of childhood cancer associated with pesticides and identify the specific pesticides responsible, it is prudent to reduce or, where possible, eliminate pesticide exposure to children, given their increased vulnerability and susceptibility. In particular, efforts should be focused to reduce exposure to pesticides used in homes and gardens and on lawns and public lands, which are the major sources of pesticide exposure for most children.
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