Journal of Toxicology and Environmental Health, Part B, 10:81–99, 2007

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937400601034589

Taylor & Francis

PESTICIDES AND CHILDHOOD CANCER: AN UPDATE OF ZAHM AND WARD'S 1998 REVIEW

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Children are exposed to pesticides through a number of sources, including residential and agricultural applications. Parental occupational exposure to pesticides is also a concern because exposures occurring during pregnancy and carry-home residues also contribute to children's cumulative burden. A number of epidemiological studies consistently reported increased risks between pesticide exposures and childhood leukemia, brain cancer, neuroblastoma, non-Hodgkin's lymphoma, Wilms' tumor, and Ewing's sarcoma. An extensive review of these studies was published in 1998 (Zahm & Ward, 1998). Fifteen case-control studies, 4 cohort studies, and 2 ecological studies have been published since this review, and 15 of these 21 studies reported statistically significant increased risks between either childhood pesticide exposure or parental occupational exposure and childhood cancer. Therefore, one can confidently state that there is at least some association between pesticide exposure and childhood cancer. However, an unambiguous mechanistic cause-and-effect relationship between pesticide exposure and childhood cancer was not demonstrated in these studies, and modifying factors such as genetic predisposition, rarely considered in the reviewed studies, likely play an important role. While the time window of exposure may be a crucial determinant for biological effects associated with pesticide exposure on children, studies have not contributed definitive information on the most vulnerable period. Accurate exposure assessment remains a challenge; future epidemiological studies need to assess gene–environment interactions and use improved exposure measures, including separate parental interviews, specific pesticide exposure questions, and semiquantitative exposure measures that can be used to confirm information obtained through questionnaires.

Pesticides are biologically active molecules that are commonly used to destroy unwanted organisms in agricultural and residential environments. However, the widespread use of these chemicals has raised concerns regarding their impact on children's health, and a potential relationship between pesticide exposures and various childhood cancers seems most troubling.

Although specific biochemical mechanisms relating pesticide exposures to childhood cancer have yet to be established, some evidence suggests that pesticides may promote the formation of chromosomal aberrations known to be associated with an increased cancer risk by upsetting the balance of free radical production in the body (Abdollahi et al., 2004; Granot & Kohen, 2004). Indeed, several studies indicate that common classes of herbicides and insecticides induce oxidative stress, and pesticide exposures have been associated with genotoxic effects in both occupational (Garaj-Vrhovac & Zeljezic, 2000) and residential (Lieberman et al., 1998) environments. A study used Comet assays to evaluate DNA damage in workers occupationally exposed to pesticides and found that lymphocyte DNA from exposed workers displayed more damage than that of unexposed workers (Garaj-Vrhovac & Zeljezic, 2000). In addition, 6 mo after being removed from the exposure zone, lymphocyte DNA from formerly exposed workers continued to display a higher amount of damage than that of control workers (Garaj-Vrhovac & Zeljezic, 2000). Another study observed chromosome breaks and chromosome translocations in men and women reporting domestic exposure to organophosphate pesticides (Lieberman et al., 1998). Findings from the latter study are important because they illustrate the potential for pesticides to produce biological effects even at levels commonly used in the residential environment. Unfortunately, however, few genotoxicity studies focused specifically on the effects of childhood pesticide exposures, and, as a result, little is known about the effects pesticide exposures exert on children's DNA. Nevertheless, studies

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in adult populations do suggest that pesticide exposures may have a direct effect on chromosome structure, and therefore a causal relationship between pesticide exposures and childhood cancer is plausible.

Increasing public concerns regarding the chronic effects of everyday environmental exposures have highlighted the need for a clearer stand on the causal relationship between pesticide exposures and childhood cancers. However, the scientific community has yet to arrive at a definitive conclusion regarding this relationship. Nevertheless, a growing amount of epidemiological evidence is currently building the foundation upon which such decisions will eventually be made. Specifically, recent epidemiological studies indicate that both direct childhood pesticide exposures and parental occupational pesticide exposures may contribute to the development of childhood cancers. Similarly, although nonspecific pesticide exposure information often limits the scope of our knowledge, various trends in the results are increasingly apparent. The goal of this review was to update results from epidemiological studies that were published after a review carried out by Zahm and Ward (1998); it addresses the relation between pesticide exposure and specific types of childhood cancers, and discusses the causal nature of this relation.

MATERIALS AND METHODS

In 1998 Zahm and Ward published a comprehensive literature review on the then current state of knowledge regarding pesticide exposure and childhood cancer (Zahm & Ward, 1998). Since then, several additional epidemiological studies have been conducted to examine the relationship between pesticide exposures and childhood cancers. Studies are included in this review if they were published in English between 1999 and 2004 and assessed the risks between childhood cancer and pesticide exposures occurring either through residential use or parental occupation. The articles were identified by systematically searching the Medline/PubMed database, and using the following keywords or combinations of these words: childhood cancer (leukemia, brain cancer, neuroblastoma, non-Hodgkin's lymphoma, Wilms' tumor, or Ewing''s sarcoma), insecticide exposure, herbicide exposure, environmental risk factors for childhood cancer, residential pesticide exposure, occupational pesticide exposures, agricultural pesticide exposures, parental pesticide exposures, paternal pesticide exposures, maternal pesticide exposures, preconceptional maternal/paternal pesticide exposures, and prenatal pesticide exposures. Additional references were also identified from the reference list of Zahm and Ward (1998). What follows is a brief summary of the findings of Zahm and Ward (1998) and a summary of more recent studies that examined the relationship between pesticide exposure and childhood cancer.

RESULTS

Leukemia

Zahm and Ward review Seventeen case-control studies and one retrospective cohort study were reviewed (Zahm & Ward, 1998). In total, 13 studies reported increased risks of childhood leukemia (Buckley et al., 1989; Gardner et al., 1990; Hemminki et al.,1981; Infante-Rivard et al., 1991; Kristensen et al., 1995, 1996; Leiss & Savitz, 1995; Lowengart et al., 1987; Magnani et al., 1990; Meinert et al., 1996; Mulder el al., 1994; Roman et al., 1993; Schwartzbaum et al., 1991; Shu et al., 1988), but only 6 showed statistically significant results (Buckley et al., 1989; Leiss & Savitz, 1995; Lowengart et al., 1987; Magnani et al., 1990; Meinert et al., 1996; Shu et al.,1988). Of note, 11 of the 17 case-control studies reviewed reported risk estimates for all leukemia types together, and not for the specific histological type of leukemia (such as acute lymphocytic leukemia [ALL], acute nonlymphocytic leukemia [ANLL]/acute myelogenous leukemia [AML], or chronic myelogenous leukemia [CML]). In the studies reviewed (Zahm & Ward, 1998), a clear pattern of risk regarding the timing of pesticide exposure, the leukemia type that is more at risk, or the exposure of which parent was more determinant could not be identified. Methodological limitations were underscored, such as small numbers of exposed cases, mixing of different leukemia types, crude exposure measures,

and absence of defined time windows for exposure. Although methodological limitations still exist, recent studies published address some of these concerns.

Recent Studies Recent studies of pesticide exposure and childhood leukemia are summarized in Table 1. A population-based case-control study including 491 cases and as many controls conducted in Québec addressed two concerns stated in Zahm and Ward (1998) by focusing on the association between a specific type of leukemia, ALL, and measuring pesticide exposures during specific time periods (Infante-Rivard et al., 1999). Maternal pesticide exposure from 1 mo before pregnancy to the end of pregnancy was determined, as well as child exposure from birth to diagnosis. The risk of ALL increased with frequency of maternal use of herbicides, plant insecticides, and products for trees during pregnancy, with the highest risk being associated with interior plant insecticide use greater than five times. For childhood exposure a rise in ALL risk was observed with exposure to herbicides, plant insecticides, and products for trees. The study also reported statistically significant case-only interaction odds ratios between CYP1A1 polymorphisms and pesticide use during pregnancy and childhood. This investigation was the first to consider both genetic susceptibility and pesticide exposure as factors influencing onset of childhood leukemia, and is still the only study to have done so. However, the case-only study design employed in the genetic portion of this investigation did not allow the direct estimation of the effect of genotype or exposure on risk, but only the interaction effect between exposure and polymorphism. Therefore, further investigations with more robust designs are needed to clarify the role of genetic susceptibility with respect to pesticide exposure and the onset of childhood leukemia. From the same study (Infante-Rivard et al., 1999), a report examining the relationship between ALL and preconceptional paternal workplace pesticide exposures was published (Infante-Rivard & Sinnett, 1999). Here, chemists determined that 175 case fathers and 107 control fathers were exposed to pesticides in the 2 yr previous to pregnancy. Increased risks were observed between preconceptional paternal exposure to all pesticides, fungicides, insecticides, herbicides, and ALL.

Another case-control study including 162 cases and an equal number of controls, conducted in northern California, also addressed the importance of pesticide exposure timing in the development of all childhood leukemias combined and ALL specifically (Ma et al., 2002). Increased risks were observed with household insecticide exposures (excluding flea control products) from 3 mo before pregnancy to 3 yr of age for all leukemias combined, and for ALL specifically with the greatest risk associated with exposures during pregnancy. In addition, more frequent household insecticide exposures were associated with a higher risk of leukemia. The use of a professional pest control service during the same time window was also associated with an excess of all childhood leukemias combined and ALL specifically, with the greatest risk associated with exposures occurring during the child's second year of life. Use of flea control products was not associated with an increased risk of all leukemias combined or ALL specifically in this study, but risk increases were reported for herbicide use 3 mo before pregnancy, during pregnancy, and during the child's second and third year of life. In general, however, outdoor herbicide use was not associated with childhood leukemia.

A pilot case-control study was conducted including infant leukemia (ALL, AML) cases from Europe, the Middle East, South America, and Asia (Alexander et al., 2001). Increased risks of infant leukemia were observed in this study with maternal pesticide exposures occurring during pregnancy. The mosquitocide Baygon was specifically examined, and exposure to this pesticide was associated with infant leukemias involving a rearrangement of the MLL gene (MLL^{+ve}). Baygon exposure was not associated with infant leukemias without this gene rearrangement (MLL^{-ve}), and therefore this pesticide may influence the risk of infant leukemia by promoting gene rearrangement in utero. Further investigation is required.

An ecological study conducted in California failed to report a statistically significant increased risk between agricultural pesticide use and childhood leukemia, with the exception of one block group having the highest use of the insecticide propargite (Reynolds et al., 2002). However, this study assumed that pounds per square mile of pesticide use represented actual child exposures, which is not necessarily the case. A second ecological study observed an increased risk of leukemia in boys and girls living in areas with greater wheat acreage (a surrogate for exposure to chlorophenoxy herbicides), but this increase was not statistically significant (Schreinemachers, 2000). On the other

TABLE 1. Summary of Studies on Pesticides and Childhood Leukemia

Reference	Study design	Cancer	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/comment
Infante-Rivard et al., 1999	Case-control	ALL	491	Maternal pesticide use in and around the home:	During pregnancy		
				Herbicides		118	1.84 (1.32, 2.57)
				Plant insecticides		78	1.97 (1.32, 2.94)
				Pesticides for trees		63	1.70 (1.12, 2.59)
				Repellants/sprays		49	0.70 (0.45, 1.09)
				Products for slugs and snails		6	1.57 (0.43, 5.62)
				Parental pesticide use during childhood:	From birth to diagnosis		
				Herbicides		178	1.41 (1.06, 1.86)
				Plant insecticides		128	1.82 (1.31, 2.52)
				Pesticides for trees		99	1.41 (1.01, 1.97)
				Repellants/sprays		73	0.65 (0.42, 0.94)
				Products for slugs and snails		11	2.23 (0.76, 6.47)
Infante-Rivard & Sinnett, 1999	Case-control	ALL	175	Paternal occupational exposure:	Preconception		
				Pesticides		66	1.56 (1.02, 2.40)
				Fungicides		15	5.11 (1.46, 17.81)
				Insecticides		50	1.38 (0.87, 2.18)
				Herbicides		19	2.05 (0.93, 4.56)
Meinert et al., 2000	Case-control	Leukemia	1184	Maternal occupational pesticide exposure	Year before pregnancy	19	2.1 (1.1, 4.2)
					During pregnancy	15	3.6 (1.5, 8.8)
					After pregnancy	12	2.5 (1.0, 6.4)
					Ever	24	2.5 (1.3, 4.7)
				Paternal occupational pesticide exposure	Year before pregnancy	62	1.5 (1.2, 2.2)
					During pregnancy	57	1.6 (1.1, 2.2)
					After pregnancy	49	1.3 (0.0, 1.9)
					Ever	68	1.6 (1.1, 2.3)
				Farm use of pesticides	From birth to diagnosis	54	1.5 (1.0, 2.2)
				Garden pesticides	From birth to diagnosis	164	1.0 (0.8, 1.2)
Ma et al., 2002	Case-control	ALL	135	Professional pest control at home	3-mo before pregnancy	15	1.9 (0.7, 4.7)
					During pregnancy	20	2.3 (0.9, 5.4)
					3-mo before pregnancy to 3 yr old	36	2.6 (1.2, 5.4)
				Insecticides at home	3-mo before pregnancy	53	1.7 (1.0, 3.1)
					During pregnancy	68	2.3 (1.3, 4.0)
					3-mo before pregnancy to 3 yr old	80	2.2 (1.0, 4.6)
				Flea control products used at home	3-mo before pregnancy	22	0.8 (0.4, 1.6)
					During pregnancy	22	0.7 (0.4, 1.4)
					3-mo before pregnancy to 3 yr old	36	1.0 (0.5, 1.8)
				Herbicides used at home	3-mo before pregnancy	24	1.6 (0.8, 3.3)
					During pregnancy	30	1.8 (0.9, 3.5)
					3-mo before pregnancy to 3 yr old	35	1.0 (0.6, 1.8)

Reynolds et al., 2002	Ecological study	Leukemia	2443	Pounds per square mile of pesticide use	1988 through 1994	NA	1.48 (1.03, 2.13) for block group with highest use of insecticide propargite.
Feychting et al., 2001	Cohort	Leukemia, nervous system tumors	235,635 cohort	Paternal occupational exposure to pesticides	Before conception	5	0.9 (0.37, 2.19)
				Paternal occupation in agricultural, horticultural, and forestry management		5	1.12 (0.46, 2.74)
Flower et al., 2004	Cohort	Leukemia, others	17,357 cohort	Paternal occupation as a pesticide applicator	Before birth	9	0.91 (0.47, 1.75)
Alexander et al., 2001	Case-control	ALL, AML	136	Maternal pesticide exposure	During pregnancy	15	ALL 2.53 (0.71, 8.97)
							AML 5.08 (1.84, 14.0)
				Baygon/mosquitocidal		7	ALL 4.30 (0.66, 28.0)
							AML 7.82 (1.73, 35.3)
Heacock et al., 2000	Cohort + nested case-control	Leukemia	19,674 cohort	Paternal occupational exposure to chlorophenate fungicides	Employment in sawmill at least 1 yr before child's birth	11	1.0 (0.5, 1.8)
				High vs. low cumulative exposure		5	0.8 (0.2, 3.6)
McKinney et al., 2003	Case-control	Leukemia, ALL	1737	Parental occupational exposure:	Periconception		
				Maternal			
				Agrochemicals		5	Leukemia 0.81 (0.31, 2.12)
						5	ALL 0.97 (0.37, 2.52)
				Agriculture		7	Leukemia 1.41 (0.60, 3.31)
						7	ALL 1.68 (0.72, 3.95)
				Paternal			
				Agrochemicals		36	Leukemia 0.83 (0.58, 1.19)
						31	ALL 0.85 (0.58, 1.24)
				Agriculture		29	Leukemia 0.90 (0.60, 1.34)
						25	ALL 0.92 (0.59, 1.40)
Rodvall et al, 2003	Cohort	Leukemia	27,329 cohort	Paternal occupation as a pesticide applicator	Offspring of pesticide applicators born 1958–1994	8	0.43 (0.19, 0.86)
Schreinmachers, 2000	Ecologic study	Leukemia	59	Wheat acreage (< 72,000 vs. >72,000)	1980 through 1989		
				Boys		15	1.40 (0.75, 2.62)
				Girls		5	1.43 (0.49, 4.18)

hand, cohort studies have failed to detect an increased risk of leukemia with paternal occupational exposure to chlorophenate fungicides (Heacock et al., 2000) or paternal occupation as a pesticide applicator (Rodvall et al., 2003). Increased risks of leukemia and ALL specifically were reported in a recent case-control study with maternal employment in agriculture at periconception, but these increases were not statistically significant (McKinney et al., 2003).

A case-control study conducted in Germany collected exposure information between the year of birth and diagnosis for 1184 cases and 2588 controls. An increase in the risk of all childhood leukemia combined was seen for outdoor pesticide use on farms, but not for pesticide use in gardens (Meinert et al., 2000). On the other hand, increased risks were reported between maternal occupational pesticide exposures the year before pregnancy, and during pregnancy, and between paternal occupational pesticide exposures the year before pregnancy and during pregnancy.

In general, these new studies are consistent with those reviewed by Zahm and Ward (1998) because they too suggest an association between pesticide exposure and childhood leukemia. Specifically, childhood exposure to household insecticides and parental exposure to pesticides before pregnancy and during pregnancy seem to present the greatest risks (Alexander et al., 2001; Infante-Rivard et al., 1999; Infante-Rivard & Sinnett, 1999; Ma et al., 2002; Meinert et al., 2000). Of these studies, those conducted by Infante-Rivard et al. (1999) and Ma et al. (2002) are most interesting because the strengths of the reported risk estimates were both greatest for insecticide exposures, and both studies observed exposure response gradients. These two studies also performed the most thorough pesticide exposure assessments of all the childhood leukemia studies identified after Zahm and Ward (1998). Therefore, the failure of the other studies to find risk increases may be due to less adequate exposure assessment for domestic exposure. However, five case-control studies published after Zahm and Ward (1998) observed elevated risks between childhood leukemia and parental pesticide exposures shortly before pregnancy or during pregnancy (Alexander et al., 2001; Infante-Rivard et al., 1999; Infante-Rivard & Sinnett, 1999; Ma et al., 2002; Meinert et al., 2000).

Brain Cancer

Zahm and Ward review Sixteen case-control studies and one retrospective cohort study were reviewed (Zahm & Ward, 1998). Seven of the 16 case-control studies (Bunin et al., 1994; Cordier et al., 1994; Davis et al., 1993; Leiss & Savitz, 1995; Pagoda & Preston-Martin, 1997; Sinks, 1985; Wilkins & Koutras, 1998) reported statistically significant increased risks between pesticide exposures and childhood brain cancer. In addition, 5 of 16 case-control studies (Gold et al., 1979; Hemminki et al., 1981; Kuijten et al., 1992; McCredie et al., 1994; Wilkins & Sinks, 1990) detected increased risks between pesticide exposures and childhood brain cancer. In general, the highest risk estimates reported by case-control studies were for parental use of pesticides in the home or garden or on pets. However, the retrospective cohort study also detected a statistically significant increased risk of nonastrocytic gliomas and nonastrocytic neuroepitheliomoas in children whose fathers engaged in agricultural work (Kristensen et al., 1995, 1996). In addition, one case-control study observed an increased risk of astrocytomas and a significantly increased risk of primitive neuroectodermal tumors in association with maternal household insecticide use during pregnancy and living on a farm for more than one year respectively (Bunin et al., 1994).

Recent Studies Recent studies of pesticide exposure and childhood brain cancer are summarized in Table 2. A case-control study conducted in Germany collected information from 466 cases with pediatric central nervous system (CNS) tumors (119 astrocytomas, 112 medulloblastomas, 50 ependymomas, 31 other gliomas, 154 unspecified CNS tumors) and 2458 controls (Schuz et al., 2001a). The questions used to assess children's pesticide exposures focused primarily on the ever/never use of pesticides in gardens or farms, and on the use of household insecticides either once a year or greater than once a year. Increased risks between household insecticide use once a year and astrocytomas, medulloblastomas, and all CNS tumors combined were observed. Increased risks between household insecticide use greater than once a year and ependymomas were also noted. However, no rise in risk was observed between household insecticide use more than once a year and astrocytomas, and no increased risk was found between pesticide use in gardens or farms and

TABLE 2. Summary of Studies on Pesticides and Childhood Brain Cancer

Reference	Study design	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/comment
Schuz et al., 2001	Case-control	466	Pesticide use:			
			On gardens	Ever	16	Astrocytomas 0.91 (0.48, 1.71)
					5	Ependymomas 0.71 (0.27, 1.89)
					13	Medulloblastomas 0.81 (0.43, 1.53)
					60	All CNS tumors 0.94 (0.68, 1.29)
			On farms		2	Astrocytomas 0.44 (0.09, 2.04)
					1	Ependymomas 0.64 (0.08, 5.05)
					0	Medulloblastomas —
					7	All CNS tumors 0.41 (0.18, 0.93)
			Household insecticide use	Once a year	8	Astrocytomas 2.45 (1.09, 5.47)
					2	Ependymomas 1.51 (0.34, 6.79)
					5	Medulloblastomas 1.14 (0.44, 2.95)
					22	All CNS tumors 1.38 (0.84, 2.25)
				More than once a year	6	Astrocytomas 0.58 (0.23, 1.49)
					5	Ependymomas 1.69 (0.63, 4.54)
					8	Medulloblastomas 1.06 (0.49, 2.28)
					38	All CNS tumors 1.19 (0.81, 1.77)
Heacock et al., 2000	Cohort + nested case-control	19,674 cohort	Paternal occupational exposure to chlorophenate fungicides	Employment at least 1 yr before child's birth	9	1.3 (0.6–2.5)
			High vs. low cumulative exposure		5	1.5 (0.4, 6.9)
McKinney et al., 2003	Case-control	1737	Parental occupational exposure:	Periconception		
			Maternal			
			Agrochemicals		3	1.26 (0.38, 4.17)
			Agriculture		3	1.55 (0.46, 5.19)
			Paternal			
			Agrochemicals		13	0.77 (0.44, 1.36)
			Agriculture		9	0.70 (0.35, 1.38)
Reynolds et al., 2002	Ecologic study	1351	Pounds per square mile of pesticide use	1988 through 1994	NA	No increased risks observed
Rodvall et al, 2003	Cohort	27,329 cohort	Paternal occupation as a pesticide applicator	Offspring of pesticide applicators born 1958–1994	17	1.03 (0.60, 1.65)
Schreinmachres, 2000	Ecologic study	35	Wheat acreage (< 72,000 vs. >72,000)	1980 through 1989		
			Boys		9	1.82 (0.78, 4.26)
			Girls		5	1.63 (0.53, 4.99)

(*Continued*)

TABLE 2. (*Continued*)

Reference	Study design	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/comment
Wijngaarden et al., 2003	Case-control	321	Parental occupational exposure:	Before or during pregnancy		Risk estimates for astrocytomas only
			Maternal		53	1.9 (1.1, 3.3)
			Insecticide		9	1.3 (0.5, 3.7)
			Herbicides		56	1.6 (0.9, 2.7)
			Fungicides	After high school		
			Paternal		82	1.5 (0.9, 2.4)
			Insecticide		51	1.6 (1.0, 2.7)
			Herbicides		99	1.6 (1.0, 2.6)
			Fungicides			
Flower et al., 2004	Cohort	17,357 cohort	Paternal occupation as a pesticide applicator	Before birth	11	1.60 (0.89, 2.89)
Feychting et al., 2001	Cohort	235,635 cohort	Paternal occupational exposure to pesticides	Before conception	11	2.36 (1.27, 4.39)
			Paternal occupation in agricultural, horticultural, and forestry management		9	2.12 (1.08, 4.16)
Cordier et al., 2001	Case-control	1218	Parental occupation in agriculture:	5 yr before birth up to birth		Risk estimates for all brain tumors combined
			Maternal		22	1.1 (0.7, 1.9)
			Paternal		80	1.3 (1.0, 1.8)

any of the CNS tumors investigated. However, the number of cases exposed to household insecticides or pesticides used in gardens or farms was small (maximum 16, minimum 1), and thus few firm conclusions can be drawn from these results. A second case-control study was conducted concurrently in Sydney, Israel, Paris, Winnipeg, Milan, Valencia, Los Angeles, San Francisco, and Seattle, WA, focusing primarily on parental occupational exposures (Cordier et al., 2001). In this study, data obtained via telephone and in-home interviews was used to categorize parental occupations. The risk of all childhood brain tumors, astroglial tumors, primitive neuroectodermal tumors, and other glial tumors was then assessed according to parental occupational category. Although no statistically significant risks were identified, increased ones were observed between maternal and paternal occupation in agriculture in the 5 yr before birth and all childhood brain tumors, astroglial cancers, and primitive neuroectodermal tumors. Similarly, a recent case-control study from the United Kingdom reported an increase in the risk of childhood CNS tumors with maternal occupation in agriculture (McKinney et al., 2003).

A case-control study including 321 cases and an equal number of controls was conducted in the United States and Canada between 1986 and 1989 and examined the relationship between parental occupational exposures and brain cancer (Wijngaarden et al., 2003). A complete history of jobs held for 6 mo or more since leaving high school was obtained for fathers, and mothers were asked about their "usual" occupation before pregnancy and all of their jobs during pregnancy. The probability and intensity of exposure to insecticides, herbicides, and fungicides were evaluated based on an extensive review of the industrial hygiene literature and a job–exposure matrix. A rise in risk was observed for maternal occupational exposure (ever vs. never) to insecticides and astrocytomas. Increased risks were also reported between paternal occupational exposures to insecticides, herbicides, and fungicides (ever vs. never) and astrocytomas, as well as primitive neuroectodermal tumors. Increased risks between astrocytomas and maternal occupational exposures to fungicides and herbicides were also observed, but exposure response gradients were absent for both maternal and paternal occupational exposures.

The first of four cohort studies published after the review by Zahm and Ward (1998) was a retrospective study conducted in Sweden (Feychting et al., 2001). Investigators identified 162 children with nervous system tumors born to married couples in 1976, 1977, 1981, and 1982; occupational hygienists assessed paternal occupational exposures reported in two different censuses conducted in 1975 and 1980. An elevated risk between paternal occupational exposures to pesticides 2 to 26 mo prior to conception and childhood nervous system tumors was observed. In this study, paternal occupation in agricultural, horticultural, and forestry management was also associated with an increased risk of nervous system tumors. The second cohort study used self-administered questionnaires among Iowa pesticide applicators who gave birth to a total of 17,357 children between 1975 and 1998, among whom 6 cases of astrocytomas and 5 other subtypes of brain cancer were observed (Table 2) (Flower et al., 2004). Standardized incidence ratios were estimated using cancer rates in Iowa. An increased risk of brain cancer was observed in the cohort of children of pesticide applicators. Likewise, a third cohort study observed an increased risk of brain cancer with paternal occupational exposure to chlorophenate fungicides, but this increase was not statistically significant (Heacock et al., 2000). Paternal occupation as a pesticide applicator was not associated with brain cancer in a cohort study by Rodvall et al. (2003), but an ecological study reported a quantitative increase in brain cancer risk among boys and girls living in areas with greater wheat acreage (Schreinemachers, 2000).

Like studies on childhood leukemia, the recent case-control studies of brain cancer suggest that the greatest risks are associated with household insecticide use and prenatal exposure to insecticides (Schuz et al., 2001a; Wijngaarden et al., 2003). In addition, these studies consistently reported rises in risks between pesticide exposures and brain cancer (Cordier et al., 2001; Heacock et al., 2000; McKinney et al., 2003; Schreinemachers, 2000; Schuz et al., 2001a; Wijngaarden et al., 2003). The results suggest that power may be an issue, with respect to specific types of brain cancer in particular, which is only compounded by imprecise measures of exposure. Genetic susceptibilities may also play some role in determining the effects of

childhood pesticide exposures, and therefore future studies should examine the role of gene–environment interactions in the development of childhood brain cancer. In general, results from these recent brain cancer studies are consistent with those from the studies reviewed by Zahm and Ward (1998). However, unlike at least three of the studies reviewed by Zahm and Ward (1998), none of the recent ones reported exposure-response gradients. Three studies (Heacock et al., 2000; Schuz et al., 2001a; Wijngaarden et al., 2003) attempted to address this issue: One used high versus low exposure levels (Heacock et al., 2000), one used categories of once a year and more than once a year to classify frequency of pesticide use (Schuz et al., 2001a), and the other used the probability of parental pesticide exposure (Wijngaarden et al., 2003). Clearly, none of these methods provides an ideal measure of pesticide exposure frequency. Brain cancers are possibly more heterogeneous than leukemias. An additional limiting factor of most recent studies, with the possible exception of Cordier et al. (2001), is power to detect associations, if any, for specific subtypes of brain cancers.

Neuroblastoma

Zahm and Ward review Four case-control studies (Bunin et al., 1990; Spitz & Johnson, 1985; Schwartzbaum et al., 1991; Wilkins & Sinks, 1990) and one retrospective cohort study (Kristensen et al., 1995, 1996) were reviewed (Zahm & Ward, 1998). All five of these studies examined parental occupational exposures to pesticides, while none specifically examined residential childhood pesticide exposures prenatally or during childhood. Two case-control studies observed increased risks with preconceptional paternal occupation as a farmer (Bunin et al., 1990), and parental gardening with pesticides during childhood (Schwartzbaum et al., 1991). A retrospective cohort study observed a statistically significant increased risk with parental occupation in agriculture before birth (Kristensen et al., 1995, 1996).

Recent Studies Recent studies of pesticide exposure and neuroblastoma are summarized in Table 3. Three case-control studies (Daniels et al., 2001; Kerr et al., 2000; Olshan et al., 1999) and one prospective cohort study (Flower et al., 2004) examined the relationship between neuroblastoma and pesticide exposures. The first of these case-control studies focused on the relationship between parental occupation and neuroblastoma in both the United States and Canada (Olshan et al., 1999). Parental occupational history included all jobs held since 18 yr of age until the diagnosis reference date, and an increased risk was observed between paternal occupation as a landscaper or groundskeeper (Olshan et al., 1999). Elevated risks were also observed with maternal occupation as a farmer or florist.

The second case-control study was conducted in New York State, and specifically examined parental occupational exposures during pregnancy (Kerr et al., 2000). Increased risks were observed with self-reported maternal and paternal occupational exposures to insecticides during pregnancy. Odds ratios were calculated according to categories of maternal insecticide exposure certainty (category 1: reported exposure and potential for exposure; category 2: no report of exposure but potential for exposure; category 3: reported exposure but no potential for exposure); the odds ratio for category 1, in comparison with mothers who reported no exposure and had no potential for exposures, was 2.6 and was the highest.

Another case-control study focused specifically on residential pesticide exposures and neuroblastoma (Daniels et al., 2001). Detailed interviews regarding the type, purpose, and timing of pesticide use from 1 mo before conception to the date of diagnosis were conducted separately with mothers and fathers of cases and controls identified in the United States and Canada (Daniels et al., 2001). When reported by both parents, elevated risks were observed with garden pesticide use, and home pesticide use in children diagnosed after 1 yr of age (Daniels et al., 2001). Herbicides were more strongly associated with neuroblastoma than insecticides (Daniels et al., 2001). When both parents reported residential pesticide use in this study the odds ratios were nearly always greater than when only one parent reported it. Therefore, the practice of questioning both parents individually about residential pesticide use may be an effective means of improving exposure assessment.

TABLE 3. Summary of Studies on Pesticides and Childhood Neuroblastoma

Reference	Study design	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/comment
Daniels et al., 2001	Case-control	538				Risk estimates for both parents reporting exposure
			Home extermination	Ever	63	1.4 (0.9, 2.1)
				Preconception to pregnancy	150	1.0 (0.5, 2.1)
				Childhood	113	1.5 (0.8, 2.6)
				Age <1 yr	22	1.5 (0.7, 3.0)
				Age 1 yr or more	41	1.3 (0.7, 2.3)
			Home pesticide use	Ever	23	1.6 (1.0, 2.3)
				Preconception to pregnancy	93	1.3 (0.8, 3.3)
				Childhood	65	1.4 (0.9, 2.2)
				Age <1 yr	44	1.2 (0.7, 2.2)
				Age 1 yr or more	106	1.9 (1.1, 3.2)
			Garden	Ever	46	1.7 (0.9, 2.1)
				Preconception to pregnancy	92	1.3 (0.8, 2.0)
				Childhood	74	1.8 (1.0, 3.1)
				Age <1 yr	31	1.0 (0.6, 2.0)
				Age 1 yr or more	82	2.2 (1.3, 3.6)
			Garden herbicide	Age <1 yr	12	1.2 (0.5, 3.1)
				Age 1 yr or more	39	2.2 (1.1, 4.3)
			Garden insecticide	Age < 1 yr	10	0.8 (0.3, 2.2)
				Age 1 yr or more	24	1.7 (0.8, 3.6)
Kerr et al., 2000	Case-control	183	Parental occupational exposure:	During pregnancy		
			Maternal insecticide exposure		40	2.3 (1.4, 3.7)
			Paternal insecticide exposure		40	1.7 (1.0, 2.7)
Olshan et al., 1999	Case-control	504	Parental occupation:	From age 18 yr to diagnosis reference date		
			Paternal work in landscaping		21	2.3 (1.0, 5.2)
			Maternal farm work		7	2.2 (0.6, 8.8)
			Maternal floral/gardening work		6	2.4 (0.6, 9.9)
Flower et al., 2004	Cohort	17,357 cohort	Paternal occupation as a pesticide applicator	Before birth	3	1.26 (0.40, 3.89)

A prospective cohort study also examined the relationship between parental occupational exposure to pesticides and neuroblastoma (Flower et al., 2004). Exposure information was collected using a self-administered questionnaire, but only three cases of neuroblastoma were identified during the study period. An increase in risk with parental occupation as a pesticide applicator was seen in comparison with the reference population.

An increased risk of neuroblastoma was observed for parental occupational exposure to pesticides or residential pesticide use in all four recent studies (Daniels et al., 2001; Flower et al., 2004; Kerr et al., 2000; Olshan et al., 1999). In summary, both previously reviewed studies (Zahm & Ward, 1998) and more recent investigations tend to support a potential relationship between parental occupational pesticide exposure and neuroblastoma in offspring. A recent study (Daniels et al., 2001) also indicates that residential use of pesticides, and herbicides specifically, may increase the risk of neuroblastoma in children.

Non-Hodgkin's Lymphoma

Zahm and Ward review Six case-control studies (Buckley, 1991; Leiss & Savitz, 1995; Magnani et al., 1990; Mulder et al., 1994; Roman et al., 1993; Schwartzbaum et al., 1991) and one retrospective cohort study (Kristensen et al., 1995, 1996) were reviewed (Zahm & Ward, 1998). Of these studies, one case-control study observed a significantly increased risk of non-Hodkin's lymphoma (NHL) with home extermination from pregnancy to 2 yr prior to diagnosis (Leiss & Savitz, 1995), and a second case-control study observed that the risk of NHL increased with increased frequency of maternal home insecticide use (Buckley, 1991). The retrospective cohort study observed a statistically significant increased risk of NHL in children living on farms with the highest pesticide expenditures (Kristensen et al., 1995, 1996).

Recent Studies Recent studies of pesticide exposure and childhood NHL are summarized in Table 4. Two case-control studies (Buckley et al., 2000; Meinert et al., 2000) and two cohort studies (Flower et al., 2004; Rodvall et al., 2003) have examined the relationship between pesticide exposures and NHL. The first case-control study was conducted in California; child pesticide exposures and maternal pesticide exposures around the time of pregnancy were assessed (Buckley et al., 2000). Increased risks were observed with childhood exposures and with maternal use of pesticides in the home around the time of pregnancy. An exposure-response gradient in which the risk of NHL increased with elevated maternal insecticide use in the home around the time of pregnancy was reported. Statistically significant increased risks were observed between NHL and professional insecticide use in the home, as well as postnatal childhood exposure to pesticides.

Another case-control study from Germany (Meinert et al., 2000) reported increased risks of NHL with maternal occupational exposure to pesticides before pregnancy, during pregnancy, after pregnancy, or ever. Increased risks for paternal occupational exposure the year before pregnancy, during pregnancy, after pregnancy, or ever were also reported but were not statistically significant. The study also observed increased risks of NHL for residential parental insecticide use more than 10 times a year and the use of a professional exterminator. An exposure response gradient was also observed in relation with more frequent applications of home insecticides.

A prospective cohort study used self-administered questionnaires to examine the relationship between parental occupational pesticide exposures and various childhood cancers (Flower et al., 2004). Only two cases of NHL were identified during the study period; this resulted in an increased measure of effect for parental employment as a pesticide applicator. The second cohort study observed only three cases of NHL and failed to detect an increased risk with paternal occupation as a pesticide applicator (Rodvall et al., 2003).

Like the studies reviewed by Zahm and Ward (1998), more recent ones suggest a role for pesticides in the development of childhood NHL (Buckley et al., 2000; Flower et al., 2004; Meinert et al., 2000). Of note are the repeated finding of statistically significant increased risks of NHL associated with residential childhood pesticide exposures, and the exposure response gradients observed in two of the three reviewed studies.

TABLE 4. Summary of Studies on Pesticides and Childhood Non-Hodgkin's Lymphoma

Reference	Study design	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/ comment
Buckley et al., 2000	Case-control	268	Maternal exposure:	In the month before pregnancy, during pregnancy, or while nursing		
			Household insecticide use on most days		6	7.33 (0.84, 63.85)
			Use of garden sprays more than once/ month		13	1.71 (0.67, 4.37)
			Exterminate around home		31	2.98 (1.44, 6.16)
			Child exposure to herbicides or insecticides	Between birth and 1 yr before diagnosis	50	2.35 (1.37, 4.03)
			Parental occupational exposure	Ever	21	1.74 (0.82, 3.69)
Meinert et al., 2000	Case-control	234	Occupational pesticide exposure:			
			Maternal	Before pregnancy	3	2.9 (0.7, 13)
				During pregnancy	4	11.8 (2.2, 64)
				After pregnancy	3	7.5 (1.1, 52)
				Ever	4	4.1 (1.1, 16)
			Paternal	Before pregnancy	11	1.5 (0.7, 3.1)
				During pregnancy	10	1.6 (0.7, 3.6)
				After pregnancy	8	1.0 (0.4, 2.5)
				Ever	14	1.9 (0.9, 3.7)
			Pesticide use:			
			On farm	From birth to diagnosis	4	0.5 (0.2,1.4)
			In garden	From birth to diagnosis	33	0.8 (0.5, 1.2)
			Exterminator use	From birth to diagnosis	10	2.6 (1.2, 5.7)
Flower et al., 2004	Cohort	17,357 cohort	Paternal occupation as a pesticide applicator	Before birth	2	1.18 (0.29, 4.70)
Rodvall et al., 2003	Cohort	27,329 cohort	Paternal occupation as a pesticide applicator	Offspring of pesticide applicators born 1958–1994	3	0.63 (0.13, 1.83)

Wilms' Tumor

Zahm and Ward review Five case-control studies (Kantor et al., 1979; Olshan et al, 1993; Schwartzbaum et al., 1984; Sharpe et al., 1995; Wilkins & Sinks, 1984) and one retrospective cohort study (Kristensen et al., 1995, 1996) examined the relationship between childhood and parental pesticide exposures and the incidence of Wilms' tumors (Zahm & Ward, 1998). Two of these five case-control studies examined parental occupational pesticide exposures beginning at birth, and none showed increased risks (Kantor et al., 1979; Wilkins & Sinks, 1984). A third case-control study failed to detected an increased risk of Wilms' tumor with parental gardening from birth to diagnosis (Schwartzbaum et al., 1991). However, one of the two remaining case-control studies conducted in the United States examined the relationship between household extermination and Wilms' tumors and detected statistically significant increased risks with extermination ever and once a year (Olshan et al., 1993). The remaining case-control study conducted in Brazil (Sharpe et al., 1995) and the retrospective cohort study conducted in Norway (Kristensen et al., 1995, 1996) focused on parental occupational exposures before birth, and both studies observed statistically significant increased risks.

Recent Studies Recent studies of pesticide exposure and Wilms' tumors are summarized in Table 5. One case-control study (Schuz et al., 2001b) and one prospective cohort study (Flower et al., 2004) examined the relationship between pesticide exposures and Wilms' tumors. The case-control study was conducted in Germany. Although detailed information was not obtained regarding the type or timing of pesticide exposures, increased risks were observed with maternal occupational exposure ever, and in house use of insecticides more than once a year (Schuz et al., 2001a). However, the observed elevated risk between maternal occupational pesticide exposure and Wilms' tumors was based on only two exposed cases, and childhood exposure to pesticides in gardens or farms and paternal occupational exposure to pesticides after birth were not associated with an increased risk.

A prospective cohort study using self-administered questionnaires from Iowa pesticide applicators identified only three cases of Wilms' tumors during the study period (Flower et al., 2004). However, an increased risk was still observed in comparison with the reference population.

In general, pesticide exposure assessment was limited and small numbers of children with Wilm's tumors in both the case-control study and the prospective cohort study prevent either of these studies from making a definitive contribution. However, the studies reviewed by Zahm and Ward (1998) suggest that childhood insecticide exposures and parental pesticide exposures before birth both increase the risk of developing Wilms' tumors.

TABLE 5. Pesticide Exposure Study of Childhood Wilms' Tumors

Reference	Study design	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/comment
Schuz et al., 2001a	Case-control	177	Occupational exposure:			
			Maternal	Ever	2	2.52 (0.50, 12.6)
			Paternal	After birth	6	0.97 (0.39, 2.37)
			Home insecticide use more then 1/yr		23	1.27 (0.78, 2.08)
			Child exposure			
			In gardens		13	0.80 (0.44, 1.47)
			On farms		5	0.84 (0.32, 2.25)
Flower et al., 2004	Cohort	17,357 cohort	Paternal occupation as a pesticide applicator	Before birth	3	1.56 (0.50, 4.84)

TABLE 6. Pesticide Exposure Study of Childhood Ewing's Sarcoma

Reference	Study design	Total number of cases	Exposure	Timing of exposure	Number of exposed cases	Risk estimate/comment
Valery et al., 2002	Case-control	106	One parent with farm-related occupation	Conception to pregnancy	Not provided	3.4 (1.1, 10.5)
			Paternal employment in farm-related job		Not provided	3.5 (1.0, 11.9)

Ewing's Sarcoma

Zahm and Ward review The risk of Ewing's sarcoma in children appears to be closely linked to parental pesticide exposure (Zahm & Ward, 1998). Three case-control studies reviewed showed increased risks of Ewing's sarcoma with parental occupation in agricultural (Daigle, 1987; Holly et al., 1992; Winn et al., 1992), and two of these were statistically significant (Daigle, 1987; Holly et al., 1992). One of the three studies showed an increased risk with household extermination during pregnancy (Winn et al., 1992); a second one reported deficits with household extermination both during pregnancy and childhood (Holly et al., 1992).

Recent Studies One Australian case-control study specifically examined farm exposures, parental occupation, and the risk of Ewing's sarcoma (Table 6) (Valery et al., 2002). Pesticide exposure information pertaining to the time period 6 mo before pregnancy to the date of diagnosis was collected. Although specific pesticide exposure information was not obtained, having at least one parent in a farm-related job at conception or pregnancy, and paternal employment in a farm related job at conception or pregnancy were associated with increased risk. However, having a "farm-related job" hardly qualifies as precise exposure assessment and further efforts should focus on specific types of pesticide exposures. Nevertheless, these recent findings are consistent with evidence provided by studies reviewed by Zahm and Ward (1998).

DISCUSSION

In 1965, Sir Austin Bradford Hill outlined nine factors that should be considered before deciding whether or not an association between an exposure and a disease is causal (Hill, 1965). In 1998, Rothman and Greenland provided more recent adaptations of these factors (Rothman & Greenland, 1998). These factors are: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy (Hill, 1965).

Pesticides are biologically active molecules, and like other biologically active chemicals it is certainly plausible that they play some role in cancer etiology because this hypothesis does not conflict with our current understanding of the natural history of cancer. Similarly, the "experiment" criterion of Hill (1965) is essentially tested by every case-control study and every cohort study through the comparison of the disease rates in exposed and nonexposed individuals. Therefore, the remainder of this discussion focuses only on the application of the remaining seven Hill (1965) criteria to recent studies of pesticide exposures and childhood cancer.

Strength

It is much easier to make a decision regarding the causal relationship between an exposure and a disease when the strength of the observed association is great because strong associations are less likely to be explained by undetected biases (Hill, 1965; Rothman & Greenland, 1998). However, in studies conducted to date, the risk estimates observed between pesticide exposures and childhood cancers are normally small, and the lower limits of the confidence intervals surrounding these risk estimates are often less than half a unit away from the null value. Nevertheless, Hill (1965) points

out that one should not automatically dismiss cause-and-effect relationships only on the grounds that they are small, because many such associations do exist. Similarly, Rothman and Greenland (1998) point out that a "strong association is neither necessary nor sufficient for causality, and weakness is neither necessary nor sufficient for absence of causality" (p. 25). Rothman and Greenland (1998) also argue that the "strength of a factor's effect on a population depends on the relative prevalence of its causal complement" (p. 11). Therefore, in the case of pesticide exposures, other causal complements such as genetic susceptibility may play key roles in the development of childhood cancers, and because these are not measured, only weak associations are observed.

Consistency

Perhaps the strongest evidence in support of a causal relationship between pesticide exposure and childhood cancer is the repeated detection of statistically significant increased risks between childhood pesticide exposures and cancer. For example, a number of studies published after Zahm and Ward (1998) reported statistically significant enhanced risks between either childhood pesticide exposures or parental occupational exposures and childhood cancer (Alexander et al., 2001; Buckley et al., 2000; Daniels et al., 2001; Feychting et al., 2001; Flower et al., 2004; Infante-Rivard et al., 1999; Infante-Rivard & Sinnett, 1999; Kerr et al., 2000; Ma et al., 2002; Meinert et al., 2000; Olshan et al., 1999; Reynolds et al., 2002; Schuz et al., 2001a; Valery et al., 2002; Wijngaarden et al., 2003). Other studies detected nonstatistically significant increases in risks for childhood pesticide exposures (Schuz et al., 2001b), parental occupational exposures (Cordier et al., 2001; Heacock et al., 2000; McKinney et al., 2003), or residing in areas with high wheat acreage assumed to be a surrogate for herbicide exposure (Schreinemachers, 2000). Therefore, the repeated detection of an association between pesticide exposure and childhood cancer tends to support a causal relationship. However, the degree to which publication bias influences the consistency of these observed increased risks remains unknown.

Specificity

Our ability to associate specific pesticide exposures with specific childhood cancers is limited by both the rarity of childhood cancer and the imprecise exposure assessment methods often employed in epidemiological studies. For example, of the 21 studies published after Zahm and Ward (1998), only 3 (Alexander et al., 2001; Flower et al., 2004; Reynolds et al., 2002) reported risk estimates for specific chemical exposures, and 2 (Alexander et al., 2001; Reynolds et al., 2002) associated this risk with a specific form of childhood cancer. All other studies used broad categories such as insecticides, herbicides, fungicides, or parental occupation to classify exposures. However, Rothman and Greenland (1998) argue that "specificity does not confer greater validity to any causal inference regarding the exposures effect" (p. 25) because many exposures have more than one effect. Therefore, the fact that recent studies associated many types of childhood cancers with several types of pesticide exposures does not rule out a casual relationship. Perhaps pesticides belong to a larger group of causal complements that must all act in order to initiate cancer development. In addition to pesticides, this group of causal complements might also include genetic susceptibility. However, more investigations are needed to identify these factors.

Temporality

If there is causal relationship between pesticide exposures and childhood cancer, it is obvious that exposure must occur before cancer develops. What is not clear is when these exposures must occur (the time window) in order to exert their causative action. In recent studies, statistically significant increased risks were observed between childhood cancer and pesticide exposures occurring either prior to conception, during pregnancy, or during childhood. However, maternal pesticide exposure during pregnancy was most consistently associated with childhood cancer.

Biological Gradients

Biological gradients were observed in 4 of the 21 studies published after Zahm and Ward (1998) (Buckley et al., 2000; Infante-Rivard et al., 1999; Ma et al., 2002; Meinert et al., 2000). Two

of these studies focused on the risk of ALL (Infante-Rivard et al., 1999; Ma et al., 2002) in association with pesticide exposure, and two focused on the risk of NHL (Buckley et al., 2000; Meinert et al., 2000). However, all of the biological gradients observed in these four studies were associated with increased frequency of insecticide exposure (Buckley et al., 2000; Infante-Rivard et al., 1999; Ma et al., 2002; Meinert et al., 2000). Therefore, although many of the studies conducted after Zahm and Ward (1998) did not attempt to assess cancer risks in response to increasing frequency of pesticide exposures, at least four identified biological gradients and support a causal relationship between insecticide exposure and childhood cancer.

CONCLUSIONS

At this point in time one can confidently state that there is at least some association between pesticide exposure and childhood cancer. Furthermore, based on the Hill (1965) causation criteria, recent epidemiological studies suggest that this relationship may be causal due to the repeated finding of pesticide exposures significantly increasing the risk of childhood cancer. In addition, the biological gradients observed in four recent studies also suggest that there may be a causal relationship between childhood insecticide exposures and the development of ALL and NHL (Buckley et al., 2000; Infante-Rivard et al., 1999; Ma et al., 2002; Meinert et al., 2000). However, a one-to-one cause-and-effect relationship likely does not exist between any single type of pesticide exposure and childhood cancer. Probably the development of childhood cancer depends on the presence of many factors, including genetic predisposition, which must all be present at the appropriate time in order to exert their effects. In order to identify these factors, and improve our current understanding of the relationship between pesticide exposures and childhood cancer, future epidemiological studies must employ improved exposure assessments that include separate parental interviews, specific pesticide exposure questions, and semiquantitative exposure measures that can be used to confirm information obtained through questionnaires.

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