Non-Hodgkin's Lymphoma and Agricultural Use of the Insecticide Lindane

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*Data from population-based case-control studies of non-Hodgkin's lymphoma among white men from Kansas, Nebraska, Iowa, and Minnesota were pooled to evaluate potential risks from environmental exposures in more detail, while controlling for potential confounding factors. These data provided the opportunity to evaluate the risk of non-Hodgkin's lymphoma from potential exposures to lindane, a pesticide that causes cancer in laboratory animals and has been associated with human cancer in a few epidemiologic investigations. This pooled data set includes 987 individuals with non-Hodgkin's lymphoma and 2,895 population-based controls. Information was obtained by telephone or in person interviews, which included detailed questions on farm practices and agricultural use of chemicals. Logistic regression was used to calculate odds ratios (ORs) adjusted for age, state of residence, and subject or proxy interviews. Reported use of lindane significantly increased the risk of non-Hodgkin's's lymphoma by 50%. Some use characteristics were suggestive of an association. ORs were greater among persons who first used the pesticide 20 years before diagnosis (OR = 1.7) than more recently (OR = 1.3), among those who reported more frequent use (OR = 2.0 for use 5 or more days per year versus 1.6 for fewer than five days per year), and from use on crops (OR = 1.9), rather than from use on animals (OR = 1.3), although these differences were not statistically significant. On the other hand, ORs were lower when based on direct interviews (OR = 1.3) than on data from proxy respondents (OR = 2.1) and adjustment for potential confounding by use of 2,4-D and diazinon reduced the ORs associated with lindane use from 1.5 to 1.2 and 1.3, respectively. Lindane does not appear to be a major etiologic factor in the development of non-Hodgkin's's lymphoma, although a small role cannot be ruled out.*Am. J. Ind. Med. 33:82–87, 1998. *© 1998 Wiley-Liss, Inc.*†

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INTRODUCTION

γ-Hexachlorocyclohexane (lindane) is an organochlorine insecticide that can act through dermal, ingestion, and respiratory routes. It has been used to control insect damage to crops, stored products, in seed application, on animals, and for public health pests such as head lice [Royal Society of Chemistry, 1987]. It was initially registered for use in the United States in 1950 [U.S. Environmental Protection Agency, 1988]. Its agricultural use today is quite restricted, but it is still used on ornamental plants, avocados, pecans, and Christmas trees, and in livestock sprays, dog shampoos, and human shampoos for head lice [Environmental Protection Agency, 1990]. The International Agency for Research on Cancer (IARC) [1987] concluded that technical grade hexachlorocylohexane (which includes γ- and other isomers) and α-hexachlorocyclohexane are carcinogenic in animals with limited evidence of carcinogenic activity for β- and γ- (lindane) forms in animals. Tumors produced in rodents by the various forms of hexachlorocyclohexane include liver, lymphoreticular, and thyroid. Few epidemio-

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logic studies have evaluated the potential for carcinogenicity from lindane exposure in humans. Most epidemiologic studies of pesticides evaluated occupational categories or exposure to chemical groups and have not focused on individual pesticides. Davis et al. [1993] reported an elevated risk of brain cancer among children treated with lindane-containing shampoo for head lice. In response to the article by Davis et al. [1993], the Food and Drug Administration reviewed the evidence for human cancer from lindane in May 1993. In the study performed by Davis et al. [1993], only seven of 45 cases were exposed to lindane in shampoo, which prevented detailed evaluation of brain cancer risks by the timing and amount of exposure. We had previously reported a statistically significant excess of non-Hodgkin's lymphoma among farmers from Iowa and Minnesota using lindane for agricultural purposes [Cantor et al., 1992] and nonsignificant excesses for leukemia [Brown et al., 1990b]. The number of exposed cases in this study was small, which made it difficult to adjust for potential confounding effects from other pesticide exposures. To evaluate further the potential risk of non-Hodgkin's lymphoma associated with lindane exposure, data from three case-control studies conducted by the National Cancer Institute (NCI) were pooled and analyzed for this report.

METHODS

Data from population-based case-control studies of non-Hodgkin's lymphoma conducted in Iowa/Minnesota [Cantor et al., 1992], Nebraska [Zahm et al., 1990], and Kansas [Hoar et al., 1986] during the 1980s were pooled for this analysis. These studies obtained detailed information on agricultural use of pesticides and on known or suspected risk factors for non-Hodgkin's lymphoma. Cases of non-Hodgkin's lymphoma among white men were assembled from Iowa and Minnesota (except for Minneapolis, St. Paul, and Rochester), Kansas, and eastern Nebraska. Women were also included in the Nebraska study, but not in these analyses because the results for women have been previously reported [Zahm et al., 1992, 1993]. Controls were selected by frequency matching on age, race, gender, and state of residence using a 2 : 1 matching ratio in Iowa and Minnesota, and approximately 4 : 1 in Kansas and Nebraska. Controls for living cases were selected by random-digit dialing for cases under the age of 65 and from the Health Care Financing Administration files for those who were 65 years and older. Controls for deceased cases were selected from death records in each state and matched to the cases by age and year of death. Interviews were conducted with subjects or next-of-kin by telephone in Kansas and Nebraska, and in-person in Iowa and Minnesota. The studies were reviewed and approved by Institutional Review Boards at the medical school in the four states and informed consent was obtained from each study subject.

Some farmers (70 cases and 280 controls) or their proxy respondents (95 cases and 325 controls) did not know whether they had used lindane, and they were excluded from the analyses. The pooled data set of nonfarmers and farmers who could provide information on pesticide use included 993 cases and 2,918 controls. In addition, six cases and 23 controls were excluded from these analyses because other essential data items were missing, leaving 987 cases and 2,895 controls available for analysis. Subjects were not asked about head lice cases and controls were well matched on age, marital status, cigarette use, and other factors, even after exclusions.

Although the questionnaires for the three studies were similar, some differences required coding modifications to allow data to be pooled. In the Iowa/Minnesota and Nebraska studies, participants were asked about their use of a predetermined list of approximately 90 pesticides, using both chemical and trade names. In Kansas, subjects were asked to volunteer the pesticides they had used (i.e., interviewers did not read a list) and the pesticides were linked to major crops grown. In Nebraska, information on days per year of use and total years of use was obtained for each pesticide. In Kansas, days per year and years of use were asked about herbicides and insecticides overall rather than specific chemicals in these two groups. Information on days per year of pesticide use in the Iowa/Minnesota study was not obtained during the original interview. Subjects in Iowa, but not in Minnesota, were recontacted approximately 4 years after completion of the original interview to obtain days per year of use of selected pesticides [Cantor et al., 1993]. Because many of the cases died during the intervening period, information on days per year of use was obtained from surrogates for approximately 55% of the cases and 28% of the controls. Because of this discrepancy in the proportion of proxy respondents among cases and controls, information on days per year of lindane use in Iowa has not been included in the analysis.

Odds ratios (ORs) and 95% confidence intervals (CIs), were calculated using unconditional logistic regression models. We used SAS for this purpose [SAS, 1990]. Nonfarmers, i.e., individuals who had not engaged in farm activities as an adult, served as the referent category.

RESULTS

ORs for various definitions of lindane exposure are shown in Table I. All ORs in the tables are adjusted for age, state of residence, and type of respondent (index or proxy) unless otherwise noted. The relative risk of non-Hodgkin's lymphoma was significantly elevated among subjects reporting agricultural use of lindane (OR = 1.5). Elevated ORs were observed in each state, although they were not statistically significant in Iowa and Nebraska, and the significant OR from Kansas was based on only three exposed

TABLE I. Odds Ratios and Confidence Intervals for Non-Hodgkin's Lymphoma from Lindane Use*

Factor	No. of exposed cases/controls	OR	95%CI
Nonfarmer	243/775	1.0	
Farmer (no lindane use)	651/1969	1.1	0.9–1.3
Farmer (used lindane)	93/151	1.5	1.1–2.0
Iowa only	52/84	1.2	0.8–1.9
Kansas only	3/4	6.1	1.3–29.0
Minnesota only	19/20	2.0	1.0–3.9
Nebraska only	19/43	1.3	0.7–2.4
First lindane use			
≥20 years ago	59/83	1.7	1.1–2.5
<20 years ago	18/30	1.3	0.7–2.3
Protective equipment			
Used	25/48	1.4	0.8–2.3
No use	63/97	1.5	1.0–2.2
Days per year of lindane use			
≤4	8/16	1.6	0.6–4.0
≥5	5/8	2.0	0.6–6.4
By histologic type			
Follicular	36/151	1.6	1.0–2.5
Diffuse	28/151	1.5	0.9–2.5
Small lymphocytic	14/151	1.9	0.9–4.0
Other types	15/151	1.1	0.6–2.1

*Adjusted for age, proxy/direct interview, and state of residence. Pooled data from case-control studies conducted in Iowa, Kansas, Minnesota, and Nebraska during the early 1980s.

TABLE II. Odds Ratios and Confidence Intervals for Non-Hodgkin's Lymphoma from Lindane Use*

Factor	OR	95%CI
Without adjustment for other pesticides	1.5	1.1–2.0
Adjusted for use of:		
Carbamate insecticides	1.5	1.0–2.3
Organophospates	1.3	0.7–2.6
Natural products	1.3	0.9–1.9
Inorganics	1.3	0.9–1.8
Phenoxyacetic acids	2.0	0.9–4.3
Triazines	2.4	1.4–4.0
Amides	2.2	1.4–3.5
Benzoics	2.1	1.4–3.2
Carbamate herbicides	1.6	1.1–2.4
Dinitroanilines	1.8	1.2–2.7
Heterocyclics	1.8	1.3–2.6
Other herbicides	1.5	1.0–2.2
Specific chemicals		
Carbaryl	1.5	1.1–2.2
DDT	1.5	0.9–2.5
Diazinon	1.3	0.9–1.9
Fonofos	1.5	1.0–2.2
2,4-D	1.2	0.5–3.2

*Adjusted for age, proxy/direct interview, state of residence, and various pesticide classes and individual chemicals.

cases and four exposed controls. The OR was slightly larger (and statistically significant) among those first using lindane 20 or more years before diagnosis (OR = 1.7) than among those whose first use was more recent (OR = 1.3). The risk did not differ according to the use of protective equipment. The risk of non-Hodgkin's lymphoma was somewhat greater among persons who reported using lindane an average of 5 or more days per year than among those using it less frequently. Numbers of exposed cases and controls, however, were small for each stratum because information on days per year of use was available only from the studies in Kansas and Nebraska. Relative risks were similar for follicular, diffuse, and small cell non-Hodgkin's lymphomas, but other types of lymphoma showed no excess risk.

Among those who first used lindane 20 or more years before interview (no table), the ORs were 1.4 (95%CI = 0.5–4.3) for 4 or fewer days days per year and 2.5 (95%CI = 0.6–11.7) for 5 or more days per year, based on 11 and five exposed cases, respectively. Further, farmers who reported use of lindane for 10 or more days per year had an OR of 3.3 (95%CI = 0.8–13.8).

Risks of non-Hodgkin's lymphoma from lindane exposure adjusted for reported use of various other pesticides or chemical classes are shown in Table II. Individual pesticides included in these analyses were those associated with non-Hodgkin's lymphoma in these data and with sufficient numbers for statistical adjustment. These are not mutually exclusive categories. Adjustments by use of chemical classes of pesticides did not result in large changes in the ORs for non-Hodgkin's lymphoma from reported use of lindane. ORs increased slightly after adjusting for phenoxyacetic acids, triazines, amides, and benzoics and decreased slightly for organophosphates and natural products. It was also possible to adjust ORs for non-Hodgkin's lymphoma from exposure to lindane for reported use of individual pesticides. Adjustment for the use of DDT and fonofos had no impact on the OR from lindane use, while adjustment for diazinon and 2,4-D decreased the OR to 1.3 and 1.2, respectively.

Risks of non-Hodgkin's lymphoma from reported use of lindane were similar among farmers who used or did not use the herbicide 2,4-D (OR = 1.5 among 2,4-D users and 1.4 among nonusers)(Table III). Among farmers who reported using 2,4-D, the risk of non-Hodgkin's lymphoma from lindane exposure was greater than among those with earlier first use than later first use, but the reverse occurred among those who did not use 2,4-D. ORs from lindane use increased slightly with days per year of use among 2,4-D users, but not among those reporting no use of 2,4-D.

TABLE III. Odds Ratios and Confidence Intervals for Non-Hodgkin's Lymphoma from Lindane Use*

	Used 2,4-D			Never used 2,4-D		
Factor	No. of exposed Ca/Co	OR	95%CI	No. of exposed Ca/Co	OR	95%CI
Ever used lindane	76/122	1.5	1.1–2.1	17/29	1.4	0.8–2.7
First use						
≥20 years ago	48/67	1.6	1.1–2.5	9/14	1.5	0.6–3.6
<20 years ago	13/25	1.1	0.5–2.1	5/4	2.6	0.7–9.7
Days per use of use						
≤4	7/10	2.2	0.8–6.1	1/4	0.8	0.1–7.2
≥5	5/6	2.7	0.8–9.2	0/2	—	—

*Adjusted for age, proxy/direct interview, and state of residence by use of the herbicide 2,4-D.

TABLE IV. Odds Ratios and Confidence Intervals for Non-Hodgkin's Lymphoma from Lindane Use*

	Index subject respondent			Proxy respondent		
Factor	No. of exposed Ca/Co	OR	95%CI	No. of exposed Ca/Co	OR	95%CI
Ever used lindane	78/123	1.3	0.9–1.8	14/27	2.1	1.0–4.4
First use						
≥20 years ago	54/69	1.6	1.0–2.4	5/14	1.6	0.5–4.8
<20 years ago	15/24	1.2	0.6–2.3	3/5	1.7	0.4–7.6
Protection used						
Yes	19/39	1.0	0.5–1.8	5/9	2.8	0.9–9.1
No	56/78	1.4	0.9–2.2	7/18	1.4	0.5–3.5
Days of per year of use						
≤4	7/13	1.0	0.4–2.9	1/3	1.9	0.2–19.5
≥5	3/6	0.9	0.2–3.9	1/2	2.4	0.2–29.3
Histologic type						
Follicular	32/123	1.3	0.8–2.1	3/27	3.6	0.8–15.1
Diffuse	21/123	1.2	0.7–2.1	7/27	2.6	1.0–7.0
Small cell	14/123	2.2	0.9–5.0	0/27	—	—
Other	11/123	0.9	0.4–1.8	4/27	1.7	0.5–5.7

*Adjusted for age, proxy/direct interview, and state of residence by type of respondent (subject or proxy).

Lindane has been used on both crops and animals. The risk of non-Hodgkin's lymphoma was greater from its use on crops (OR = 1.9; 95%CI = 1.1–3.3) than on animals (OR = 1.3; 95%CI = 0.9–1.8). Some farmers used lindane on both crops and animals, therefore these categories are not mutually exclusive. The risk was greater for earlier, rather than later, first use on animals (OR = 1.5; 95%CI = 1.0–2.3) and 0.8; 95%CI = 0.4–1.7, respectively). However, this pattern was reversed for use on crops (OR = 1.9; 95%CI = 1.0–3.8 and 2.9; 95%CI = 0.9–9.1). Regular use of protective equipment diminished ORs from use of lindane on animals (OR = 1.1; 95%CI = 0.6–2.1), but not for use on crops (OR = 1.6; 95%CI = 0.6–4.7). ORs rose with increasing days per year of use on animals, but not on crops.

We calculated ORs for non-Hodgkin's lymphoma from various characteristics of lindane use stratified by presence of 1st degree relatives with cancer. OR from lindane exposure was 1.8 (95%CI = 1.1–2.8; 51 cases/73 controls among those with a first degree relative with cancer and 1.1 (95%CI = 0.7–1.8; 41 cases/77 controls) for those without a first degree relative with cancer. For individuals without a first degree relative with cancer, the relative risks for different aspects of lindane use (i.e., use of protective equipment, time since first use, days per year of use) were similar to the pattern in the entire data set, while among participants with a first degree relative with cancer ORs were smaller.

Table IV provides ORs based on index subjects and proxy respondents reporting use of lindane. The OR for non-Hodgkin's lymphoma was 2.1 from proxy respondents and from 1.3 from index respondents. For most comparisons, the ORs were greater among proxies than among the subjects themselves. Among the index respondents, a larger OR was observed for first use of lindane 20 or more years prior to interview than more recent first use (OR = 1.2) and among those generally not using protective equipment, although none of these differences was statistically significant.

Simultaneous adjustment for hair dye use, smoking, use of water from private wells and use of other pesticides, in addition to age, type of respondent and state of residence yielded an OR from ever using lindane of 1.7 (95%CI = 1.2–2.6).

DISCUSSION

Technical grade hexachlorocyclohexane (which includes the lindane isomer) causes cancer in laboratory animals [IARC, 1987]. The report by Davis et al. [1993] of an excess of brain cancer among children exposed to lindane-containing shampoo for the control of head lice increased interest in the potential for human carcinogenicity from exposure to this pesticide. The association was based on fairly small numbers. We previously reported an association between agricultural use of lindane and risk of non-Hodgkin's lymphoma and leukemia [Cantor et al., 1992; Brown et al., 1990a]. Combining data from the three population-based, case-control studies of non-Hodgkin's lymphoma conducted by the NCI provided the opportunity for a more detailed evaluation of the potential risk of cancer from exposure to lindane. In this pooled analysis, farmers who reported using lindane had a 50% greater risk of non-Hodgkin's lymphoma than that of nonfarmers (OR = 1.5, 95%CI = 1.1–2.0). ORs in this pooled analysis varied by state from 1.2 in Iowa to 6.1 in Kansas. The OR from the Kansas study, however, was based on very small numbers (three exposed cases and four exposed controls). The ORs from the other states were smaller and fell in a much narrower range (1.2–2.0). Simultaneous adjustment for effects of family history of cancer, use of hair dyes, tobacco, use of private wells, use other pesticides, age, state of residence, and type of respondent increased the risk of non-Hodkgin's lymphoma from reported use of lindane from 1.5 to 1.7, therefore these factors could not account for the excess. A number of different aspects of lindane use was evaluated. Some tendencies occurred, although many were not statistically significant. The excess risk was largely confined to individuals who first used lindane 20 or more years before interview. This may be due to chance, to a latency requirement, or to the occurrence of heavier exposures during early years of use. Risk rose with reported frequency of use of lindane (OR = 2.0 for 5 or more days per year of use and 3.3 for 10 or more days), but this pattern was not consistent across subgroups. Interpretation of results by frequency of use is complicated because they are based on data from Kansas and Nebraska only, thus numbers were small (i.e., only five cases and eight controls reported using lindane 5 or more days per year). Furthermore, in the Kansas study, information on days per year of use was for insecticides as a class, and not for lindane specifically, and this would most likely result in nondifferential misclassification.

Risk was greater from use of lindane on crops than on animals. The patterns for ORs by first year of use and frequency of use also differed by animal or crop use greater risks occurring with early first use and more frequent use on animals and the converse for crops. We know of no biologic explanation for these patterns; they may be due to chance.

Farmers use may use several pesticides [Blair and Zahm, 1993] and earlier investigations have noted associations between non-Hodgkin's lymphoma and several herbicides and insecticides [Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992]. Adjustment for reported use of most other pesticides or pesticide classes did not have major effects on the ORs for non-Hodgkin's lymphoma associated with lindane use. The largest effects occurred from the adjustment for use of diazinon and 2,4-D and reduced the overall OR of 1.5 to 1.3–1.2, respectively.

We saw no evidence of interaction between pesticide exposure and family history of cancer as was observed in a study of non-Hodgkin's lymphoma and pesticide exposure among women in Nebraska [Zahm et al., 1993]. In fact, the risk from use of lindane was primarily confined to subjects without a first degree relative with cancer. The strongest effect in the Nebraska study [Zahm et al., 1993], however, occurred among those with a first-degree relative with lymphatic and hematopoietic cancer, and there were too few farmers in this analysis with exposure to lindane and a family history of these tumors for meaningful analysis.

Several methodologic issues needed to be considered when interpreting our findings. Use of proxy respondents may introduce nondifferential misclassification because they cannot provide as accurate information on pesticide use as the subjects themselves [Brown et al., 1990b; Boyle et al., 1992; Blair and Zahm, 1993; Johnson et al., 1993; Blair et al., 1995]. Proxies are more likely to provide ''don't know'' responses [Blair and Zahm, 1993] and are less likely to report use of specific pesticides than are the subjects [Blair et al., 1995]. The larger OR for non-Hodgkin's lymphoma from lindane use reported by proxies than from subjects themselves is, therefore, an unexpected finding and tends to diminish one's confidence in the overall association. The larger ORs among proxy than index subjects could be due to differential reporting bias, to chance, or to larger risks among deceased individuals who may have had a more aggressive disease. Differential reporting bias is always a concern in case-control studies [Checkoway et al., 1989] and may occur because of better, or preferential, recall by the cases. This type of bias could occur among both index subjects and proxy respondents. Some information on the potential for differential reporting bias is available from the literature, as well as for subjects included in this report. Comparison of responses of case and controls regarding pesticide use with information obtained from pesticide suppliers in the Kansas study provided no indication of differential response bias [Hoar et al., 1986]. In addition, the proportion of respondents requiring a probe by the interviewer to elicit a positive response for the use of individual pesticides did not differ between cases and controls in the Nebraska study [Blair and Zahm, 1993], suggesting that differential misclassification was not a problem. On the other hand, in a comparison of relative risks of leukemia and non-Hodgkin's lymphoma from pesticide use based on information obtained from subjects and their proxy respondents, Johnson et al. [1993] found that the ORs were larger among proxies than among subjects for about one-third of the comparisons. It is unclear whether this pattern is a result of differential misclassification, or whether it reflects a combination of the forces of chance and nondifferential misclassification. The latter could occur because in any re-interview study, one would expect that approximately 50% of the ORs from the re-interview to be greater than the original interview and 50% would be smaller simply due to chance variation. Imposition of nondifferentiation misclassification from use of proxies upon this 50 : 50 split could diminish the portion of instances where the larger relative risks occurred among the proxies and create a pattern similar to that observed by Johnson et al. [1993].

In summary, agricultural use of lindane was associated with a 50% increase in the risk of non-Hodgkin's's lymphoma. This may be a chance finding because the relative risk was reduced, but not completely eliminated, by adjustment for potential exposure to other pesticides and was greater among proxy than nonproxy respondents. Relative risks by timing of first exposure, frequency of lindane use, or use of protective equipment were somewhat suggestive of an association, but they were not entirely consistent in the analyses of various subgroups.

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