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Adipose Tissue Levels of Organochlorine Pesticides and Polychlorinated Biphenyls and Risk of Non-Hodgkin's Lymphoma

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In this nested case–control study we examined the relationship between non-Hodgkin's lymphoma (NHL) and organochlorine pesticide exposure. We used a data set originally collected between 1969 and 1983 in the U.S. Environmental Protection Agency National Human Adipose Tissue Survey. Adipose samples were randomly collected from cadavers and surgical patients, and levels of organochlorine pesticide residues were determined. From the original study population, 175 NHL cases were identified and matched to 481 controls; 173 controls were selected from accident victims, and 308 from cases with a diagnosis of myocardial infarction. Cases and controls were mainly from cadavers (> 96%) and were matched on sex, age, region of residence within the United States, and race/ethnicity. Conditional logistic regression showed the organochlorine pesticide residue heptachlor epoxide to be significantly associated with NHL [compared with the lowest quartile: third quartile odds ratio (OR) = 1.82, 95% confidence interval (CI), 1.01–3.28; fourth quartile OR = 3.41, 95% CI, 1.89–6.16]. The highest quartile level of dieldrin was also associated with elevated NHL risk (OR = 2.70; 95% CI, 1.58–4.61), as were higher levels of oxychlordane, *p,p′*-DDE [*p,p*-1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene], and β-benzene hexachloride (ORs = 1.79, 1.99, and 2.47, respectively). The *p*-values for trends for these associations were significant. In models containing pairs of pesticides, only heptachlor epoxide and dieldrin remained significantly associated with risk of NHL. Limitations of this study include collection of samples after diagnosis and a lack of information on variables affecting organochlorine levels such as diet, occupation, and body mass index. Given the persistence of pesticides in the environment, these findings are still relevant today. *Key words:* adipose tissue, chlordane, DDT, dieldrin, heptachlor, non-Hodgkin's lymphoma, organochlorine, PCBs, pesticides, polychlorinated biphenyls. *Environ Health Perspect* 112:854–861 (2004). doi:10.1289/ehp.6726 available via *http://dx.doi.org/* [Online 2 March 2004]

Non-Hodgkin's lymphoma (NHL) is a type of cancer that develops in the B or T cells of the human lymphatic system (Evans and Hancock 2003). NHL is the sixth leading cause of cancer-related death in the United States (Ries et al. 2003). The overall 5-year survival rate is 50–60%, and the cure rate for patients with NHL is about 30–60% (Devesa and Fears 1992). The incidence of NHL has been rising steadily in the developed world since the 1960s. This increase is present independent of sex, age, or geographic locale even after accounting for changes in diagnostic ascertainment and the AIDS epidemic (Evans and Hancock 2003; Freedman and Adler 1996; Ries et al. 2003).

Exposure to organochlorine compounds, including organochlorine pesticides, has been investigated as a potential risk factor for NHL (Palackdharry 1994). These compounds are lipophilic and have prolonged half-lives of years to decades; as a consequence, they accumulate in human adipose tissues and can cause chronic toxicity after long-term exposure, even if the exposure is at a relatively low dose (Dich et al. 1997). Many organochlorine pesticides have been found to be carcinogenic in rodent studies (McConnell 1994). In studies of NHL, the use of pesticides has been associated with increased risk of NHL in farmworkers and other occupationally exposed groups (Baris et al. 1998; Cantor et al. 1992; Morrison et al. 1994; Woods et al. 1987; Zahm 1997). Self-report of exposure to pesticides has been linked to NHL in recent case–control studies (Hardell et al. 2002; Mao et al. 2000). Farming as an occupation is associated with an increased risk of NHL (Keller-Byrne et al. 1997; Zahm and Blair 1992). Residential exposure to pesticides has also been implicated as a risk factor for NHL in both adults and children (Buckley et al. 2000; Meinert et al. 2000).

However, human data on NHL risks associated with exposure to specific pesticides are limited. Furthermore, many previous studies have not used direct exposure measures but instead relied on surrogate measures such as occupation or self-reported frequency of pesticide use. Studies in which biologic exposure measurements are available have generally been small, and findings have not been consistent across populations. For example, serum pesticide and polychlorinated biphenyl (PCB) concentrations were studied in relation to NHL in 74 cases and 174 matched controls from a population-based sample in the northeastern United States (Cantor et al. 2003; Rothman et al. 1997). In this population, a significant dose-related increase in NHL risk was associated with prediagnosis serum levels of PCBs but not with levels of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), hexachlorobenzene, or chlordane- and heptaclor-related compounds. In contrast, a small (n = 27 cases) hospital-based study in Sweden found a significant increase in risk of NHL associated with adipose tissue concentrations of the chlordane metabolite *trans*-nonachlor (Hardell et al. 1996a) but not with adipose concentrations of PCBs, hexachlorobenzene, or *p,p*-1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p′*-DDE) (Hardell et al. 1996b, 1997). Hardell et al. (2001) also studied organochlorine pesticide residues in blood from 82 NHL patients and 83 controls in relation to Epstein-Barr virus (EBV) early antigen antibody titers (EA). In subjects with higher titers to EBV EA, higher levels of PCBs, chlordane-related compounds, and hexachlorobenzene were associated with increased risk of NHL (Hardell et al. 2001). Blair et al. (1998) investigated the common organochlorine pesticide γ-BHC (lindane) as a possible risk factor for NHL; the authors concluded that, at most, a minor role could be ascribed to lindane, due to other coexposures.

In the present study we used a unique database of human adipose tissue samples that were analyzed for organochlorine pesticides and PCBs to investigate the hypothesis that organochlorine exposure is associated with NHL. The adipose tissue samples were collected for the U.S. Environmental Protection Agency (U.S. EPA) National Human Adipose

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Tissue Survey (NHATS), part of the National Human Monitoring Program for Pesticides started by the U.S. Public Health Service in 1967 and operated by the U.S. EPA during 1970–1987 (Kutz et al. 1979, 1991). The study was designed to provide the U.S. EPA with information about the level of exposure to pesticides that existed in the U.S. population and to provide information about how pesticide exposure changed over time. Human adipose tissue was obtained from postmortem and surgical specimens collected throughout the continental United States. Concentrations of 20 organochlorine pesticides or pesticide metabolites and PCBs for more than 20,000 people were determined. Using these data, we examined the association between the risk of NHL and adipose organochlorine pesticide and PCB levels using a case–control study design.

Materials and Methods

U.S. EPA NHATS. The sampling strategy for this survey has been described elsewhere (Kutz et al. 1991; Yobs 1971). Cities with populations > 25,000 in the 1960 U.S. census were selected from within the 48 contiguous states for sample collection. Cooperating physicians, pathologists, and medical examiners at locations in the selected cities collected human adipose tissue samples during surgery and postmortem from 1969 through 1983. At the time of sample collection, other data were also collected, such as age, sex, race, and diagnoses (Kutz et al. 1979; Yobs 1971). The sampling approach used by the U.S. EPA was a proportionate, stratified-random sampling design. Sampling of nonwhites was proportional to their occurrence in the respective census region or division, approximately 10% of the sample. Because the purpose of the survey was to estimate levels in the general U.S. population, persons with pesticide poisoning, chronic wasting diseases, or cachexia and those who had been institutionalized for long periods of time were excluded from the study by the participating pathologist at the time of collection. Surgical samples were from tissue that was extracted for the therapeutic or diagnostic intent of the surgical procedure, not for the purpose of the study. Postmortem sampling of adipose tissue from cadavers occurred as soon as possible after death, or at least within 24 hr. Samples were stored at 4°C until shipped on dry ice and subsequently frozen at –20°C until analyzed. Analysis was performed by contracted laboratories using approved methods for cleanup and gas chromatography (GC) analysis, with confirmation by thin-layer chromatography, Coulson electrolytic conductivity detectors, microcoulometry, or GC–mass spectrometry (as described by Thompson 1977). All laboratories participated in a quality assurance program consisting of provision of analytical standards in an adipose media, standardized reagents, and quarterly external evaluation of performance with chemical confirmation of residues in every tenth sample. Details of the quality assurance procedures were described by Thompson (1977). All data used in these analyses came from Batelle (Columbus, OH), which was contracted by the U.S. EPA to manage and archive the data set. The institutional review boards of the University of California at Irvine, Brigham and Women's Hospital, and San Diego State University approved the present research.

Matching procedure. The cases (n = 203) were those in the NHATS data set who had a diagnosis of NHL according to *International Classification of Diseases,* Version 8 [ICD-8; World Health Organization (WHO) 1967] code 200 (n = 122) and ICD-8 code 202 (n = 81). Of the 203 cases, 28 were excluded because of missing lipid-adjusted pesticide exposure data (19 had no lipid data available, 7 had < 10% lipid in tissue samples, and 2 had no pesticide data), leaving 175 cases. Of the 175 cases, 83.4% had NHL coded as the primary diagnosis. ICD-8 codes were provided by the participating physician, pathologist, or medical examiner, and not from the death certificate. Controls were selected from two groups: subjects with a diagnosis of accidental injury (or death) and no cancer diagnosis, and subjects with a diagnosis of myocardial infarction (MI) and no cancer diagnosis. Controls were matched on age (same age as cases or up to 5 years older than cases), sex, geographic region of the subject's hospital, and race (white and black). Information on Hispanic ethnicity was limited; only one case was identified as Mexican American, and this case was matched to a control identified as white. For region, the first matching criterion was based on nine U.S. Census divisions (New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, and Pacific). No matching control was found for census divisions in 17 of the 175 cases. In these instances, the census region was used (North East, North Central, South and West). Three controls were successfully matched to each case for 133 cases, two controls were matched to each case for 40 cases, and one control was matched to two cases. Therefore, the final study population included in analyses was 175 cases and 481 controls.

Of the 173 selected accidental injury controls, 168 fatty tissue specimens were collected at autopsy (97%). Of the 308 selected MI controls, 304 specimens were collected at autopsy (99%). Of 175 cases, 167 specimens were collected at autopsy (95%). All remaining specimens were taken from pathology samples collected during surgical procedures.

Independent variables. The exposure variable used for each pesticide included in the logistic regression models was the lipid-adjusted concentration of the pesticide obtained by dividing the measured pesticide residue concentration in the total tissue sample by the decimal fraction of the sample that consisted of ether-extractable lipid (Kutz et al. 1979). This was done to account for differences in percentage of lipid of the tissue samples submitted for analysis. Samples that contained < 10% lipid were excluded from analysis. For cases and controls, the range of the percentage of lipid in the tissue sample was 10.2–100%, with a median 69% and mean (± SD) of 65.2 ± 17.3%. MI control samples had a significantly higher average percentage of lipid than did accident controls (mean, 68.1% vs. 63.6%; $p < 0.01$) and case samples (mean, 68.1% vs. 61.9%; $p < 0.001$, respectively, by Wilcoxon rank sum test). Accident controls were not significantly different from cases ($p = 0.36$). Analysis was carried out in a total of seven different contract laboratories, although three laboratories accounted for 93% of cases and 90% of controls. Cases and controls did not differ in the length of time between sample collection and analysis ($p = 0.2095$ by Fisher's exact test). Most samples (83.1% of cases and 86.9% of controls) were analyzed within 1 year of collection.

Values reported were above the limit of detection (LOD) for the approved testing methods used in the U.S. EPA contract laboratories. Samples that contained chemical residue < LOD were given a value of 0. The LOD differed between laboratories and over time, but for fiscal year 1970 the LODs were reported to be approximately 0.01 ppm for dieldrin, heptachlor epoxide, hexachlorobenzene, *p,p′*-DDT, and *p,p′*-DDE and 0.02 ppm for β-BHC (Kutz et al. 1974; Thompson 1977). For seven pesticide residues (aldrin; endrin; α-, δ-, and γ-BHC; Mirex, and heptachlor), fewer than 20% of the samples had detectable levels for either cases or controls; therefore these pesticides were not included in our analysis. For DDT-related compounds, only *p,p′*-DDT and *p,p′*-DDE were retained in the analysis because these compounds comprised 19% and 80%, respectively, of the total geometric mean lipid-adjusted concentration for the six DDT-related compounds (*p,p′*-DDD, *o,p′*-DDD, *p,p′*-DDE, *o,p′*-DDE, *p,p′*-DDT, *o,p′*-DDT). Both *p,p′*-DDT and *p,p′*-DDE were strongly correlated with the total concentration of these DDT-related compounds (Spearman ρ = 0.83 and 0.99, respectively).

The lipid-adjusted concentrations for pesticide residues in the analysis were categorized according to the distribution in controls. Quartiles were created for *p,p′*-DDT, *p,p′*-DDE, β-BHC (also called β-hexachlorocyclohexane or HCH), dieldrin, and heptachlor epoxide. The lowest quartile was used as the referent exposure category. There were

two other technical-grade chlordane- or heptachlor-related compounds (oxychlordane and *trans*-nonachlor). All data were missing in the first 5 years of the study for *trans*-nonachlor (1969–1973) and nearly all in the first 2 years for oxychlordane. Because of the small numbers, three exposure categories were created for oxychlordane, and *trans*-nonachlor was analyzed as a dichotomous variable with two exposure categories. For hexachlorobenzene, almost all data was missing for the first 2 years, and around two-thirds were missing in the third and fourth years. Also, 25% of the study population was not exposed above the LOD. Therefore, three exposure categories were created: the referent exposure was < LOD (coded by the U.S. EPA as 0), and the top two tertiles were made by apportioning control subjects approximately equally. In all cases, categorical cut points were constructed using controls for whom the pesticide data for matched cases were not missing. PCB data represent exposure to Aroclor 1254 and 1260 and were only available as categorical data. The referent category was a combination of no PCBs detected, PCBs detected but levels not quantifiable, and PCBs < 1 ppm. The two higher categories were 1–3 ppm and > 3 ppm. However, 24% of subjects had no PCB data (37 cases, 123 controls).

Statistical methods. Epilog (Epicenter Software, Pasadena, CA) was used to perform conditional logistic regression on matched case–control sets. Because data for some pesticide residue levels for oxychlordane, *trans*-nonachlor, hexachlorobenzene, and PCBs were missing for controls, some models included more cases with only one matched control. Multivariate unconditional logistic regression models were run with covariates for the matching variables (age, sex, race, and census region) to test the robustness of the matched analysis. Effect magnitudes of the pesticides were not confounded by the matching variables, all of which were nonsignificant ($p > 0.3$). Therefore, only the conditional logistic regression models without the matching variables are presented. Year of sample collection was positively associated with risk of being a case [odds ratio (OR) per year = 1.13; 95% confidence interval (CI), 1.07–1.18]. Year of sample collection confounded the regression parameters of pesticides by up to 12%, so all regression models controlled for year of sample collection.

ORs and 95% CIs from regression analyses are presented for higher categories of pesticide exposure compared with the lowest referent exposure level. Pesticides were log-normally distributed. Therefore, the *p*-value for linear trend is presented from models using the continuous log-transformed pesticide variable, which gave the best-fitting model. Statistical significance for univariate case–control differences in continuous adipose pesticide concentrations was attributed to two-sided *p*-values < 0.05 from Wilcoxon rank sum tests.

Results

Demographic characteristics of the study population are presented in Table 1. Cases and controls did not differ demographically, which is consistent with the matched design. The study population was composed of slightly more men (56.6% of cases and controls) than women. The mean age (± SD) of cases was 49.0 ± 22.4 years, and that of controls was 50.0 ± 21.9 years. Approximately half of the study population was from the Mid-Atlantic and East North Central census divisions. The study population was composed predominately of those who were categorized as white (91% of cases and 92% of controls), with the remainder composed of those categorized as black.

Lipid-adjusted adipose tissue levels of pesticides for cases and controls are shown in Table 2. For all residues, the mean was higher in cases than in controls, and levels were significantly higher for dieldrin, oxychlordane, heptachlor epoxide, and hexachlorobenzene by Wilcoxon rank sum test (Table 2).

Table 3 shows results of conditional logistic regression models for individual pesticides. *p,p′*-DDT was not significantly increased among cases when divided into quartiles, but there was a significant trend for the log-transformed continuous variable ($p < 0.05$). The DDT-related residue *p,p′*-DDE was significantly increased among cases in the highest quartile (OR = 1.99; 95% CI, 1.14–3.47), and the trend was significant ($p = 0.002$). β-BHC and dieldrin levels were significantly associated with increased NHL risk among cases in the highest exposure quartiles (respective ORs = 2.47 and 2.70; Table 3). There were no significant associations of hexachlorobenzene or PCBs with NHL risk in this analysis (Table 3).

Higher levels of the chlordane- and heptachlor-related compounds oxychlordane and heptachlor epoxide were significantly associated with the odds of NHL (Table 3).

Table 1. Demographic characteristics of 175 cases of NHL and 481 matched controls.

Variable	Cases No. (%)	Controls No. (%)
Sex		
Male	98 (56.0)	273 (56.8)
Female	77 (44.0)	208 (43.2)
Age (years)		
2–18	28 (16.0)	71 (14.8)
19–34	13 (7.4)	41 (8.5)
35–49	35 (20.0)	90 (18.7)
50–64	51 (29.1)	146 (30.4)
≥ 65	48 (27.4)	133 (27.6)
Census division		
New England	15 (8.6)	34 (7.1)
Mid-Atlantic	46 (26.3)	131 (27.2)
East North Central	41 (23.4)	115 (23.9)
West North Central	18 (10.3)	46 (9.6)
South Atlantic	11 (6.3)	31 (6.4)
East South Central	7 (4.0)	23 (4.8)
West South Central	15 (8.6)	39 (8.1)
Mountain	4 (2.3)	7 (1.5)
Pacific	18 (10.3)	55 (11.4)
Race/ethnicity		
White	160 (91.4)	441 (91.7)
Black	15 (8.6)	40 (8.3)

Table 2. Adipose tissue pesticide concentrations (ppm lipid) in cases of NHL ($n = 175$) and matched controls ($n = 481$).

Pesticide residue (ppm; μg/g lipid)	Mean ± SD	Median	Minimum	Maximum	Percent < LOD
p,p′-DDT					
Cases	1.32 ± 1.60	0.87	0.03	10.34	0.0
Controls	1.27 ± 1.26	0.92	0.04	10.86	0.0
p,p′-DDE					
Cases	6.90 ± 6.27	5.31	0.25	40.06	0.0
Controls	5.76 ± 5.33	4.34	0.14	42.73	0.0
β-BHC					
Cases	0.42 ± 0.57	0.28	0.00	4.91	2.3
Controls	0.34 ± 0.38	0.24	0.00	4.43	1.7
Dieldrin					
Cases	0.24 ± 0.23	0.18	0.00	1.72	1.1
Controls	0.20 ± 0.17*	0.15	0.00	1.27	1.7
trans-Nonachlor					
Cases	0.22 ± 0.18	0.18	0.00	0.77	7.9
Controls	0.17 ± 0.11	0.15	0.02	0.52	0.0
Oxychlordane					
Cases	0.20 ± 0.26	0.15	0.02	2.85	0.0
Controls	0.14 ± 0.10**	0.13	0.00	0.77	2.7
Heptachlor epoxide					
Cases	0.14 ± 0.12	0.12	0.00	0.87	1.1
Controls	0.11 ± 0.11#	0.09	0.00	1.36	2.1
Hexachlorobenzene					
Cases	0.05 ± 0.04	0.05	0.00	0.17	18.2
Controls	0.04 ± 0.05#	0.03	0.00	0.55	28.6

p-Value for case–control difference in concentrations from two-sided Wilcoxon rank sum test: *$p < 0.05$; **$p < 0.01$; #$p < 0.0001$.

Another chlordane- and heptachlor-related compound, *trans*-nonachlor, was not significantly associated with risk of NHL. However, the sample size was limited to 38 cases and 54 controls for *trans*-nonachlor measurements. Excluding surgical subjects from the models made little to no difference in the magnitude of associations (< 10% ± change) or in the significance of the results (data not shown). Adjustment for analytical laboratory in the logistic regression models did not alter our findings (data not shown).

All compounds showed low to moderate correlation with each other (Table 4). The correlations did not differ between cases and controls (data not shown). To explore the possibility of between-pesticide confounding, we constructed conditional regression models containing two of the pesticides that were significantly associated with NHL (*p,p′*-DDE, β-BHC, dieldrin, and heptachlor epoxide). Oxychlordane was excluded because of low numbers. Regression results for these pesticides are based on the same set of person-observations in the single pesticide models shown in Table 3, so that results are directly comparable with ORs displayed in Table 3. The ORs for heptachlor epoxide in two pesticide models were similar to results from the single pesticide model, as were the ORs for dieldrin (Table 5). In contrast, ORs for *p,p′*-DDE and β-BHC were not significantly elevated when included in the model with heptachlor epoxide or dieldrin (Table 5). For example, for heptachlor epoxide, the OR remained significantly elevated for the top two quartiles with little change (+8.2% and –1.4%, respectively) when *p,p′*-DDE was included in the model, but *p,p′*-DDE no longer had a significant association with NHL (Table 5).

Table 3. Odds of NHL in relation to adipose tissue concentrations of pesticides and PCBs (ppm lipid).

Pesticide residue (ppm)	Cases No. (%)	Controls No. (%)	OR	95% CI	*p*-Value for trend[a]
p,p′-DDT					
< 0.55	58 (33.1)	118 (24.5)	1.00		
0.55–0.92	34 (19.4)	120 (24.9)	0.80	0.47–1.35	
0.92–1.56	38 (21.7)	121 (25.2)	0.97	0.56–1.70	
> 1.56	45 (25.7)	122 (25.4)	1.39	0.78–2.47	0.04
p,p′-DDE					
< 2.40	48 (27.4)	116 (24.1)	1.00		
2.40–4.38	24 (13.7)	129 (26.8)	0.53	0.29–0.96	
4.38–7.21	38 (21.7)	114 (23.7)	1.12	0.64–1.98	
> 7.21	65 (37.2)	122 (25.4)	1.99	1.14–3.47	0.002
β-BHC					
< 0.15	50 (28.6)	118 (24.5)	1.00		
0.15–0.24	28 (16.0)	118 (24.5)	0.74	0.40–1.34	
0.24–0.37	30 (17.1)	123 (25.6)	0.88	0.48–1.64	
> 0.37	67 (38.3)	122 (25.4)	2.47	1.34–4.55	0.0001
Dieldrin					
< 0.09	37 (21.1)	121 (25.2)	1.00		
0.09–0.15	37 (21.1)	120 (24.9)	1.24	0.71–2.17	
0.15–0.24	38 (21.7)	119 (24.7)	1.56	0.88–2.74	
> 0.24	63 (36.0)	121 (25.2)	2.70	1.58–4.61	0.0002
trans-Nonachlor					
0.00–0.15	16 (42.1)	26 (48.2)	1.00		
> 0.15	22 (57.9)	28 (51.8)	1.48	0.51–4.27	0.25
Oxychlordane					
< 0.09	47 (33.6)	107 (35.6)	1.00		
0.09–0.15	25 (17.9)	96 (31.9)	0.64	0.35–1.17	
> 0.15	68 (48.6)	98 (32.6)	1.79	1.04–3.08	0.0002
Heptachlor epoxide					
< 0.06	23 (13.1)	115 (24.0)	1.00		
0.06–0.09	34 (19.4)	121 (25.2)	1.35	0.71–2.55	
0.09–0.14	46 (26.3)	124 (25.8)	1.82	1.01–3.28	
> 0.14	72 (41.1)	120 (25.0)	3.41	1.89–6.16	0.0001
Hexachlorobenzene					
0.00 (< LOD)	20 (18.2)	61 (28.6)	1.00		
0.00–0.04	33 (30.0)	72 (33.8)	0.78	0.35–1.74	
> 0.04	57 (51.8)	80 (37.6)	1.29	0.58–2.83	0.06
PCBs					
Trace, not detected, or < 1 ppm	79 (57.3)	184 (51.4)	1.00		
1–3 ppm	50 (36.2)	151 (42.2)	1.05	0.63–1.76	
> 3 ppm	9 (6.5)	23 (6.4)	1.08	0.40–2.92	—

[a]From conditional logistic regression models for the log-transformed pesticide.

Discussion

Among a general population sample, adipose tissue levels of the organochlorine pesticide residues heptachlor epoxide, oxychlordane, dieldrin, *p,p′*-DDE, and β-BHC were associated with increased risk of NHL in single pesticide analysis, and the trend was significant for increasing log-transformed continuous pesticide residue concentrations (Table 3). For heptachlor epoxide, which had the highest OR (3.4) among the analytes studied, the OR increased across exposure quartiles in a dose-dependent manner, and the two highest quartiles were associated with significant and increasing risk of NHL. The single pesticide models did not, however, account for the correlation between pesticide levels, which ranged from 0.22 to 0.58 in most pairs (Table 4). In two-pesticide models of residues for which sufficient numbers of subjects had reported levels, ORs for heptachlor epoxide were the most stable, followed by dieldrin. ORs for other residues were no longer significantly elevated (Table 5). Taken as a whole, these results implicate heptachlor epoxide and dieldrin as the residues with the strongest and most robust associations with risk of NHL.

The organochlorines studied were commonly used in the United States in previous decades. Chlordane was used for household pest management, termite control, and agricultural treatment of food crops, and heptachlor for crops and mosquito and termite control. Chlordane was banned in the United States for most uses by 1978 but was still used

Table 4. Spearman rank correlation matrix for lipid-adjusted pesticide concentrations in adipose tissue.

	p,p′-DDT	*p,p′*-DDE	β-BHC	Dieldrin	*trans*-Nonachlor	Oxychlordane	Heptachlor epoxide	Hexachlorobenzene
p,p′-DDT	1.00	0.76	0.58	0.53	0.40	0.38	0.38	–0.15
p,p′-DDE		1.00	0.57	0.44	0.52	0.51	0.35	0.09
β-BHC			1.00	0.47	0.56	0.56	0.44	0.01
Dieldrin				1.00	0.37	0.38	0.54	0.04
trans-Nonachlor					1.00	0.73	0.57	0.47
Oxychlordane						1.00	0.50	0.22
Heptachlor epoxide							1.00	0.11
Hexachlorobenzene								1.00

as a structural termiticide until 1988. Similarly, the use of heptachlor for most purposes was banned in the United States in 1978, but its production continued until 1997. It was used against fire ants as recently as 2000. Heptachlor epoxide, the residue most strongly associated with risk of NHL (Tables 3 and 5), is a biologic oxidation product of heptachlor (Tashiro and Matsumura 1978). However, because technical-grade heptachlor contains some chlordane and technical-grade chlordane contains heptachlor (Kutz et al. 1991), human adipose levels could occur after exposure to either chlordane, heptachlor, or both compounds. The other chlordane-related compounds studied were *trans*-nonachlor, the primary human metabolite of chlordane and also a component of technical-grade chlordane, heptachlor, and oxychlordane, a human metabolite of chlordane metabolic intermediates (Tashiro and Matsumura 1978). Oxychlordane was associated with NHL in single-pesticide models (Table 3), but numbers were too low to be included in two-pesticide models (Table 5). *trans*-Nonachlor was not significantly associated with NHL in this study, although the sample size was very low (Table 3). Elevated *trans*-nonachlor levels in adipose tissue have previously been linked to NHL (OR = 4.1; 95% CI, 1.1–15) when subjects with *trans*-nonachlor levels above the median level of the study population (0.061 ppm) were compared with those less than the median (Hardell et al. 1996a).

Dieldrin, the other residue that was most strongly linked to NHL in this study, was used until the 1970s in agriculture and for soil applications such as termite control. It is also the stable metabolite of aldrin (Kutz et al. 1991). In breast milk samples from Australian women, concentrations of dieldrin, heptachlor epoxide, and oxychlordane were associated most strongly with termite control in the home (Sim et al. 1998). Our findings may implicate termite control as a risk factor in the development of NHL, although elevated adipose tissue levels of these organochlorines can arise from direct inhalation or dermal exposure (e.g., to heptachlor or chlordane residues from termite treatments) or from diet. For the organochlorines studied, both parent compounds and metabolites can be found in foods (Dougherty et al. 2000; Stehr-Green et al. 1988), especially fish (Karl et al. 1998) and meats (DeVoto et al. 1998; Salman et al. 1990). A limitation of the present study is that occupational information was missing for most subjects; therefore, the relation of occupational exposures to NHL could not be explored (Persson et al. 1989).

Previous studies have reported increased odds of NHL with exposure to organochlorine pesticides from agricultural (Cantor et al. 1992; Woods et al. 1987; Zahm et al. 1993) and home applications (Buckley et al. 2000; Meinert et al. 2000). However, in many of these studies, identifying the risk associated with individual pesticides is difficult because exposure was defined by proxy measures, such as self-reported use or occupation, and the study populations often had multiple pesticide exposures. Where biologic measures of individual pesticide exposures have been available, studies have generally been smaller than the population of the present study. In a nested case–control study (n = 74 cases) using prediagnosis serum samples, no association was reported between levels of chlordane- and heptachlor-related compounds, dieldrin, or hexachlorobenzene and NHL (Cantor et al. 2003). In the same data set, investigators reported an increased risk of NHL with highest quartile serum PCB levels (1.07–2.07 ppm), with an OR of 4.5 (95% CI, 1.7–12.0) (Rothman et al. 1997). Hardell et al. (1997) also reported a nonsignificant increase in adipose levels of PCBs and risk of NHL in 27 cases studied previously (Hardell et al. 1996b). The OR for NHL for adipose tissue from subjects with sum of PCBs greater than the median value of 1.300 ppm was 1.8 (95% CI, 0.4–7.4). Hardell et al. (2001) also found an apparent interaction between organochlorines and EBV: in subjects with elevated EBV EA antibody titers, higher serum PCB levels were associated with increased risk of NHL (OR = 4.0; 95% CI, 1.2–14), as were higher levels of sum of chlordanes (OR = 4.0; CI, 1.2–14) and hexachlorobenzene (OR = 5.3; 95% CI, 1.6–19). We found no association with PCBs, although the laboratory analysis was not quantitative (Table 3) and missing values for PCBs may have introduced bias. In addition, because our controls were collected, on average, slightly earlier than were cases and because PCB levels in the U.S. population were generally decreasing during this time period (Kutz et al. 1991), our analysis could have been biased toward a null finding. Rothman et al. (1997) also reported finding no significant association between total lipid-corrected serum concentrations of DDT and risk of NHL, and this finding is supported by the present study, in which we found no clear association between exposure to DDT and NHL. We report associations with *p,p′*-DDE that were confounded by heptachlor epoxide (Table 5).

Levels of heptachlor epoxide and dieldrin in adipose tissue from our control subjects were generally similar to or slightly higher than levels reported in other U.S. studies at the time [reviewed by Kutz et al. (1991)]. In a 1970 study of 200 subjects in Idaho (Wyllie et al. 1972), mean adipose heptachlor epoxide levels were 0.10 ppm and mean dieldrin levels were 0.20 ppm, compared with 0.11 ppm and 0.20 ppm, respectively, in our study. In a study of 221 subjects in Texas during 1969–1972 (Burns 1974), levels of heptachlor epoxide

Table 5. Odds of NHL in relation to adipose tissue pesticide concentrations (ppm lipid): two-pesticide models.

Exposure categories[a]	OR (95% CI)	Percent change[b]	OR (95% CI)	Percent change[b]
Pesticides	Heptachlor epoxide		*p,p′*-DDE	
Level 1	1.00		1.00	
Level 2	1.25 (0.64–2.42)	–7.7	0.40 (0.21–0.74)	–29.1
Level 3	1.98 (1.06–3.67)	8.2	0.75 (0.40–1.39)	–40.1
Level 4	3.36 (1.78–6.35)	–1.4	1.32 (0.73–2.39)	–41.2
Pesticides	Heptachlor epoxide		β-BHC	
Level 1	1.00		1.00	
Level 2	1.38 (0.72–2.62)	2.0	0.63 (0.34–1.18)	–15.9
Level 3	1.85 (0.97–3.46)	1.4	0.64 (0.33–1.24)	–32.0
Level 4	2.88 (1.50–5.52)	–16.8	1.55 (0.79–3.04)	–46.6
Pesticides	Heptachlor epoxide		Dieldrin	
Level 1	1.00		1.00	
Level 2	1.26 (0.65–2.43)	–6.9	1.06 (0.59–1.91)	–15.4
Level 3	1.58 (0.82–3.04)	–14.2	1.14 (0.61–2.15)	–31.0
Level 4	2.60 (1.30–5.21)	–27.2	1.62 (0.85–3.06)	–51.3
Pesticides	*p,p′*-DDE		β-BHC	
Level 1	1.00		1.00	
Level 2	0.55 (0.30–1.02)	3.3	0.69 (0.37–1.32)	–6.4
Level 3	1.12 (0.61–2.08)	0.5	0.74 (0.37–1.45)	–18.1
Level 4	1.64 (0.88–3.04)	–19.5	1.81 (1.09–1.22)	–31.2
Pesticides	*p,p′*-DDE		Dieldrin	
Level 1	1.00		1.00	
Level 2	0.48 (0.26–0.89)	–9.9	1.23 (0.687–2.20)	–0.9
Level 3	0.87 (0.49–1.64)	–22.3	1.59 (0.87–2.92)	2.0
Level 4	1.49 (0.82–2.73)	–28.7	2.35 (1.32–4.16)	–14.0
Pesticides	β-BHC		Dieldrin	
Level 1	1.00		1.00	
Level 2	0.64 (0.34–1.19)	–15.0	1.32 (0.74–2.38)	6.4
Level 3	0.69 (0.36–1.33)	–24.3	1.61 (0.88–2.96)	3.3
Level 4	1.76 (0.91–3.38)	–34.1	2.34 (1.30–4.19)	–14.5

[a]Levels of pesticides in adipose tissues are the same as those shown in Table 3. [b]Percent change is from ln(OR) from univariate analysis shown in Table 3.

(mean, 0.11 ppm) were similar to ours. Dieldrin levels were higher, with a mean of 0.35 ppm (Burns 1974), which might be because the authors reported samples were taken from an area with heavy agricultural use of pesticides. In a study of 70 subjects in Arizona during 1968–1969, Morgan and Roan (1970) reported mean dieldrin levels in adipose tissue of 0.14 ppm. In autopsy specimens from 146 subjects in Florida during 1965–1967, mean levels of dieldrin were 0.22 ppm (Edmundson et al. 1968). Levels in other countries such as Canada were generally lower: Canadian studies from 1969–1981 reported adipose values for dieldrin ranging from 0.043 to 0.17 ppm (Kutz et al. 1991).

We can only speculate on reasons for the discrepancy between our results regarding the risks associated with heptachlor- and chlordane-related compounds and dieldrin and the results of Cantor et al. (2003). One reason could be that our reported association is real and is detected in our study because of our larger sample size (174 cases vs. 74 cases), larger geographic area, and/or our use of adipose tissue measurements instead of serum measurements. In addition, the magnitude of the organochlorine exposure could differ between subjects in the two studies. A direct comparison is difficult, however, because Cantor et al. (2003) measured serum levels (medians: heptachlor epoxide, 0.111 ppm for cases vs. 0.103 ppm for controls; dieldrin, 0.130 ppm for cases vs. 0.117 ppm for controls; neither difference was significant), whereas we report adipose tissue levels (medians: heptachlor epoxide, 0.120 ppm for cases vs. 0.090 ppm for controls; dieldrin, 0.180 ppm for cases vs. 0.150 ppm for controls; both residues were significantly higher in cases). Ratios of lipid-adjusted serum to adipose tissue levels can vary by organochlorine residue and among populations (Mussalo-Rauhamaa 1991; Needham et al. 1990; Patterson et al. 1988; Waliszewski et al. 2000), so a direct comparison of levels of organochlorine residues between our study and the Cantor et al. (2003) study cannot be made.

Another explanation for the differing results between the two studies could be that the association between adipose tissue levels and NHL is an artifact of the samples having been collected both postdiagnosis and primarily postmortem in our study, limitations not present in the Cantor et al. (2003) study. This latter explanation would be supported if adipose tissue residue levels increased postdiagnosis or at the end stages of NHL. Our results, however, are in agreement with elevated levels of chlordane-related compounds in adipose tissue from NHL patients obtained pretreatment (Hardell et al. 1996a) and increased levels of chlordane-related compounds in serum obtained pretreatment in NHL patients with EBV EA > 80 (Hardell et al. 2001), although both studies had smaller numbers and also reported significant increases in other organochlorines in samples from NHL cases.

Data on the potential for change in chlordane-related compound levels in adipose tissue postdiagnosis for NHL are lacking, although adipose tissue levels of organochlorines may be more stable than are serum levels. In a study of organochlorine pesticides before and after treatment for NHL, Baris et al. (2000) found that serum levels of PCBs and DDE decreased approximately 25% posttreatment. If adipose tissue levels did decrease in our subjects, the associations found would underestimate the true relationship. In contrast, studies of organochlorine levels after sudden weight loss in obese individuals have reported an increase in serum and adipose levels of PCBs and other organochlorines (Charlier et al. 2002; Chevrier et al. 2000). This effect was not noted for chlordane-related compounds in a longitudinal study of Swedish women, where body mass index (BMI) and a recent change in weight were not associated with a difference in serum *trans*-nonachlor and oxychlordane levels, although these factors were associated with a difference in most serum PCB congener levels (Glynn et al. 2003). In our study, the collection protocol explicitly called for the exclusion of cachexic patients by the collecting pathologist or physician; however, the effectiveness and balance of this procedure could not be determined. It should be noted that our case samples did not have a lower percentage of lipid than did accident controls, although both cases and accident controls had a lower percentage of lipid than did MI control subjects (see "Materials and Methods"). However, because direct information on the percent change in body mass after diagnosis is not available for subjects in this study, and the potential for associated change in adipose organochlorine levels exists, it must be emphasized that collection postdiagnosis and primarily postmortem is an important limitation of this study.

Two groups of subjects were used as controls, one with a diagnosis of accidental injury or death and the second of subjects with a diagnosis of MI. In an unconditional regression analysis comparing cases with each control group, findings were generally consistent with results from the matched analysis (data not shown). Little is known about the association of organochlorine exposure with risk of MI. However, obesity is a risk factor for MI, and obese persons and persons with higher BMI have been reported to have higher serum and adipose levels of some, but not all, organochlorines (Chevrier et al. 2000; James et al. 2002; Pelletier et al. 2002; Schade and Heinzow 1998). In addition to possibly greater obesity prevalence in MI controls than cases, adipose tissue samples from MI controls in our study had a higher percentage of lipid than did either the accident controls or the cases (see "Materials and Methods"). If MI controls had a greater prevalence of obesity than cases and, if obesity were independently associated with higher levels of our measured organochlorines, then we may have underestimated the magnitude of the organochlorine-related risk of NHL. Conversely, as described above, if the cases experienced diagnosis- or treatment-related weight loss and associated increases in adipose tissue organochlorine levels, then we may have overestimated the magnitude of the organochlorine-related risk of NHL. Unfortunately, a limitation of this study is that weight loss information and BMI were not available, so that the possible influence of these factors on adipose levels of organochlorines and their relationship to NHL could not be assessed.

The subtypes of NHL were not known in detail for the cases in our study. It may be that the risk associated with organochlorine insecticides differs by subtype. The t(14;18) translocation is a common somatic mutation found in cancer cells from some NHL patients, and Schroeder et al. (2001) found that risk from self-reported exposure to pesticides was elevated in t(14;18)-positive NHL cases only. Hardell et al. (2001) reported that the elevated risk for NHL associated with higher levels of organochlorine pesticides in subjects with elevated EBV antibodies was highest for the low-grade B-cell type of NHL. This type of analysis may be very useful in elucidating risks in future studies. Other data that would be helpful in future studies include information about autoimmune or immunodeficiency illness among study participants, because immunologic disorders may play a role in development of NHL (Palackdharry 1994) and some changes in immune function are potentially associated with organochlorine exposures. We chose to exclude lymphatic leukemias from NHL to ensure comparability of our findings to previous studies of organochlorines and NHL in which clinical categorization schemes for these tumors were used [SEER (Surveillance, Epidemiology, and End Results) classification; Ries et al. 2003]. More recent classifications for NHL would include lymphatic leukemias [REAL (Revised European-American Classification of Lymphoid Neoplasms) classification; Harris et al. 2000); therefore, our results would not apply to risks of all types of NHL as currently defined.

A potential limitation of this study is that the organochlorine analyses were done in different laboratories over a relatively extended period of time. However, any interlaboratory differences in chemical analyses are likely to be random with respect to case status and

therefore unlikely to have biased our findings except to the null. Adjustment for analytical laboratory in the logistic regression models did not alter our findings. Because the controls were collected overall slightly earlier than cases, and pesticide levels were generally decreasing over time, the effect would have been to increase levels in controls and decrease levels in cases, biasing our study toward the null. Thus, it is unlikely that potential interlaboratory or temporal differences in the organochlorines analysis affected our results.

Another limitation of this study is that it includes predominantly NHL cases with poor prognosis or those cases in which the patient died of their disease. Because only about one-third of NHL cases are fatal, our estimated increased risks from exposures to organochlorine compounds may not be applicable to all patients with NHL. Alternatively, exposure to chlordane or heptachlor, their metabolites, or dieldrin may play a role in worsening the prognosis of NHL patients. An analogous effect was reported in a case–control study of the association of breast cancer risk and tumor aggressiveness with plasma organochlorine concentrations (Demers et al. 2000). Demers et al. (2000) provide evidence that organochlorine pesticide exposure may increase breast cancer disease severity but does not show that exposure to organochlorines alone is related to increased risk of breast cancer. A potential role for dieldrin in worsening the survival of breast cancer patients has also been reported (Hoyer et al. 2000). Therefore, it is possible that exposure to the analytes studied either may lead the initial NHL to be a more aggressive type or may worsen the disease course and prognosis once it is initiated.

Timing of exposure relative to disease is unknown for our study population, although latencies between exposure and disease onset likely varied between the children and adults included among our cases. Because residues in adipose tissue were used as the exposure marker, no dose rate information is available. This means that there is no way to determine if exposure occurred over a short time period at a high level or over a long time period at a lower level. Also, because study samples were analyzed during the 1970s and 1980s, the limits of detection for these pesticides were higher then than they are now. This means the true extent of the relationship between exposure and outcome may not be realized in this study.

Strengths of this study are that patient recall of exposure is not relied on for exposure data, that cases and controls were matched on demographic variables, that the study covers a wide geographic area, and that the study size is relatively large compared with similar studies that make use of human tissue analysis for pesticide exposure data. Important limitations of this study include the lack of detailed information about the subjects such as lifestyle factors, occupation, diet, and other disease conditions; the sample collection having occurred after diagnosis and primarily postmortem, so organochlorine levels in tissue may have changed from prediagnosis levels; a lack of information on BMI, which might influence adipose tissue levels of organochlorines; and no confirmation as to the effectiveness of the procedure for the exclusion of cachexic subjects. Results from this study generally support the findings of previous research showing an association between elevated levels of organochlorine pesticides in biologic samples and NHL. Because many pesticides that have been used in the past in domestic settings may still persist in the environment, and some pesticides no longer used in the United States are still used in other countries, these organochlorine pesticides may still represent a significant health concern.

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