

Concentrations of Organochlorines Related to Titers to Epstein-Barr Virus Early Antigen IgG as Risk Factors for Hairy Cell Leukemia

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Hairy cell leukemia (HCL) is a rare chronic B-cell malignancy that, according to modern classifications, is a subgroup of non-Hodgkin lymphomas (NHLs). A rapid increase in incidence of NHL has been reported in many countries. The reasons for this increase are largely unknown, but exposure to organochlorines has been suggested as a risk factor. Epstein-Barr virus is a human herpesvirus that has been associated with certain subgroups of NHL. In this study, we measured lipid adjusted blood concentrations (in nanogram per gram) of 36 congeners of polychlorinated biphenyls (PCBs), *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE), hexachlorobenzene (HCB), and four subgroups of chlordanes (*trans*-nonachlor, *cis*-nonachlor, MC6, and oxychlordanes) in incident cases of HCL and controls from the general population. We obtained results on organochlorines and antibodies for 54 cases and 54 controls. Titers of antibodies to the Epstein-Barr early antigen and Epstein-Barr nuclear antigen, measured as P107, were correlated to concentrations of organochlorines to evaluate the possibility of an interaction between these factors in the pathogenesis of HCL. We found no significant difference in lipid-adjusted blood concentrations of total PCBs, *p,p'*-DDE, HCB, or the sum of the chlordanes between cases and controls. Titers of antibodies to Epstein-Barr early antigen IgG ≥ 40 were correlated to an increased risk for HCL. This risk was further increased in those with a level above the median value of *p,p'*-DDE, HCB, or the sum of the chlordanes, suggesting an interaction between Epstein-Barr virus and a higher concentration of these chemicals. We also found increased risk for the sum of immunotoxic PCB group. **Key words:** Epstein-Barr virus, hairy cell leukemia, organochlorines. *Environ Health Perspect* 108:441–445 (2000). [Online 28 March 2000] <http://ehpnet1.niehs.nih.gov/docs/2000/108p441-445nordstrom/abstract.html>

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies originating from the lymphoid system. There has been a rapid increase in NHL incidence in the Western world during the last 20–30 years (1–3).

Hairy cell leukemia (HCL) is, according to modern classifications, a rare type of malignant lymphoma that expresses a B-cell phenotype (4). HCL is 4–5 times more frequent in males. The possible effects on environmental factors in the pathogenesis of HCL have been investigated (5–11), although the impact of genetic factors has not been evaluated.

Many conditions characterized by severe immunosuppression, such as immunosuppressive treatment after organ transplantation, certain inborn immunodeficiencies, and human immunodeficiency virus (HIV) infection are correlated to an increased risk for NHL (12–14). Some factors suggested as possible risk factors for NHL, such as exposure to ultraviolet light and organochlorines, have been reported to induce immunologic changes (15,16), although the clinical importance of these findings has not been fully evaluated (17).

Epstein-Barr virus (EBV) is a human herpesvirus that has a tropism for B-lymphocytes and is found worldwide. The majority of the world's adult population has antibodies to

EBV viral antigens. The primary infection usually occurs during childhood and is often subclinical. A latent infection is established, which is balanced by the immune response of the host, and antibodies to the Epstein-Barr early antigen (EA), viral capsid antigen (VCA), and Epstein-Barr nuclear antigen (EBNA) may be detected (18).

EBV has been associated with certain types of NHL such as Burkitt lymphoma and lymphomas occurring in immunologically compromised or HIV-infected subjects (19). In HCL, elevated levels of antibodies to EA and VCA have been reported (20,21).

Polychlorinated biphenyls (PCBs) are aromatic chemically stable compounds. They do not occur naturally, but have been widely used in electrical equipment and building construction because of their physical properties. Theoretically, 209 congeners of PCBs are possible, but only approximately 130 of these are likely to occur in commercial products. Humans are exposed to PCBs mainly through the food chain by the consumption of contaminated fish, meat, and dairy products, and PCB is stored mainly in the adipose tissue (22). PCBs were used in Sweden until 1973, when their use was prohibited by law.

Exposure to PCBs has been suggested to induce measurable changes in the immune system (23,24), although in doses higher

than background exposure. Increased concentrations of some specific PCBs have been shown in patients with NHL as compared to controls (25). A recent study found a dose–response relation between total lipid-corrected blood concentrations of total PCB (quartiles) and risk of NHL overall (26).

DDT is an insecticide that has been widely used because of its chemical stability. DDT and its metabolites *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) and DDD are lipid soluble and bioaccumulate. No association has been found between exposure to DDT and concentrations of *p,p'*-DDE and NHL in samples from adipose tissues in serum levels from epidemiologic studies (25–27).

Hexachlorobenzene (HCB) has been used in agriculture as a fungicide and occurs in industry as an intermediate in chemical processes. HCB is a contaminant in pesticides (28). In a previous study using adipose tissue samples, no association was found between concentrations of HCB and NHL (25).

Chlordanes are substances originating from the synthesis of cyclodienes; they are distributed throughout the biosphere. Technical chlordanes has been used both in agriculture and in the control of termites. Production of chlordanes started in the United States in 1947 and chlordanes were registered in Sweden until 1969. In humans, these compounds are stored mainly in adipose tissue. Exposure to chlordanes has been suggested to induce immunologic changes measured in lymphocyte functions *in vitro* (29). An association between concentrations of chlordanes in adipose tissue and NHL has been suggested (30).

According to the model of causality by Rothman and Greenland (31), there may be different factors acting as component causes

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in the pathogenesis of disease. To evaluate the possibility of more than one factor acting at the same time in the pathogenesis of HCL, concentrations of organochlorines were correlated to titers of antibodies to EBV. The purpose of this investigation was to determine concentrations of organochlorines in blood samples from HCL patients as compared to controls. The titers of antibodies to EBV were correlated to concentrations of these substances.

Materials and Methods

Case and control ascertainment. To investigate risk factors for HCL, we performed a population-based case-control study. The design and other details of the study have been published in detail elsewhere (10,11). In short, the study included all Swedish cases of HCL among males diagnosed between 1987 and 1992 that were reported to the Swedish Cancer Registry and who were alive at the time of the investigation. One case later turned out to be diagnosed in 1993 but was still included in the analysis. The study included 121 cases and 484 controls drawn from the national population registry and matched for age, sex, and county.

The participants were sent an extensive questionnaire with detailed questions about previous occupations and exposure to potential risk factors such as pesticides, organic solvents, animals, and exhausts. The response rate was 91% among the cases (111 of 121) and 83% among the controls (400 of 484). All data were coded blindly to the person's case or control status. We obtained informed consent from all participants.

Because of the high cost of analyzing organochlorines, it was not possible to offer blood tests to all of the participants of the case-control study. Among these participants, 71 cases and 186 controls were randomly chosen among 5-year age strata. Sixty-two cases and ninety-four controls agreed to participate in this part of the study. Three cases and seven controls were not able to participate because of medical reasons. Two cases and twenty-three controls chose not to participate although they had agreed to give a blood sample. Blood tests were obtained from a total of 121 individuals: 57 cases and 64 controls. One case was excluded from the analysis of antibody titers to EBV antigens for technical reasons, and the identity of the blood samples from four subjects could not be identified with certainty, so they were also excluded. Levels of organochlorines were not obtained for three subjects for technical reasons. Six controls were excluded because they had a diagnosis of a malignant disease that might interfere with the results; organochlorines had not been analyzed for one of these subjects

because of technical reasons. Results on both viral antibodies and organochlorines were obtained for 108 subjects: 54 cases and 54 controls. The blood samples were kept frozen at -20°C until analysis. Results for the sum of PCBs (36 congeners), the sum of chlordanes (oxychlordanes, MC6, and *trans*- and *cis*-nonachlor), *p,p'*-DDE, HCB, and antibody titers to EBV antigens are presented for these 108 subjects.

The participants of this part of the study were sent an additional questionnaire in which they were asked about their present weight and height, the weight at diagnosis of HCL (or the year of diagnosis for the corresponding case of the control), and the weight at the time of blood sampling. We calculated body mass index (BMI) as the weight in kilograms divided by the square of the height in meters. All subjects were asked if they had been diagnosed with a malignant disease. The cases were further asked if they had been treated with chemotherapy or α -interferon.

EBV antigens. Antibodies to different EBV antigens were analyzed according to published and accredited procedures (32,33), with the exception that whole blood was used because serum or plasma were not available. The whole EDTA-blood was thawed, and diluted in phosphate-buffered saline without calcium and magnesium, but with the addition of 0.5% Tween and 5% bovine serum albumin. In brief, we used indirect immunofluorescence for IgG and IgM antibodies to the VCA and the combined restricted and diffuse components of early antigens (EA R + D). The VCA IgG antibodies were end-point titrated in 4-fold dilutions from 1/20, whereas EA IgG was analyzed in one dilution, allowing for the detection of antibodies in serum dilution $\geq 1/40$ (titer $\geq 1/40$). Positive samples were end-point titrated. EBNA-1 IgG antibodies were screened in a peptide ELISA with the alanine-glycine repeat as antigen (33). We included well defined positive controls in each assay. We allowed a 2-fold interassay variation in titers of the controls in the immunofluorescence assays. However, in the six assays used for examination of the samples of this study there was no variation of titers of the controls, except for one assay where the EA control had a titer of 640 instead of 320. The long-term coefficient of variation in optical density of the p107 IgG assay was < 10%; it was 3% in the six assays for the dilution of the positive control with an expected absorbance of 0.6–0.8. The quality of the assays used was monitored by participation in external quality control schemes (External Quality Control in Sweden), and by international serum exchange (mainly with E.T. Lennette, Virolab, Inc., Berkeley, CA). The EA and VCA IgG

titers in healthy Swedes using these methods have been published previously (32).

Because whole frozen EDTA blood was the only material available for this study, comparisons with titers found at serum or plasma examinations were not relevant and anticomplement studies for EBNA antibodies could not be performed. The samples were coded at the time of examination, and the identity of the patients was unknown to the laboratory. The completed results were uncoded by the clinicians, and titers and seroprevalences in cases and controls were compared statistically.

Organochlorine analysis. We used a subsample of approximately 20 mL blood plasma for the analyses of 36 individual PCB congeners, *p,p'*-DDE, HCB, and four chlordanes congeners. The plasma samples were fortified with ^{13}C -labeled internal PCB, DDE, HCB, and chlordanes standards. The lipid fraction, including the organochlorines, was retained from the plasma by use of a Hydromatrix column (Varian, Harbor City, CA) (34). Thereafter the lipid content was determined gravimetrically and further cleaned up by multilayer chromatography. We used high resolution gas chromatography and mass spectrometry (HRGC-MS) selected ion monitoring (SIM) with electron impact ionization for congener-specific identification and quantification of the analytes. We achieved chromatographic separation by splitless injection of 2 μL of the sample (approximately 1/10) on a nonpolar DB-5 column using helium as the carrier gas. The gas chromatography (GC) oven was programmed as follows: 180°C initial hold for 2 min, increase at a rate of 15°C/min to 205°C, followed by an increase of 3.7°C/min to 300°C, and a final hold at 300°C for 20 min. In the SIM mass spectrometry (MS) recording we monitored the two most intense ions of the molecular ion clusters for the analytes, target compounds, and standards at a dwell time of 40 msec and an interchannel delay of 1 msec. We achieved quantification by comparing the relative responses of the target compounds against the ^{13}C internal standards in both the samples and in a standard solution. The method detection level was in the range of 0.3–1 ng/g lipid depending on the analyte's response and the fat content of the individual sample. The recoveries of the internal standards were in the range of 70–90% for the various organochlorines. Laboratory blank samples were performed in the same way as the plasma samples, and they did not contain analyte levels exceeding 10% of the levels found in the samples. Further, we performed quality assessment/quality control confirmation and quantification when a) the signal to noise ratio was > 3 for the quantification ions in

the SIM GC/MS mode, *b*) the ratio of the two most abundant ions in the chlorine clusters was within 15% of the theoretical values, and *c*) the HRGC retention times for the analyte signal and the signal of a corresponding standard were not more than 2 sec apart.

Statistical methods. We performed unconditional logistic regression using the SAS system (SAS Institute, Cary, NC) for the calculation of odds ratios (OR) and 95% confidence interval (CI). In the analyses, adjustments were made for age and BMI at the time of sampling. In addition, risk factors for HCL (11) were controlled for by including them in the analysis (exhausts, fungicides, herbicides, impregnating agents, insecticides, occupational animal exposure, and organic solvents). Antibody variables and organochlorine variables were dichotomized using the median concentration of the controls. We also used the SAS system for descriptive statistics and Wilcoxon rank sum tests. In one of the analyses we grouped PCBs according to immunotoxic properties (PCB nos. 66, 110, 105, 118, 74, 128/167, 156, 138, and 170/190), as previously suggested (35). Because of the small number of observations, formal tests of interaction were not considered to have enough statistical power to be informative. Furthermore, a test without the power to give significant results does not exclude the possibility of interaction.

Results

Results for the sum of PCBs (36 congeners), the sum of chlordanes (oxychlordanes, MC6, and *trans*- and *cis*-nonachlor), *p,p'*-DDE, HCB, and antibody titers to EBV antigens are presented for 108 subjects, 54 cases, and 54 controls.

The blood samples were drawn from the cases a median of 7.1 years (range 4–10 years) after the diagnosis of HCL and from the controls a median of 7.0 years (range 4–10 years) after the diagnosis of the corresponding case. The mean age at the time of blood sampling was 62.1 years (range 39–79) for the cases and 63.2 (range 39–83) for the controls.

Concentrations of organochlorines for cases and controls are shown in Table 1. No significant differences were found. A division of the concentrations into tertiles to look for a threshold effect did not change the results.

Analysis was also performed using the median level of lipid-adjusted blood concentrations (in nanogram per gram) of organochlorines among the controls as cut-off. Adjusted ORs and CIs are presented in Table 2. We found a somewhat increased OR for the sum of the chlordanes; however, it was not statistically significant. Of the different chlordanes the risk was increased for MC6 and *trans*-nonachlor.

Results for analysis of the interactions between titer to EA IgG and organochlorines are presented in Table 3. The highest risk for *p,p'*-DDE, HCB, and chlordanes was found in the high concentration group and when the titer to EA IgG ≥ 40 . The risk for different chlordanes was highest for MC6 and *trans*-nonachlor. No clear interaction was found for the sum of PCBs, although the OR was highest in the high concentration group, provided that the EA titer was high. The OR was statistically significant only in the high PCB exposure group, but was borderline statistically significant in the other group as well. For the sum of immunotoxic PCBs the risk was highest in the high-concentration group (PCB > 285.4 ng/g, EA IgG > 40) with OR = 11.3 (CI, 2.3–73.1) as compared to in the same PCB group but with EA IgG < 40, OR = 0.4 (CI, 0.1–1.5). The OR = 1.7 (CI, 0.4–7.3) in the high EA IgG titer group with low PCB (< 285.4 ng/g).

Changes in body weight might influence concentrations of organochlorines.

Table 1. Levels of organochlorines calculated on a lipid basis as nanograms per gram blood fat in cases ($n = 54$) and controls ($n = 54$).

Organochlorine ^a	Mean	Median	Range
Sum of PCBs			
Cases	847.3	811.2	382.1–1,582.7
Controls	860.2	831.6	424.0–2,138.6
<i>p,p'</i> -DDE			
Cases	488.2	318.7	56.1–1,757.1
Controls	617.2	430.5	70.0–3,724.7
HCB			
Cases	44.7	38.8	15.0–158.5
Controls	45.2	43.8	22.3–78.7
Chlordanes			
Cases	48.5	40.0	14.4–267.3
Controls	50.5	44.3	16.4–198.2

^aWilcoxon *p*-value 0.73, 0.08, 0.11, and 0.42 for the sum of PCBs, *p,p'*-DDE, HCB, and chlordanes, respectively.

Table 3. OR and CI for HCL for different exposures with the median value of the controls used as a cut-off in relation to titer of EBV EA IgG.

Exposure ^a	EA < 40			EA ≥ 40		
	No. exposed cases/controls	OR	CI	No. exposed cases/controls	OR	CI
Sum of PCBs						
≤ 831.6	15/23	(1.0)	–	16/4	4.4	0.99–23.4
> 831.6	10/21	0.4	0.1–1.4	13/6	4.4	1.2–18.5
Immunotoxic PCBs ^b						
≤ 285.4	14/20	(1.0)	–	14/7	1.7	0.4–7.3
> 285.4	11/24	0.4	0.1–1.5	15/3 ^c	11.3	2.3–73.1
<i>p,p'</i> -DDE						
≤ 430.5	16/20	(1.0)	–	19/7	2.8	0.8–10.7
> 430.5	9/24	0.3	0.1–1.0	10/3	6.6	1.3–41.6
HCB						
≤ 43.8	14/20	(1.0)	–	18/7	3.2	0.8–13.1
> 43.8	11/24	0.7	0.2–2.3	11/3	10.7	2.2–68.7
Chlordanes						
≤ 44.3	11/20	(1.0)	–	18/7	4.3	1.1–19.1
> 44.3	14/24	1.3	0.4–5.2	11/3 ^c	15.5	2.8–111.0

All analyses were adjusted for age and BMI at the time of sampling, and for exposure to organic solvents, herbicides, insecticides, fungicides, impregnating agents, animals, and exhausts.

^ang/g blood fat. ^bPCB nos. 66, 110, 105, 118, 74, 128/167, 156, 138, and 170/190. ^cSame control subjects.

Furthermore, the concentrations increase with age (36). Thus, adjustment was made for BMI and age at the time of blood sampling. We studied the change of body weight from diagnosis to the time of blood sampling for cases and controls. There was a high correlation for the weight at diagnosis and at the time of blood sampling for both cases and controls; $r = 0.90$ and $r = 0.92$, respectively. The mean increase in weight between diagnosis and blood sampling was 3 kg among the cases and 1.8 kg among the controls. The mean BMI at the time of blood sampling was 26.0 for cases and 26.6 for controls as compared to the mean BMI at the time of diagnosis (25.1 and 26.1, respectively). In one analysis we adjusted the results for BMI at the time of diagnosis, with similar results. Adjustment for change in body weight in kilograms for cases and controls gave similar results. Thus, in the final statistical model adjustment was made for age and BMI at the time of blood sampling. Adjusting only for BMI and weight at diagnosis gave similar results as when including other risk factors in the model.

Table 2. OR and CI for different organochlorines.

Agent (ng/g)	Exposed cases/controls		
	Exposed cases/controls	OR	CI
PCB (> 831.6)	23/27	0.8	0.3–1.9
Chlordanes (> 44.3)	25/27	1.4	0.5–4.1
Oxychlordanes (> 14)	18/26	0.8	0.3–2.2
MC6 (> 4.8)	27/26	1.6	0.6–4.4
<i>trans</i> -Nonachlor (> 22.1)	24/27	1.6	0.6–4.8
<i>cis</i> -Nonachlor (> 2.8)	20/27	0.7	0.3–1.7
<i>p,p'</i> -DDE (> 430.5)	19/27	0.6	0.2–1.5
HCB (> 43.8)	22/27	1.0	0.4–2.7

The median concentration (nanograms per gram fat) for controls was used as a cut-off. The results were adjusted for age and BMI at the time of sampling, and for exposure to herbicides, fungicides, insecticides, impregnating agents, organic solvents, animals, and exhausts.

No clear pattern of association was found regarding antibodies to P107 IgG and concentrations of the studied organochlorines (data not shown). The risk was highest for PCBs (OR = 2.1; CI, 0.4–10.5) and chlordanes (OR = 3.5; CI, 0.9–15.5) in the high-exposure group, defined as concentrations of these organochlorines and titer of antibody over the median for controls. The risk for different chlordanes was highest for MC6 [OR = 8.2 (CI, 1.6–52.7)] and *trans*-nonachlor [OR = 4.0 (CI, 0.9–18.6)], whereas no pattern of interaction was found for *cis*-nonachlor and oxychlordane.

The titer to the EBV (VCA IgG and IgM) showed no difference between cases and controls.

Discussion

One disadvantage in this study was that blood was drawn several years after the diagnosis of HCL. Thus it cannot be excluded that treatment might interfere with the results. Most of the cases had been treated with α -interferon or chemotherapy, most often 2-chlorodeoxyadenosine. Only four cases had not received any treatment at all. Thus it was not possible to analyze nontreated patients separately. It was not possible to resolve the issue of a possible effect due to the disease and/or its treatment in this case-control study because no baseline blood tests were performed. In a recent study (37), changes in blood levels of PCBs and *p,p'*-DDE were seen in women treated with chemotherapy for breast carcinoma. However, the results were not adjusted for possible changes in body weight during treatment.

The presently studied organochlorines are fat-soluble chemicals that bioaccumulate in the human body. The half-life in plasma for *p,p'*-DDE is approximately 10 years (38) and is approximately 10–20 years for chlordanes (39). No half-life time has been documented in humans for HCB. The half-life of PCBs is estimated to be between 7 and 30 years (40). Thus it is possible to estimate previous exposure by measurement of lipid-based concentrations of certain organochlorines. The blood samples were drawn for all cases and controls over a time period of a few months and not all at one time: This might bias the results. However, in a study of nonoccupational exposures, chlorinated hydrocarbons were measured twice in healthy women, an average of 2 months apart. It was concluded that measurements of organochlorines are stable over a short time period (41).

Because the concentrations are declining in the Swedish population because of restrictions in the use of these chemicals and because no new high-exposure sources are known to exist, the measured concentrations reflect exposure some decades in the past

(42). No information exists that shows different metabolism or elimination of these organohalogenated hydrocarbons between cases and controls. Thus, it would be possible to use our method to study past exposures.

The cases and controls in this study were derived from a case-control study investigating possible risk factors for HCL. Exposure to herbicides, insecticides, fungicides, impregnating agents, organic solvents, animals, and exhaust were risk factors (11). Thus, in this part of the study, we made adjustments for these exposures. In one analysis, adjustment was also made for smoking because smoking was associated with decreased risk for HCL (11). This did not change the results, however (data not shown).

We found a slightly (not significantly) elevated OR for the presence of antibodies to EBV early antigen IgG. Patients with HCL have high anti-VCA and anti-EA titers that may reflect reactivation of a latent EBV infection (20). An excess risk of malignant lymphoma/leukemia has been shown in a large Finnish cohort of subjects with elevated EA and EBNA-antibody titers (43). The main result in our investigation was the suggestion of a possible interaction between elevated EA IgG and chlordanes, *p,p'*-DDE, and HCB. We found no clear interaction for PCBs, although there was an interaction in the analysis of cases with the shortest time between diagnosis blood sampling. This interaction might indicate that the half-life time and metabolism could have influenced the results, at least for some PCBs. Furthermore, when PCBs were grouped according to immunotoxic properties, we obtained results similar to those from other organochlorines. Interestingly, when analyzing the chemicals only, without considering EBV infection, we found no significant association, whereas in the high titer and high-exposure group we found significant associations. This suggests an interaction between these chemicals and EBV. No clear pattern was observed in the relationship between titer to P107 IgG and concentrations of these chemicals.

A recent study found a correlation between the concentration of PCBs and the risk for NHL in general (25). Another study found a dose-response effect showing increasing risk with increasing concentration of PCBs, and interaction with EBV was suggested (26). An increased risk for NHL has also been suggested for high consumers of fish from the Baltic Sea, which is contaminated by PCBs and other organochlorines (44). One study of male capacitor-manufacturing workers with PCB exposure found an increased risk for NHL (45); another study found no increased risk (46).

Increased concentrations of chlordanes in adipose tissue samples from NHL patients as

compared to controls without cancer have been reported in a Swedish study (30). This is in agreement with our present finding. In a case-control study on NHL, an increased risk was found for farmers exposed to chlordanes (47), whereas no increased risk for lymphatic malignancies was found in a cohort of chlordanes and heptachlor applicators (48).

In a multivariate analysis of self-reported exposure to insecticides (11), such exposure was not a risk factor for HCL. A pooled analysis of three case-control studies in the United States concluded that exposure to DDT was not a risk factor for NHL (27); similar results were found in previous Swedish case-control studies on NHL (49,50). However, the present study found an interaction between concentrations of *p,p'*-DDE, the main metabolite of DDT, and titers to EA IgG. Thus, an increased risk cannot be excluded in subjects with seropositivity for EBV EA.

Data of an association between HCB and HCL are still lacking. In addition, HCB has not been associated with NHL (25).

In conclusion, we found an increased risk for HCL for subjects with titer to EA IgG above the median for controls. The risk increased further with increased concentration of certain organochlorines. Because these organochlorines may have immunotoxic properties, an interaction between EBV and immunotoxic chemicals may increase the risk for HCL, as has been discussed for NHL (14). This suggests the possibility of EBV and organochlorines acting as component causes in the pathogenesis of HCL. However, the results must be interpreted with caution because many comparisons were made and the number of exposed individuals was low in some of the calculations.

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