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Polychlorinated biphenyls and non-Hodgkin's lymphoma: A case–control study in Northern Italy☆,☆☆

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ABSTRACT

Background: Polychlorinated biphenyls (PCBs) have been hypothesized to increase the risk of non-Hodgkin lymphoma (NHL), although conclusive evidence is still lacking. High levels of PCBs were found in soil in some areas close to a PCB-producing factory in Brescia, North Italy. We conducted a population-based case-control study among residents of the town to investigate the possible association between PCB pollution and NHL in this area.
Methods: We included both incident and deceased NHL cases, and a random sample of the town residents as controls, frequency matched to cases as regards age and gender. Exposure to PCBs was estimated on the basis of the lifetime residential history of cases and controls in four different areas of the town—A, B and C (polluted areas) and D (control area).
Results: A total of 495 cases (287 incident cases) and 1467 controls were enrolled. Positive associations were found between NHL and having resided for at least 10 years in the area A, the most polluted area (odds ratio, OR=1.8; $p=0.02$) and for having resided in any of the polluted areas considered together (A+B+C) (OR=1.4; $p=0.08$). However, no associations were evident for having resided 20 years or longer in the polluted areas or when analyzing the association with each subject's main residence in his/her lifetime.
Conclusion: This study provides some evidence for an association between PCB exposure and NHL, though results should be considered with caution in the absence of individual biological measures of exposure.

1. Introduction

Polychlorinated biphenyls (PCBs) are 209 possible congeners, chemically formed by the substitution of one to ten hydrogen atoms by chlorines on a biphenyl ring (Agency for Toxic Substances and Disease Registry (ATSDR), 2000). They have been widely used since the 1930s in numerous industrial and commercial applications, including the electrical, plastics, paint and pesticide industries. They stopped being produced in most countries during the 1970s and 1980s, due to an increasing awareness of their impact on the environment and human health (ATSDR, 2000). Despite being produced no longer, PCBs are still widespread in the environment as they are highly persistent, and tend to accumulate in soil, plants and animals (ATSDR, 2000). Humans are exposed to PCBs mainly through the food chain (La Rocca and Mantovani, 2006). A chemical factory located in Brescia, a highly industrialized town in North of Italy with about 200,000 inhabitants, produced PCBs and other organochlorine compounds from the 1930s to 1984. An area adjacent to the factory was found to be highly polluted by PCBs and other persistent organic pollutants (POPs), with a soil concentration of total PCBs as high as 8.3 mg/kg (Donato et al., 2006), the Italian limit for residential areas being 0.06 mg/kg (GU, 2006). The mean PCB levels found in animal and plant food samples collected in the most highly polluted area were 2099 and 86 μg/kg, respectively (about 70 and 40 times the levels found in the least polluted area, respectively).

Serum PCB measurement was performed in a random sample of 527 adults from the general population living in Brescia in 2003, finding high serum levels of total PCBs, up to 38,679 ng/g lipid, in many subjects (Apostoli et al., 2005; Donato et al., 2006).

Abbreviations: PCB, polychlorinated biphenyl; NHL, non-Hodgkin's lymphoma; POP, persistent organic pollutant; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran

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PCBs are classified as probable carcinogens by the United States Environmental Protection Agency (US EPA) and the International Agency for Research on Cancer (IARC), with sufficient evidence in animals and limited evidence in humans (IRIS (Integrated Risk Information System), 2005; IARC (International Agency for Research on Cancer), 1998). PCBs act as tumor promoters (ATSDR, 2000; Silberhorn et al., 1990) and may increase the risk of an NHL through their dioxin-like effects and their ability to induce immunotoxicity and to activate enzyme systems (Safe, 1993). Various epidemiological studies have shown an association between PCBs and NHL, as recently reviewed (Engel et al., 2007b). Data from the Cancer Registry of the Brescia Local Health Authority, including the town of Brescia and surrounding area, show that NHL incidence rates are among the highest in Italy, similar to those found in other industrialized areas in the country (AIRT, 2006).

We conducted a population-based case-control study among residents in the municipality of Brescia to investigate the possible association between PCB pollution and NHL in this area.

2. Methods

2.1. Study population

Both incident and deceased adult cases were included, registered under codes 200 and 202 of the International Classification of Diseases version 9 (ICD-9). Subjects present in both groups were considered as incident cases.

Incident cases were identified from the Cancer Registry of the Brescia Local Health Authority as subjects with a new diagnosis of an NHL between 1993 and 1995 and between 1999 and 2001, the periods for which information on incident cases was available. Deceased cases were identified from the Local Health Authority archive for the years 1990–2004. Possible duplicates were eliminated.

The population of Brescia was 187,567 inhabitants at the 2001 census.

Approximately three controls were randomly selected for each case from the Brescia National Population Registry and frequency matched to both incident and deceased LNH cases according to age and sex. Two series of controls were selected: the first one was sampled among all residents alive on 31st December 1995 matched to the NHL cases diagnosed between 1993 and 1995; the second one sampled among all residents alive on 31st December 2001 matched to the cases diagnosed between 1999 and 2001. Control subjects who were affected by an NHL according to our database and the duplicates were excluded.

Data from the 2001 population census were used to define the educational level of cases and controls.

2.2. Assessment of exposure

Exposure to PCBs was attributed on the basis of the lifetime residence history of cases and controls, provided by the Brescia Municipal Authority, since residence in the contaminated areas was considered a proxy of individual exposure to these substances. Two cases were excluded because their residential histories were not available.

Administrative data were obtained from the Municipality register, which are of high quality in Italy and have been widely used for epidemiological reports in international journals and databases.

The town of Brescia consists of nine districts divided into 30 suburbs; exposure was defined on the basis of both spatial and temporal criteria. With regard to the spatial criterion, the town was divided into the following four areas according to PCB soil levels and administrative boundaries (Fig. 1):

- Area A: immediately south of the PCB-producing factory, with a population of about 1200 inhabitants, the most highly polluted area. In 48 soil samples, the arithmetic mean, median and range of total PCBs were 1.14, 0.55 and 0.01–8.3 mg/kg, respectively.
- Area B: a larger area south of Area A, with 15,000 inhabitants and intermediate levels of soil contamination. In 129 soil samples, the arithmetic mean, median and range of total PCBs were 0.21, 0.07 and <0.01–2.6 mg/kg, respectively.
- Area C: east of area A, with about 2000 inhabitants and intermediate levels of soil contamination. In 21 soil samples, the arithmetic mean, median and range of total PCBs were 0.15, 0.08 and 0.01–0.8 mg/kg, respectively.
- Area D: the least polluted area, which includes all the other parts of the town, representing the control population, with about 170,000 inhabitants. In 82 soil samples, the arithmetic mean, median and range of total PCBs were 0.03, 0.02 and <0.01–0.38 mg/kg, respectively.

In the analysis, we considered polluted areas A, B and C separately and all together.

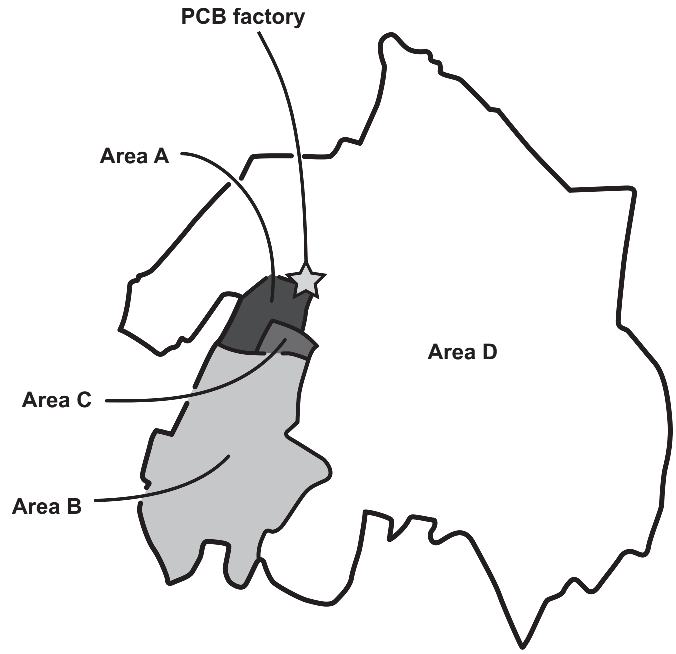

Fig. 1. Division of the town into four areas according to PCB soil concentrations and administrative boundaries.

We used three definitions of time exposure: (1) main residence, where each subject had lived for most of his/her life; (2) residence for at least one year, considered as the minimum exposure time for developing possible PCB-related NHL; (3) duration of residence, categorized in three classes, 1–9, 10–19 and 20+ years, or dichotomized as 1–9 and 10+ years.

In the analysis for duration of residence, separate analyses were performed for areas A, B and C. Subjects who resided in more than one area for 1–9, 10–19 or 20+ years were considered among the exposed in each analysis. Subjects who resided for 1–9 years in one area (e.g., area A) and 10–19 or 20+ years in the other areas (e.g., B and C) were excluded from the analyses for the first area (e.g., area A).

We did not exclude any period longer than one year of residence before diagnosis or death for cases or before enrollment for controls, because latency between carcinogen exposure and neoplasm development is extremely variable and may be as short as a few years (Engel et al., 2007b). A latency analysis is not feasible in our study, however, due to its retrospective design, since duration and latency are strongly related to each other and cannot be analyzed separately. The years spent outside the town were considered as non-exposure periods. In each analysis, we considered those subjects as not exposed who had never resided, or had resided for less than one year in any of the polluted areas, according to the spatial and temporal residence criteria.

Since some workers at the PCB-producing plant may have had higher exposure to PCBs than the general population, we checked whether the cases and controls had worked at the factory in their lifetime by means of record-linkage with the files of the factory workers.

2.3. Statistical analysis

The odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were calculated using multivariate logistic regression, adjusting for age and education, although socio-economic factors do not appear to be associated with an NHL incidence or mortality (Faggiano et al., 1997; Fabbro-Peray et al., 2001; Hermann et al., 2009). To evaluate the role of duration of residence, categorized in three classes, we performed linear trend tests using logistic regression models and adjusting for age and gender. Education was omitted in the final regression models as it did not influence the OR estimates for residence. Separate analyses were carried out for incident cases only. Statistical tests were performed using the common cut-off of $p = 0.05$ with two tails, for rejecting the null hypothesis. All the analyses were conducted using the Stata statistical software package (version 10.0, Stata Corporation, College Station, Texas).

3. Results

A total of 495 NHL cases (254 men and 241 women) and 1467 controls (750 men and 717 women) were included in the study. The subjects' mean age was computed at the date of diagnosis for incident cases, at the date of death for deceased cases, and at the date of enrollment for controls. It was 68.3 (±14.2) years for cases and 68.2 (±14.3) years for controls (Table 1). No differences were found between cases and controls by gender, or by education, which was available in 63.8% of cases and 65.1% of controls.

The study comprised 287 incident cases (58.0% of all cases), 89% of which had an anatomopathologic diagnosis. As shown in Tables 2 and 3, 7.3% of incident cases were coded as an NHL not otherwise specified (code 9591/3), 31.7% as malignant lymphoma, diffuse or not otherwise specified (from 9670/3 to 9686/3) and 9.4% as other specified NHL (from 9710/3 to 9713/3).

Analysis of the association between NHL and the main residence in the polluted areas is shown in Table 3. For all cases, the ORs for an NHL were positive and near statistical significance for all areas, excluding area A (1 case only). When the analysis was restricted to incident cases only, the OR for the main residence was 1.6 ($p=0.08$) for all the polluted areas considered together.

When we considered duration of residence as dichotomized into 1–9 and 10+ years, we observed an increased risk of an NHL for having resided 10+ years in area A, with an OR of 1.8 ($p=0.08$) and in the polluted areas considered together (A+B+C), with an OR of 1.4 ($p=0.02$) (Table 4). When we restricted the analysis to incident cases only, similar results in the OR estimates were observed, with an OR of 1.7 for having resided 10+ years in an area A and an OR of 1.3 for having resided 10+ years in any of the polluted areas (Table 4).

Table 5 shows the results of the analysis of an NHL risk according to the duration of residence in the polluted areas categorized as 1–9, 10–19 and 20+ years. An association was found for having resided 10–19 years in area A (OR=3.8; $p=0.005$) and in the polluted areas considered together (A+B+C) (OR=1.7; $p=0.04$). A linear trend next to the cut-off of statistical significance was present for the polluted areas considered together (A+B+C) ($p=0.06$). When we restricted the analysis to incident cases, we found a statistically significant association for having resided 10–19 years in area A (OR=4.0; 95% CI: 1.4–11.7; $p=0.01$), but not for the polluted areas considered together (data not shown in tables).

Table 1
Demographic characteristics of cases and controls.

	Cases ($n=495$)	Controls ($n=1467$)
Age in years, mean (SD)	68.3 (14.2)	68.2 (14.3)
Sex, no. (%)		
Male	254 (51.3)	750 (51.1)
Female	241 (48.7)	717 (48.9)
Education, no. (%)[a]		
0–5 Years	113 (35.8)	315 (33.0)
6–8 Years	148 (46.8)	466 (48.8)
≥9 Years	55 (17.4)	174 (18.2)

[a] Education was available for 316 cases (63.8%) and 955 controls (65.1%).

Table 2
Distribution of 287 NHL incident cases included in the study, collected by the Cancer Registry of the Brescia Local Health Authority in 1993–1995 and 1999–2001, according to morphology.

Morphology	ICD-O-2[a]	No.	%
Malignant lymphoma, NOS[b]	9590	19	6.6
Non-Hodgkin's lymphoma, NOS[b]	9591	107	37.3
Malignant lymphoma, specified type, diffuse or NOS[b]	967–968	91	31.7
Malignant lymphoma, follicular or nodular, with or without diffuse areas	969	23	8.0
Specified cutaneous and peripheral T-cell lymphomas	970	17	5.9
Other specified non-Hodgkin's lymphomas	971	27	9.4
Leukemic reticuloendotheliosis	9941	3	1.0
Total		287	100

[a] International Classification of Diseases for Oncology, second edition.
[b] Not otherwise specified.

Table 3
Distribution of NHL all cases and incident cases only, and controls according to the main residence in the four areas of Brescia, Italy.

Area	All cases		Incident cases only	
	Ca/Co[a]	OR (95% CI)[b]	Ca/Co[a]	OR (95% CI)[b]
A	1/8	0.4 (0.1–3.0)	1/8	0.7 (0.1–5.5)
B	25/55	1.4 (0.8–2.2)	17/55	1.6 (0.9–2.8)
C	7/10	2.1 (0.8–5.5)	4/10	2.0 (0.6–6.6)
A, B, C	33/73	1.4 (0.9–2.1)	22/73	1.6 (0.9–2.5)*
D	462/1394	Reference	265/1394	Reference

Areas A, B and C: polluted areas; area D: control area. See Fig. 1 and the text for a more precise definition.
[a] Cases/controls.
[b] OR, odds ratio adjusted for age and gender using logistic regression; CI, confidence interval.
* $p=0.08$.

Table 4
Distribution of NHL all cases and incident cases only, and controls with 10+ years of duration of residence in any of the three polluted areas of Brescia, Italy.

Area	All cases		Incident cases only	
	Ca/Co[a]	OR (95% CI)[b]	Ca/Co[a]	OR (95% CI)[b]
A	15/26	1.8 (0.9–3.9)*	8/26	1.7 (0.7–3.8)
B	55/129	1.3 (0.9–1.8)	31/129	1.2 (0.8–1.9)
C	12/25	1.5 (0.7–3.0)	6/25	1.2 (0.5–3.0)
A, B, C	80/176	1.4 (1.1–1.8)†	44/176	1.3 (0.9–1.8)

Areas A, B and C: polluted areas. See Fig. 1 and the text for a more precise definition.Reference group: people who have never resided in any of the polluted areas (394 cases and 1208 controls).
[a] Cases/controls.
[b] OR, odds ratio adjusted for age and gender using logistic regression; CI, confidence interval.
* $p=0.08$.
† $p=0.02$.

4. Discussion

The main findings of this study are the increased risks of an NHL for having resided 10 years or over in the polluted areas considered together (A+B+C) (OR=1.4; $p=0.02$) and particularly for having resided 10+ years in the most polluted area (A) (OR=1.8, $p=0.08$). However, no statistically significant increase in an NHL risk was found in subjects with either the main residence or having resided 20 years or over in the polluted areas. The test of the linear trend of an increasing risk of an NHL with an increasing duration of residence in the polluted areas considered together (A+B+C) was next to the statistical significance threshold ($p=0.06$).

Area A is by far the most highly PCB-polluted area of the town. In an effect, the population survey showed that median serum levels of total PCBs were 849, 854, 724 and 793 ng/g lipid in subjects living in areas A, B, C and D, respectively, and proportions of subjects with total PCB serum levels above the 90th percentile were 15.6%, 8.2%, 8.8% and 8.2% in areas A, B, C and D, respectively (comparison between area A and the others together: $p=0.02$)

Table 5
Distribution of NHL cases and controls according to duration of residence in the four areas of Brescia, Italy.

Area	1–9 years		10–19 years		20+ years		*p* Trend[*]
	Ca/Co[a]	OR (95% CI)[b]	Ca/Co[a]	OR (95% CI)[b]	Ca/Co[a]	OR (95% CI)[b]	
A	13/28	1.4 (0.7–2.8)	10/8	3.8 (1.5–9.8)[§]	5/18	0.8 (0.3–2.3)	0.13
B	11/43	0.8 (0.4–1.5)	16/32	1.5 (0.8–2.8)	39/97	1.2 (0.8–1.8)	0.18
C	8/27	0.9 (0.4–2.0)	3/10	0.9 (0.3–3.3)	9/15	1.8 (0.8–4.2)	0.27
A, B, C	21/83	0.8 (0.5–1.3)	25/45	1.7 (1.0–2.8)[#]	55/131	1.3 (0.9–1.8)	0.06

Areas A, B and C: polluted areas. See Fig. 1 and the text for a more precise definition.
Reference group: people who have never resided in any of the polluted areas (394 cases and 1208 controls).

[a] Case/controls.
[b] OR, odds ratio, adjusted for age and gender by using logistic regression; CI, confidence interval.
[*] *p* Trend: test for linear trend of increasing or decreasing NHL risk for duration of residence.
[§] $p=0.005$.
[#] $p=0.04$.

(Donato et al., 2006). Therefore, a higher proportion of people living in area A has actually been highly exposed to PCBs. However, the lack of an association for having the main residence, or having resided longer than 10 years, in the polluted areas and the weak evidence for a dose–effect relationship suggest some caution in interpreting these results as supporting evidence for an association between NHL and PCB exposure.

A possible explanation for these conflicting results is that, since area A was devoted mainly to agriculture and animal breeding, very few people have had their main residences there (one of 495 cases and 8 of 1467 controls, 0.5%).

The analysis restricted to incident cases provided results similar to those found when including all the cases, suggesting no bias in including dead cases in the study. Having worked at the factory did not affect the results of the study, as only two cases and three controls, all men, had worked at the PCB-producing factory. There were no other factories with PCB exposure in the province of Brescia.

At present, the association between PCBs and NHL is still unclear, with one recent review concluding that there is an increasing evidence of a positive association (Engel et al., 2007b) and another one drawing the opposite conclusion of no evidence supporting a causal association (Golden and Kimbrough, 2009).

Some case-control and cohort studies with PCB measures on biological specimens found an association between the blood concentrations of PCBs and the risk of an NHL, with a dose–response relationship, adjusting for the most common confounders (Bertrand et al., 2010; Colt et al., 2009; Engel et al., 2007a; Spinelli et al., 2007; Rothman et al., 1997; De Roos et al., 2005; Hardell et al., 2001). On the other hand, negative findings have been found in other case-control and cohort studies with biological measures (Cocco et al., 2008; Quintana et al., 2004; Laden et al., 2010). Furthermore, historical mortality cohort studies of electric utility or capacitor-manufacturing workers who were occupationally exposed to PCBs found no risk excess for cancer of the lymphatic and haematopoietic systems, although none of them collected biological specimens and the number of expected NHL deaths in most studies was low (Engel et al., 2007b; Bosetti et al., 2003).

Some researchers have suggested that the association between exposure to PCBs and other POPs and NHL may be specific for some histological subtypes (Cocco et al., 2008). No separate analysis for an NHL morphology could be performed in our study, due to the small number of some subtypes and the relatively high proportion of ones classified as "not otherwise specified" according to the international classification followed by cancer registries (ICD-0-2).

In considering the plausibility of the association between PCB exposure and NHL in our study, two points should be taken into account.

First, it was found that the Brescia area was polluted not only by PCBs, but also by other POPs, particularly polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), as by-products or contaminants of the PCB production. PCDD/Fs have in fact been detected at relatively high concentrations in soil, food and humans in the Brescia area, with a high correlation with the levels of total PCBs, (Turrio-Baldassarri et al., 2007, 2008). The most toxic dioxin, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), is classified by the IARC as a human carcinogen (IARC, 1998) and dioxin exposure has been reported to increase the risk of an NHL in the exposed populations (Consonni et al., 2008; Floret et al., 2003).

Therefore, PCBs can be seen as indicators of exposure to other POPs, including dioxins, in this area, which may have contributed to the possible association between PCB and NHL.

Second, since PCBs are usually a mixture of several congeners as a result of industrial production (e.g., Aroclor 1248, 1254 or 1260), with different chemical and biological properties, the specific congeners found in a polluted area should be pointed out. We found that 8 of the 24 PCB congeners tested accounted for 99.5% of total serum PCB values in people living in town: 118 (3.4% of total PCBs), 138 (17.3%), 153 (28.7%), 156 (2.8%), 170 (8.3%), 180 (31.0%), 194 (6.8%) and 209 (1.1%) (Apostoli et al., 2005). It is worth noting that the immunotoxic congeners PCBs 138, 153 and 180 (Cocco et al., 2008) are the most widely represented in the general population of Brescia (74.7%) (Donato et al., 2006; Apostoli et al., 2005). Immune system alterations are well known risk factors for an NHL, therefore the high concentration of PCB immunotoxic congeners in our area provides a biological plausibility for the association between PCB exposure and an occurrence of NHL. Indeed, Colt et al. (2009) found that polymorphisms in genes involved in immune and inflammatory response can affect the association between exposure to PCBs, especially PCB 180, and an NHL. Accordingly, Hardell et al. found an OR of 3.2 for the group of immunotoxic congeners and an OR of 6.4 for the group with the highest titres of antibodies to the Epstein-Barr early antigen (Hardell et al., 2001). A recent study also found a positive association between the total PCB concentration and the risk of NHL with an OR for the highest versus the lowest quintile of 1.9 and a positive association for immunotoxic congeners (Bertrand et al., 2010). PCBs 138 and 153 were also associated with an increased risk of an NHL in a report by three cohorts (Engel et al., 2007a), and PCBs 138, 153 and 180 were all associated with an NHL in a case-control study (Spinelli et al., 2007).

Our study presents some strengths and some limitations. It had a population-based design, as all the incident and dead cases occurring in the study period and a random sample of residents in the town were included. Most of the incident cases had a pathology diagnosis, whereas the use of mortality data does not seem to have introduced a bias as shown by a good concordance of the study results when using all the data set or the incident data only.

The levels of PCB pollution in the different areas of the town were measured accurately when analyzing both soil and food samples (Donato et al., 2006; CTS (Comitato Tecnico Scientifico), 2008). PCB serum levels were available in a random sample of adults living in various areas of the town. PCDDs, PCDFs and other POPs were also investigated in soil and biological matrices, including humans beings. Although the study lacks individual exposure data, area of residence seems to be a reasonable proxy for the exposure estimate; a similar approach has been followed in studies evaluating the risk of soft tissue sarcoma and an NHL in association with dioxin pollution from solid waste incinerators (Viel et al., 2000; Comba et al., 2003), in the Seveso cohorts (Consonni et al., 2008) and others.

One of the limitations of this study is the fact that we did not take account of possible confounding variables apart from age and education. However, a possible confounder should have been associated with residence in different areas of the town and also causally related with the occurrence of an NHL. At present, the known risk factors for an NHL seem to play a modest role, since the causes of many NHL cases remain undefined (Ekström-Smedby, 2006), although a causal role of pesticides, dioxins and other organochlorines has been proposed, which could explain the levelling-off of the incidence rates of an NHL observed in the last decade of the 20th century in various Western countries, after an increasing trend since the 1960s (Dreiher and Kordysh, 2006; Belpomme et al., 2007; Hardell and Eriksson, 2003). Furthermore, other studies found that associations between PCBs and NHL are not confounded by other POPs, body mass index (BMI) or demographic factors (Bertrand et al., 2010; De Roos et al., 2005). Lastly, the relatively small number of subjects residing in the most heavily contaminated area may have reduced the power of finding a statistically significant association between PCB and NHL.

In conclusion, this study performed in an industrialized town with some areas highly contaminated by PCBs and other POPs provide some evidence for an association between having resided in the polluted areas and NHL, although these results should be considered with caution, due to the lack of individual biological measures.

Conflict of interest statement

The authors declare they have no conflicts of interest.

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