Occupational and environmental exposure to polychlorinated biphenyls and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis of epidemiology studies

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We carryied out a meta-analysis of studies on exposure to polychlorinated biphenyls (PCBs) and risk of non-Hodgkin lymphoma (NHL). Through a systematic search of the literature, we identified relative risks (RRs) for PCB exposure and NHL risk in 30 populations (10 occupational exposure, seven high environmental exposure, 13 without special exposure). We performed random effects meta-analyses for exposure to all PCBs, specific PCB congeners and risk of all NHL and NHL subtypes. The meta-RR for studies of occupational exposure, high environmental exposure, and no special exposure were 0.94 [95% confidence interval (CI): 0.84–1.03], 1.05 (95% CI: 0.94–1.16), and 1.03 (95% CI: 0.72–1.34), respectively, and the cumulative meta-RR was 0.96 (95% CI: 0.85–1.07). No positive associations were found for exposure to specific congeners, nor for NHL subtypes. The meta-RR for an increase of 100 ppb serum or fat PCB level was 1.02 (95% CI: 1.00–1.04). There was weak indication of publication bias. Our meta-analysis found no association between PCB exposure and NHL risk, in particular in studies of occupational exposures. We detected a weak dose-response relation; the possibility of residual confounding and other sources of bias cannot be ruled out. PCBs are not likely to cause NHL in humans. ***European Journal of Cancer Prevention*** **00:000–000 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Polychlorinated biphenyls (PCBs) are a class of aromatic chemical compounds with a variable degree of chlorination. There are 209 congeners, of which 12 have chemical and toxicological properties, comparable with those of dioxins and furans, and are therefore defined as dioxin-like PCBs.

PCBs are produced by industrial processes deliberately; they have been used as dielectric fluids and as additives in pesticides, flame retardants, varnishes, and other products. Production peaked between the 1950s and the 1970s, and was banned in most countries by the 1980s (International Agency for the Research on Cancer, 2006).

PCBs persist in the environment and in the food chain, and are stored in the adipose tissue; they are detected in the lipid components of blood and breast milk. Because they are resistant to metabolism and have long half-lives, measurement of these compounds in biological media is a good indicator of exposure over time (Agency for Toxic Substances and Disease Registry, 2000).

Exposure to PCB mixtures has been shown to cause cancer in animals under experimental conditions (International Agency for the Research on Cancer, 2006), and associations have been reported in early studies of occupational and environmental exposure to PCBs and risk of several types of cancer, including non-Hodgkin lymphoma (NHL) (Golden and Kimbrough, 2009).

NHL is a histologically and genetically heterogeneous group of malignancies originating from B-lymphocytesand T-lymphocytes that account for 2.7% of the global cancer burden, with important variations in geographic and temporal patterns of incidence (Roman and Smith, 2011). In particular, the incidence rate of NHL has increased in many developed countries during the second half of the 20th century, while the increase has slowed down or has disappeared in the 21st century (Teras *et al.*, 2016). The current classification system, based on immunohistochemistry, cytogenetics and increasing knowledge of the clinical presentation and course of NHL, identifies more than 50 different subtypes of NHL, the main types being diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and

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chronic lymphocytic leukemia (Morton *et al*., 2006; Teras *et al*., 2016).

Despite their relatively high incidence and fatality, little is known about the etiology of NHL (Zhang *et al*., 2011). Populations at high risk of developing NHL include patients undergoing chemotherapy and those with severe immune system dysregulation (Hartge *et al*., 2006). Other established risk factors include infection with Epstein–Barr virus, hepatitis C virus, and *Helicobacter pylori*, as well as autoimmunity and atopic conditions, high BMI, and tobacco smoking (for FL) in addition to family history of lymphatic neoplasms, which reflects genetic susceptibility factors. These risk factors, however, account for a small proportion of cases, while the epidemiological evidence suggests a largely environmental component to the etiology of this group of diseases (Roman and Smith, 2011; Chiu and Hou, 2015).

The hypothesis of an etiologic role of exposure to PCBs in NHL arose in the 1990s, on the basis of results of small-scale, hospital-based case–control studies from Sweden (Hardell *et al*., 1996; 2001), and one prospective study from Norway (Rothman *et al*., 1997), which reported an association between serum PCB level and risk of NHL, which was not one of the underlying hypotheses. None of the studies published before 1995 reported an increased risk of NHL from PCB exposure (Brown and Jones, 1981; Brown, 1987; DeGuire *et al*., 1992; Sinks *et al*., 1992). A biologic rationale of an association between PCB exposure and NHL risk was developed, on the basis of the supposed immunotoxic effect of these agents (Fisher and Fisher, 2004). The hypothesis of an association between PCB exposure and NHL risk was tested in several studies of both retrospective and prospective design; these studies investigated three types of populations, including workers exposed in manufacturing and use of PCBs, subjects experiencing circumstances of heavy environmental exposure, such as food contamination, and members of the general population. Reviews and meta-analyses have been published recently and in past years (Freeman and Kohles, 2012; Kramer *et al*., 2012; Zani *et al*., 2017), which, however, did not follow established guidelines and did not provide summary estimates of the dose response, the risk for exposure to PCB congeners, or the effect on NHL subtypes.

We aimed at carrying out a meta-analysis on exposure to PCBs and risk of NHL, including exposure to individual congeners, risk of specific NHL subtypes, and dose-response analyses, thus providing more comprehensive and definitive evidence compared with recent reviews.

Materials and methods

The systematic review and meta-analysis were performed according to the guidelines specified in the PRISMA-statement (Liberati *et al*., 2009). The methods were specified and documented in a protocol (available upon request); the PRISMA checklist is included in Supplementary Table 1 (Supplemental digital content 1, *http://links.lww.com/EJCP/A210*).

Literature searches and study selection

We conducted comprehensive literature searches of Scopus and PubMed, up to 9 March 2018; PubMed 'related article' links and reference lists of key studies and reviews were used to complement the searches. The search included the keywords ('polychlorinated biphenyl' OR PCB') AND ('cancer' OR 'neoplasm' OR 'lymphoma' OR 'non-Hodgkin lymphoma').

To be included in the meta-analysis, studies had to fulfill the following criteria: (a) original reports of workers exposed to PCBs, populations with special environmental PCB exposure, or individuals whose general environmental exposure to PCBs was measured via exposure markers; and (b) studies in which a measure of association between PCB exposure and risk of NHL, expressed as standardized mortality ratios, standardized incidence ratios, relative risk (RR) or odds ratio, was either reported or could be derived from the data reported in the article.

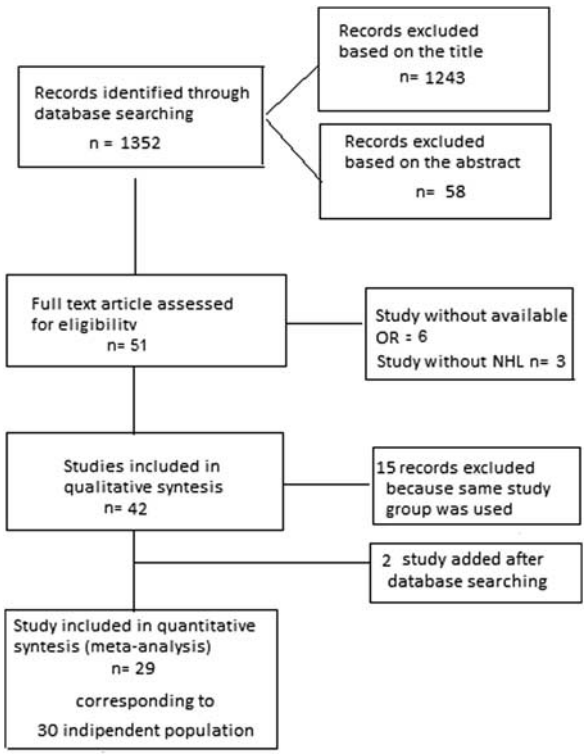
Two authors (S.C., F.D.) independently reviewed the list of titles and abstracts, to determine which studies potentially met the inclusion criteria. Duplicates or irrelevant references were eliminated. The final selection was based on the examination of the full text of potentially relevant articles. Cases of disagreement or doubt were resolved with the inclusion of a third author (P.B.). The search and selection process is shown in Fig. 1.

After reviewing the titles of 1352 articles, we eliminated 1243 of them that did not seem to be relevant and reviewed the abstracts of the remaining 109 articles; we further eliminated 58 that did not meet the inclusion criteria, leaving 51 articles for detailed review. Nine of the 51 articles were then eliminated because they did not report results for NHL, were not epidemiological studies, or did not consider PCB exposure.

We retained 42 articles; when more than one report was available from the same study population, we selected the report with more complete information (i.e. longer follow-up). For these reasons, we eliminated 15 reports, leaving 27 reports for the meta-analysis, to which two studies have been added as a completion of our research (DeGuire *et al*., 1992; Kelly *et al*., 2017) (Table 1).

Several articles were published on three cohorts of US capacitor workers from New York, Indiana, and Massachusetts, USA (Brown and Jones, 1981; Brown, 1987; Sinks *et al*., 1992; Prince *et al*., 2006a, 2006b; Kimbrough *et al*., 1999, 2003, 2015; Ruder *et al*., 2006, 2014, 2017). In the meta-analysis, we included the report by Ruder *et al*. (2014), as it included the three cohorts with the more specific results on NHL risk. The more

Fig. 1



Flow chart of search and selection of studies included in the review and meta-analysis.

recent study of Ruder *et al.* (2017) reported data for generic malignant neoplasm of lymphatic and hematopoietic organs.

Similarly, we selected the paper by Engel *et al.* (2007), which superseded that by Rothman *et al.* (1997), the paper by De Roos *et al.* (2005) instead of those by Colt *et al.* (2005, 2009) and Wang *et al.* (2011), and the paper by Pesatori *et al.* (2013) instead of that by Bertazzi *et al.* (1987). With respect to a case–control study from Canada with multiple publications (Ng *et al.*, 2010), we selected the article by Spinelli *et al.* (2007), because it reported the RR for total PCBs and eight congeners. The authors of this last paper provided us with some unpublished data. The analysis by Engel *et al.* (2007) included three cohorts (Janus, CLUE I, and NHS); the latter cohort was reanalyzed by Laden *et al.*, (2010), and we used this latter report; results for the other two cohorts were based on the original report (Engel *et al.*, 2007) and were considered as independent studies in the meta-analysis.

The meta-analysis comprised therefore results from 30 independent populations (17 included in case–control studies and 13 in cohort studies) reported in 29 papers (Table 1).

Data extraction

We extracted key characteristics of each of the studies retained for the meta-analysis (Table 1). We aimed at investigating NHL [i.e. International Classification of Diseases, version 9 (ICD9) codes 200–202 and ICD10 codes C82–C85]; however, results from some studies were available only for different disease categories, for example, ICD9 codes 200 or 200–208. When results were reported on the basis of different strategies of adjustment for potential confounders, we included the fully adjusted risk estimates. If available, we abstracted results for exposure to specific PCB congeners as well as on congeners selected *a priori* as potentially immunotoxic, for which results were available from at least four studies (PCBs 118, 138, 153, and 180); we also abstracted results on risk of NHL subtypes.

We evaluated the quality of the studies by applying a modified version of the Newcastle–Ottawa scale (Wells *et al.*, 2011). Details on the score criteria are provided in the Appendix, and quality scores of the individual studies are provided in Supplementary Table 2 (Supplemental digital content 2, *http://links.lww.com/EJCP/A211*).

Data synthesis

In the first stage, we used fixed-effect meta-analyses to obtain summary RRs and their 95% confidence intervals (CIs) for studies that reported results only for subsets of the data, for example, men and women or single congeners.

We subsequently obtained summary RRs and 95% CIs for studies that reported results for studies on occupational PCB exposure, special environmental exposure, and general environmental exposure. In studies that analyzed PCB exposure in categories (e.g. quartiles) of a continuous variable (e.g. serum PCB level), we selected the comparison of the highest versus the lowest category. In the analysis of the group of immunotoxic PCBs, we combined within each study, through a fixed-effect meta-analysis, the results for high exposure to each congener.

We evaluated heterogeneity using the general variance-based method, and we applied a random effects model that incorporates between-study variation into the summary variance estimate (DerSimonian and Laird, 1986). When more than four independent risk estimates were available for a specific PCB congener or NHL subtype, we carried out stratified meta-analyses.

We conducted sensitivity analyses by excluding one study at a time from the meta-analysis, and by stratifying the studies according to the quality score (above vs. below the median). We also conducted a cumulative meta-analysis according to the year of publication of the individual studies.

For studies that analyzed PCB exposure according to categories of serum or fat tissue level, we conducted a meta-analysis of RRs and corresponding 95% CIs for an increase in 100 ppm serum/fat PCB level.

Table 1 Selected characteristics of studies included in the meta-analysis

References	Country	Study design	Study period	Population	Assessment of exposure	Outcome	I/M	*N* (% men)
Occupational exposure								
DeGuire *et al.* (1992)	Canada	Co	1976–1983; 1976–1983	TW	Job title	ICD8 200-209	M	~7190 (100)
Tynes *et al.* (1994)	Norway	Co	1920–1985; 1953–1991	EW	Job title	ICD7 200-202	I	5088 (100)
Yassi *et al.* (1994)	Canada	Co	1946–1975; 1946–1989	TCW	Job title	ICD9 200-202	M	812 (100)
Greenland *et al.* (1994)	USA	NCC	NA; 1969–1984	TCW	JEM (exposure to pyranol)	Lymphoma	M	1821 (NA)
Loomis *et al.* (1997)	USA	Co	1950–1986 1950–1988	EW	Job title	ICD9 200, 202-203	M	138 905 (100)
Gustavsson and Hogstedt (1997)	Sweden	Co	1965–1978; 1965–1991	TCW	Job title	ICD8 200-202	M	242 (100)
Mallin *et al.* (2004)	USA	Co	1944–1977; 1944–2000	TCW	Job title	ICD9 200-208	M	3301 (41)
Fritschi *et al.* (2005)	Australia	CC	2000–2001	General occupational history	Expert assessment	NHL	I	694 (58)
Pesatori *et al.* (2013)	Italy	Co	1946–1980; 1946–1996	TCW	Job title	ICD9 200, 202	M	2565 (36)
Ruder *et al.* (2014)	USA	Co	1938–1977 1940–2007	TCW	Job title	NHL	M	24 865 (48)
Special environmental exposure								
Pavuk *et al.* (2004)	Slovakia	Co	NA; 1985–1994	Residence in polluted area	Place of residence	ICD9 200, 202	I	112 000 (NA)
Mikoczy and Rylander (2009)	Sweden	Co	1968–2002; 1968–2002	Fish consumption	Fishermen on East Coast	ICD7 200, 202	I	2904 (100)
Tomasallo *et al.* (2010)	USA	CC	1986–1993 1995–2006	Fish consumption	Great Lakes' fishermen	ICD9 200-208	M	2275 (75)
Viel *et al.* (2011)	France	CC	2003–2005	Residence near incinerator	Serum PCB level	NHL	I	34 (44)
Maifredi *et al.* (2011)	Italy	CC	1990–2004	Residence in polluted areas	Place of residence	ICD9 200, 202	IM	495 (80)
Helmfrid *et al.* (2012)	Sweden	Co	NA 1960–2003	Residence in polluted area	Place of residence	ICD 200-202	I	~3000 (NA)
Li *et al.* (2013)	Taiwan	Co	1979 1980–2008	Yucheng accident	Residence in Yucheng area	ICD9 200-208	M	1803 (46)
General environmental exposure								
Nordström *et al.* (2000)	Sweden	CC	1987–1992	General population	Serum PCB level	Hairy cell leukemia	I	54 (100)
Hardell *et al.* (2001)	Sweden	CC	1994–1999	General population	Serum PCB level	NHL	I	82 (55)
Quintana *et al.* (2004)	USA	CC	1969–1983	Surgery, patients and necropsies	Fat PCB level	ICD8 200, 202	IM	175 (56)
De Roos *et al.* (2005)	USA	CC	1998–2000	General population	Serum PCB level	NHL	I	100 (49)
Engel *et al.* (2007) (Janus)	Norway	NCC	1972–1978; 1974–1998	General population	Serum PCB level	ICD8 200, 202	I	190 (71)
Engel *et al.* (2007) (CLUE I)	USA	NCC	1974; 1975–1994	General population	Serum PCB level	ICD8 200, 202	I	47 (30)
Spinelli *et al.* (2007)	Canada	CC	2000–2004	General population	Serum PCB level	NHL	I	422 (55)
Cocco *et al.* (2008)	France, Germany, Spain	CC	1998–2003	General population	Serum PCB level	NHL	I	174 (59)
Hardell *et al.* (2009)	Sweden	CC	2000–2002	General population	Serum PCB level	NHL	I	99 (59)
Bertrand *et al.* (2010)	USA	NCC	1982–1984; 1983–2003	Health professionals	Serum PCB level	NHL	I	205 (100)
Laden *et al.* (2010)	USA	NCC	NA	Nurses	Serum PCB level	NHL	I	145 (0)
Bräuner *et al.* (2012)	Denmark	NCC	1993–1997; 1993–2008	General population	Fat PCB level	NHL	I	239 (53)
Kelly *et al.* (2017)	Italy, Sweden	NCC	NA; 1990–2006	General population	Serum PCB level	NHL	I	49 (NA)

CC, case–control study; Co, cohort study; E, environmental exposure; EW, electrical workers; I, incidence; ICD, International Classification of Diseases; M, mortality; *N*, number of cohort members (cohort studies) or number of cases (case–control studies); NA, not available; NCC, case–control study nested in a cohort; NHL, non-Hodgkin lymphoma; NR, not relevant; TCW, transformer and capacitor workers; TW, telecommunication workers.

We produced funnel plots of the results included in the meta-analysis and used the test proposed by Egger *et al.* (1997) to assess the presence of publication bias.

We used the commands *metan* (overall, stratified and cumulative meta-analyses), *glst* (dose-response), and *metafunnel* and *metabias* (publication bias) of the statistical package STATA v. 14 (Stata Corp LP, College Station, Texas, USA).

Results

Ten of the studies included in the meta-analysis considered occupational cohorts of electrical workers, telecommunication

workers, and transformer and capacitor workers; seven studies were conducted in populations at high PCB exposure from food contamination or residence in polluted areas, and 13 studies included populations without special PCB exposure circumstances (Table 1).

Five studies (Loomis *et al.*, 1997; Pavuk *et al.*, 2004; Tomasallo *et al.*, 2010; Viel *et al.*, 2011; Helmfrid *et al.*, 2012) reported risk estimates for population subgroups, and one study (Kelly *et al.*, 2017) reported RRs for individual PCB congeners but not for the total. We combined these results through study-specific fixed-effect meta-analyses. The results of the main meta-analysis are reported in Fig. 2; no single study contributed more than 15% of the total weight. The summary RR was 0.96 (95% CI: 0.85–1.07; P for heterogeneity, het = 0.001; I^2 50%). When stratified according to source of exposure, the meta-analysis of occupational studies resulted in a summary RR of 0.94 (95% CI: 0.84–1.03; P het = 0.8; I^2 0.0%), that of studies of populations at high environmental exposure resulted in a summary RR of 1.05 (95% CI: 0.94–1.16; P het = 0.3; I^2 14.3%), and that of general population studies resulted in a summary RR of 1.03 (95% CI: 0.72–1.34; P het = 0.05; I^2 42%).

The cumulative meta-analysis did not clearly suggest a trend over time in the summary RR (not shown in detail). Excluding one study at a time resulted in summary RRs ranging from 0.95 to 0.98, except for the study by Kelly *et al.* (2017), whose exclusion led to a summary RR of 1.03 (95% CI: 1.01–1.05; other results not shown in detail).

Results of the meta-analyses of results for individual or group of congeners are reported in Fig. 3 (single forest plot in Supplementary Material Figs 1–6, Supplemental digital content 1, *http://links.lww.com/EJCP/A210*). The highest summary risk estimates were for PCB 180 (meta-RR 1.07; 95% CI: 0.67–1.47; 7 studies, P het = 0.2; I^2 31.9%) and PCB 153 (meta-RR 1.10; 95% CI: 0.68–1.53; nine studies, P het = 0.01; I^2 58.3%). The meta-analysis for the four immunotoxic congeners yielded a meta-RR of 1.01 (95% CI: 0.70–1.33; seven studies, P het <0.001; I^2 81.1%).

The meta-analysis of risk of NHL subtypes and exposure to all PCBs resulted in summary RRs of 0.68 for DLBCL (95% CI: 0.24–1.12; six studies, P het = 0.17; I^2 35.7%), 1.21 for FL (95% CI: 0.79–1.64; five studies, P het = 0.55; I^2 0.0%), and 0.63 for CLL (95% CI: 0.39–0.87; four studies, P het 0.4; I^2 0.0%) (Single forest plot in Supplementary Material Figs 7–9, Supplemental digital content 1, *http://links.lww.com/EJCP/A210*).

The sensitivity analysis according to quality score resulted in summary RRs of 0.91 (95% CI: 0.76–1.06) for studies with a score below the median (i.e. higher quality) and 1.07 (95% CI: 0.91–1.23) for other studies (P het between the groups, 0.12).

We carried out additional meta-analyses on individual components of the quality score. The summary RR of the studies with PCB exposure assessment based on measurements or historical evaluation was 1.14 (95% CI: 0.92–1.36; 20 studies) vs. 1.04 (95% CI: 0.87–1.21; six studies) for studies with assessment based on proxy information or without details on the methods used. The summary RR of studies that adjusted for main potential confounders was 1.09 (95% CI: 0.88–1.31; 19 studies), that of studies that did not was 1.21 (95% CI: 0.78–1.64; six studies). Finally, among case–control studies conducted in populations without special PCB exposure, there was no difference between the summary RR of retrospective studies (RR: 0.98; 95% CI: 0.58–1.38; eight studies) and that of studies nested in prospective cohorts (RR: 1.11; 95% CI: 0.63–1.58; five studies; P het between groups 0.62).

The visual assessment of the funnel plot (Fig. 4), the result of the Egger's test ($P = 0.26$), suggested that publication bias was present in the data set, with results of small, nonpositive studies being less likely to be published.

Dose-response results were available for seven studies on the basis of serum or fat PCB level; detailed results are reported in Table 2. The meta-RR for an increase in 100 ppb PCB level was 1.02 (95% CI: 1.00–1.04; $P = 0.045$).

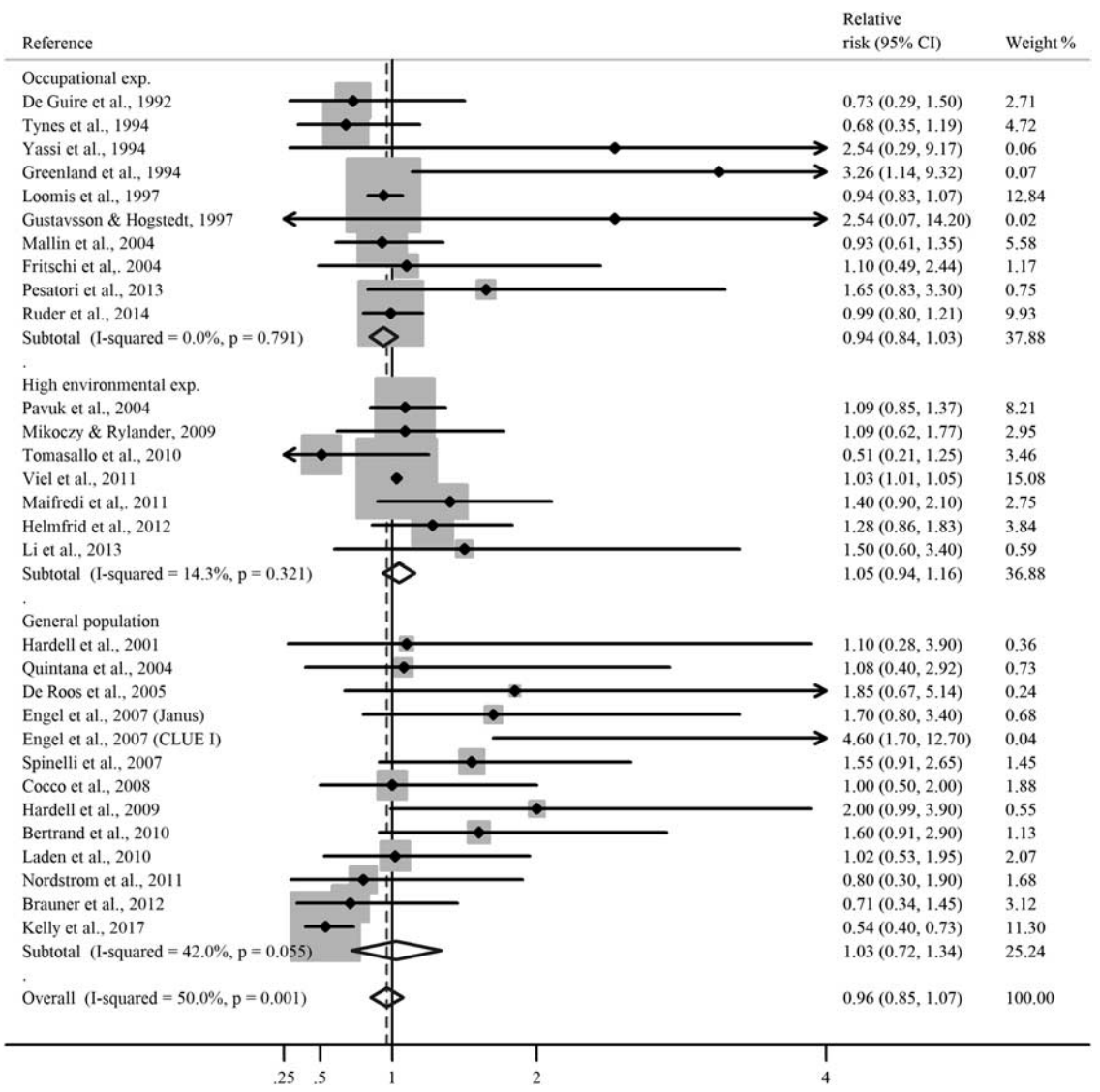
Discussion

Our meta-analysis of studies of individuals exposed to PCBs provided no overall evidence of an increased risk of NHL.

We selected 30 populations comparing exposed and unexposed individuals, or subjects with high versus low exposure. Ten of these populations were workers exposed to PCBs as electrical capacitor manufacturing workers, electrical workers, transformer manufacturing workers and in other jobs; the meta-analysis of the results of this study resulted in an RR of 0.94. Among the remaining populations, seven were studied because of specific PCB exposure circumstances; the meta-RR of these results was 1.05 and that of the remaining 13 studies, comprising populations with normal PCB exposure, was 1.03. None of these meta-RRs was significantly different from 1.

Although a relatively large number of investigations provided results on risk of NHL following PCB exposure, there was substantial heterogeneity in study design, PCB exposure assessment, congeners under investigation, strategy for adjustment for potential confounders, and definition of outcome; however, we attempted to control for it by conducting additional analyses aimed at addressing these potential sources of heterogeneity, and did not identify any subgroup of studies, suggesting an association between PCB exposure and NHL risk. Our

Fig. 2



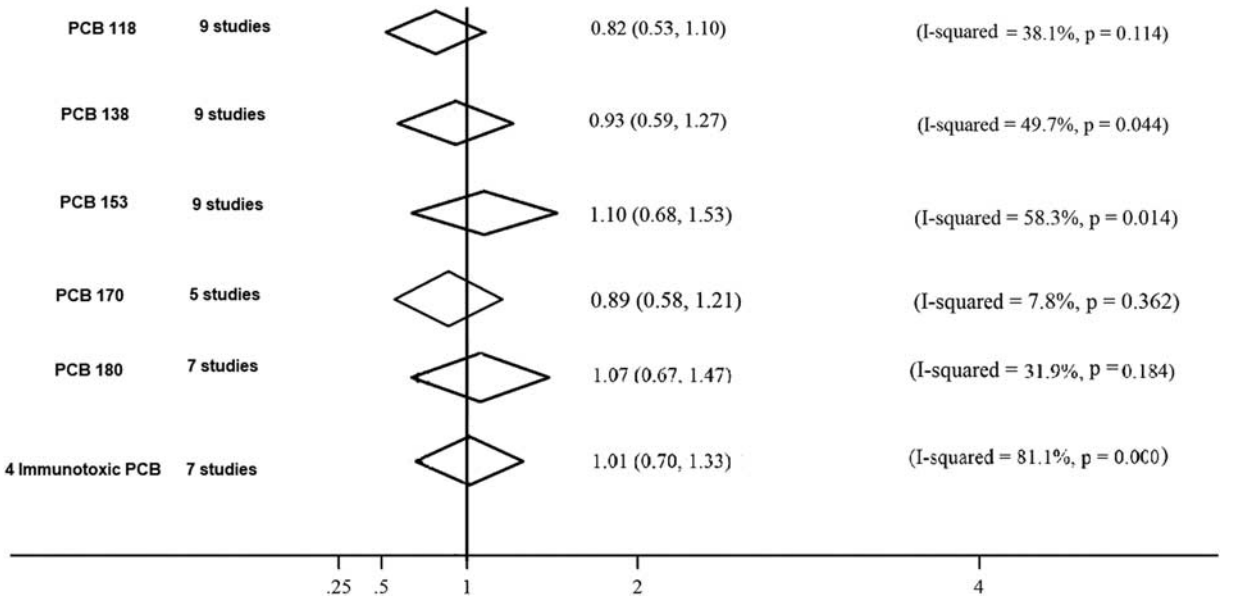
Meta-analysis of studies on total polychlorinated biphenyl exposure and risk of non-Hodgkin lymphoma. CI, confidence interval.

assessment of publication bias provided a suggestion that small, nonpositive results may have not been reported. It should be noticed, however, that the subgroup analyses that were based on relatively small sample sizes, and the heterogeneous effects of exposure and disease, as shown for other risk factors of NHL (Morton *et al*., 2014), may mask underlying associations between particular PCBs and particular NHL subtypes, thus preventing conclusive statements about lack of association.

Additional important aspects of our meta-analysis comprised summary estimates of the associations between exposure to specific PCBs and risk of NHL, and between total PCB exposure and specific NHL subtypes. Although these analyses were somewhat limited by the small number of independent studies available, none of them provided evidence of a positive association. In fact, the only statistically significant result was a reduced risk of CLL, based on results of four studies: the most plausible explanation of this finding is chance, due to multiple comparisons. In addition, we performed a metaregression of the categorical results of eight studies based on serum or fat PCB levels, which resulted in a small increase in NHL risk of borderline statistical significance.

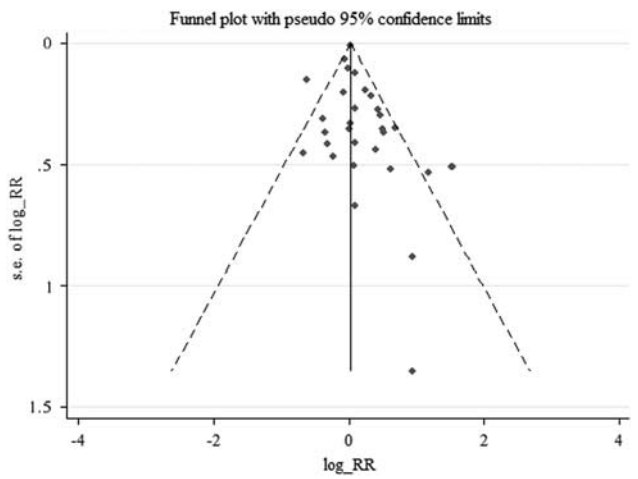
Our meta-analysis was based on a larger number of studies compared with other recent reviews and meta-analyses (Freeman and Kohles, 2012; Kramer *et al*., 2012; International Agency for the Research on Cancer, 2006; Zani *et al*., 2013, 2017), which in general did not consider results for specific PCBs or NHL subtypes, or results of dose-response analyses.

Fig. 3



Results of the meta-analysis on exposure to polychlorinated biphenyl congeners and groups of congeners and risk of non-Hodgkin lymphoma. PCB, polychlorinated biphenyl.

Fig. 4



Funnel plot of studies on total polychlorinated biphenyl exposure and risk of non-Hodgkin lymphoma.

The new evidences of our meta-analysis as well as the updating of the literature are the results on categorical serum or fat PCBs' exposure and risk of NHL and results of meta-analysis of on exposure to PCB congeners and groups of congeners and risk of NHL.

Although some of these authors concluded that an association between PCB exposure and NHL is possible, our conclusion of the lack of an association concurs with that of the most recent review (Zani *et al.*, 2017).

The fact that the occupational studies did not provide evidence of an increased risk is an important result, as workplace PCB exposures were much higher than those of individuals included in studies based on environmental exposure. In addition, some studies reported results according to duration of employment or cumulative exposure to PCB (Ruder *et al.*, 2006; Prince *et al.*, 2006a, b); these results were too sparse to perform a meta-analysis, but they did not show a dose-response relationship with NHL mortality. Even if workers were mainly exposed to mixtures of low-chlorinated PCB, their exposure to high-chlorinated PCB was still higher than that experienced under environmental exposure, and results on serum levels in workers showed up to 100 times higher total PCB levels than those found in the general US population (Acquavella *et al.*, 1986). Incidentally, it is not plausible that the 'healthy worker effect', which has been shown not to be relevant for malignant diseases (Choi, 1992), explains the lack of association found among PCB-exposed workers. It should be stressed, however, that most occupational studies were based on mortality, which may not be a very sensitive indicator of NHL risk, given the relatively good survival of patients suffering from several types of this group of diseases (Al-Hamadani *et al.*, 2015).

Taken together, known and suspected causes of NHL (see above) explain a relatively small proportion of cases of NHL; in addition, none of these factors is known to be strongly correlated with occupational or environmental exposure to PCB. Nonetheless, residual confounding by

Table 2 Results on categorical serum or fat polychlorinated biphenyl exposure and risk of non-Hodgkin lymphoma

References	PCB level[a]	PCB level[b]	*N* cases	*N* controls	RR	95% CI
De Roos *et al.* (2005)	< 0.446[c]	33.79	19	22	1	Ref.
De Roos *et al.* (2005)	0.446–0.667[c]	84.32	21	25	1.30	0.51, 3.53
De Roos *et al.* (2005)	0.668–0.900[c]	118.79	25	24	1.66	0.61, 4.53
De Roos *et al.* (2005)	0.901 + [c]	204.77	27	23	1.85	0.67, 5.14
Engel *et al.* (2007) (Janus)	1048.3	1048.3	44	48	1	Ref.
Engel *et al.* (2007) (Janus)	1398.3	1398.3	48	47	1.1	0.7, 2.0
Engel *et al.* (2007) (Janus)	1674.9	1674.9	38	48	1.01	0.5, 1.9
Engel *et al.* (2007) (Janus)	2148.2	2148.2	60	47	1.7	0.8, 3.4
Engel *et al.* (2007) (CLUE I)	551.4	551.4	10	37	1	Ref.
Engel *et al.* (2007) (CLUE I)	726	726	13	37	1.6	0.6, 4.3
Engel *et al.* (2007) (CLUE I)	911.5	911.5	21	37	3.0	1.1, 8.3
Engel *et al.* (2007) (CLUE I)	1377.3	1377.3	30	36	4.6	1.7, 12.7
Spinelli *et al.* (2007)	< 100.9	50.45	81	115	1	Ref.
Spinelli *et al.* (2007)	101–155.6	128.3	103	114	1.19	0.74, 1.92
Spinelli *et al.* (2007)	155.7–220.0	188.3	77	115	0.84	0.49, 1.41
Spinelli *et al.* (2007)	221 +	331.5	142	115	1.55	0.91, 2.65
Cocco *et al.* (2008)	< 200.4	100.2	41	51	1	Ref.
Cocco *et al.* (2008)	200.5–387.8	294.15	50	51	1.2	0.6, 2.2
Cocco *et al.* (2008)	387.9–576.4	482.15	33	50	0.7	0.3, 1.4
Cocco *et al.* (2008)	576.5 +	864.75	50	51	1.01	0.5, 2.0
Bertrand *et al.* (2010)	518	518	33	81	1	Ref.
Bertrand *et al.* (2010)	678	678	31	82	0.86	0.47, 1.6
Bertrand *et al.* (2010)	815	815	34	82	0.99	0.55, 1.8
Bertrand *et al.* (2010)	980	980	46	82	1.3	0.71, 2.3
Bertrand *et al.* (2010)	1385	1385	61	82	1.6	0.91, 2.9
Laden *et al.* (2010)	406.9	406.9	33	72	1	Ref.
Laden *et al.* (2010)	547.8	547.8	41	73	1.25	0.68, 2.28
Laden *et al.* (2010)	678	678	41	73	1.32	0.71, 2.43
Laden *et al.* (2010)	945.4	945.4	30	72	1.02	0.53–1.95
Bräuner *et al.* (2012)[d]	150–770	460	62	59	1	Ref.
Bräuner *et al.* (2012)[d]	770–939	854.5	55	66	0.74	0.44, 1.24
Bräuner *et al.* (2012)[d]	939–1143	1041	57	62	0.81	0.48, 1.35
Bräuner *et al.* (2012)[d]	1143–1351	1247	42	32	1.15	0.63, 2.11
Bräuner *et al.* (2012)[d]	1351–2157	1754	23	26	0.71	0.34, 1.45

CI, confidence interval; PCB, polychlorinated biphenyl; Ref, reference category; RR, relative risk.
[a]Categories of serum or fat PCB level (ppb), range or median.
[b]Value used in the meta-analysis (ppb; midpoint of categories; x1.5 for open upper categories).
[c]mol/g lipid (conversion factor to ppb, 0.0066).
[d]Fat PCB level.

unknown causes of NHL remains a possible source of bias of the results of the meta-analysis, especially for studies based on environmental exposure to PCB: analyses of the US National Health and Nutrition Examination Survey showed that the serum level of PCB correlates (negatively or positively) with that of other exogenous and endogenous agents (Patel *et al.*, 2012). It is worth noticing that in one of the case–control studies based on serum PCB level, adjustment for a chlorinated insecticide, oxychlordane, reduced the RR for the category of highest PCB exposure from 2.1 (95% CI: 1.38–3.30) to 1.55 (95% CI: 0.91–2.65) (Spinelli *et al.*, 2007).

Other aspects of validity of the results concern sources of selection and information bias, which operated to a various degree in the studies included in our review: we attempted to address them through the use of quality scores (Wells *et al.*, 2011), and there was no indication that the lack of an association between PCB exposure and NHL risk was explained by the potential sources of bias. In particular, the use of biological samples collected after development of the disease in cases included in retrospective case–control studies can be a source of bias, because of the possibility that the disease influences the level of the biomarker (reserve causality) (Rothman *et al.*, 1995). We addressed this potential source of bias by stratifying the results of studies based on exposure biomarkers according to the timing of biospecimen collection, and found no difference in the results of studies in which biospecimens were collected before versus after NHL diagnosis.

A recent study (Roswall *et al.*, 2018) does not support an increased risk of death among NHL patients with high tissue concentrations of organochlorines impact; in this study, no statistical association between PCBs in adipose tissue and survival after NHL has been found in 232 NHL cases of a cohort studied by Bräuner *et al.* (2012).

Immunotoxicity has been discussed as the possible mechanism underlying an association between PCB exposure and risk of NHL (Fisher and Fisher, 2004). A detailed review of this hypothesis falls outside the scope of this work, but we attempted to address it by performing a meta-analysis of combined exposure to four PCB congeners, for which an immunotoxic effect has been postulated (PCBs 118, 138, 153, 180), as well as

separate meta-analyses for each of them: no indication of an association with NHL risk can be derived from these results.

In conclusion, we found no indication from our meta-analysis of an association between occupational or environmental exposure to PCBs and risk of NHL. The lack of an increased risk among PCB-exposed workers is particularly important, as occupational exposure circumstances are much higher than those encountered in the general environment. No association was detected in subset analyses focused on specific PCB congeners and on risk of DLBCL, FL or CLL. A weak dose-response relation was detected in the meta-analysis of studies based on serum or fat PCB level in populations without specific sources of exposure; the possibility of residual confounding, however, cannot be ruled out. Overall, PCBs are not likely to cause NHL in humans.

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Conflicts of interest

Paolo Boffetta consulted with Monsanto, a former PCB producer, on cancer risk from exposure to PCBs and other chemicals. For the remaining there are no conflicts of interest.

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