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Review

Association between exposure to polychlorinated biphenyls and risk of hypertension: A systematic review and meta-analysis

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HIGHLIGHTS

- Total PCB, especially DL-PCB exposure, was associated with a higher risk of hypertension independently of other risk factors.
- A linear dose-effect relationship was found for total PCB serum levels using a dose-response meta-analysis.
- The positive association was confirmed when stratifying the analyses by study design and level of exposure.
- Odds ratio estimates were similar using different lipid adjustment approaches.

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ABSTRACT

Experimental and epidemiological studies have suggested an association between exposure to polychlorinated biphenyls (PCBs), ubiquitous environmental toxic compounds, and the risk of hypertension. We conducted a systematic review and meta-analysis of epidemiological studies of the association between PCB exposure and the risk of hypertension. Studies were identified by searching PubMed, Embase and Web of Science and by reviewing reference lists. Study-specific risk estimates comparing the highest versus lowest quantile of PCB distribution were combined using random-effects models.

We identified 10 cross-sectional studies, 6 cohort studies, and 1 nested case-control study. A pooled excess risk of hypertension was found for total PCBs (OR 1.70, 95% CI 1.28−2.26), dioxin-like (DL)-PCBs (OR 1.46, 1.19−1.79), but not for non-dioxin like (NDL)-PCBs (OR 1.19, 0.81−1.73) comparing the highest with the lowest quartile of the distribution. According to a dose-response meta-analysis, a linear dose-effect relationship was found for total PCBs [OR 2.23 (95% CI: 1.59−3.14) for 1000 ng PCB/g lipid increase]. This positive association remained when stratifying the analyses by study design (cohort vs cross-sectional studies) and population (general population vs high exposed workers/residents). Among single PCB congeners, DL-PCB 105 and 118, and non-DL-PCB138 and 153 were related to hypertension.

In conclusion, this meta-analysis suggests that exposure to PCBs, particularly to DL-PCBs, may be a risk factor for hypertension, independently of other risk factors.

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Contents

1. Introduction

Polychlorinated biphenyls (PCBs) are mixtures of up to 209 individual organic chlorine compounds. They are included among persistent organic pollutants (POPs) and have been widely dispersed in the environment for decades (IARC-Monograph, 2016). These lipophilic compounds are highly resistant to metabolism in vertebrate species and accumulate in the food chain, resulting in an age-dependent human body burden. After ceasing PCB production in most countries by the end of the 1970s - early 1980s, PCB contamination has decreased in the environment (Riget et al., 2004; Sturludottir et al., 2014). However, the general population is still exposed to these pollutants at low doses through diet worldwide (EFSA, 2012; Consonni et al., 2012; Raffetti et al., 2017).

PCBs have been classified as “human carcinogens” (group 1) by the International Agency for Research on Cancer (IARC) and are included among the “endocrine disruptors” because of their endocrine and metabolic effects (EFSA, 2012). The potential link between PCB exposure and hypertension has also been suggested in the last decades. Toxicological studies in vitro have shown a direct toxic effect of PCBs on endothelial cells, increasing cytokines, adhesion molecules levels and oxidative stress, ultimately leading to endothelial cell dysfunction and atherosclerosis progression (Andersson et al., 2011; Helyar et al., 2009). The first evidence of a possible effect of PCB exposure on the onset of hypertension in human beings was described in 1981 among fish eaters in Triana, Alabama, accidently exposed to wastewater discharge (Kreiss et al., 1981). Two previous reviews on the topic (Everett et al., 2011; Park et al., 2016) concluded that overall evidence on the association between PCB exposure and hypertension was still weak with few data sustaining a causal relationship, especially due to paucity of prospective studies.

Since then, new studies have been published (Donat-Vargas et al., 2015, Donat-Vargas et al., 2018; Dusanov et al., 2018; Pavuk et al., 2019; Raffetti et al., 2018, 2020; Raymond et al., 2016; Van Larebeke et al., 2015), including three cohort studies (Donat-Vargas et al., 2018; Pavuk et al., 2019; Raffetti et al., 2020). Therefore, we aimed to undertake an updated and more exhaustive systematic review and meta-analysis also considering the design, population, potential sources of bias and overall quality of the study as well as the applied lipid-adjustment methods for estimates. We further evaluated a possible dose-effect relationship between measures of PCB body burden and hypertension.

2. Methods

The study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati et al., 2009) and MOOSE guidelines (Stroup et al., 2000).

The PECO (Population, Exposure, Comparator, Outcome) (Morgan et al., 2016) question was termed as follows: Participants were the general population or PCB exposed populations, Exposure was the concentration of PCBs, Comparator subjects were people with the lowest PCB exposure, Outcomes were hypertension or high blood pressure (i.e. “For the general population (P), is PCB exposure above [dose] (E), compared to PCB exposure below [dose] (C), associated with an increased risk of hypertension or high blood pressure (O)?”).

2.1. Criteria for study selection

The epidemiological studies were included if fulfilled the following criteria: 1) any population or group of subjects; 2) cohort, case-control, and cross-sectional study designs; 3) PCBs measured directly in biological samples (blood or adipose tissue) or estimated indirectly through the diet (i.e. dietary PCB intake); 4) hazard ratios (HR), relative risks (RR), or odds ratios (OR) for incidence or prevalence of hypertension or high blood pressure with corresponding 95% confidence intervals (CI) reported; 5) English, French, Italian,

German or Spanish language of the article. If multiple publications of one study were found, only the most recent or suitable publication was included.

2.2. Exposure and outcome measures

∑PCBs, ∑dioxin-like (DL)-PCBs, ∑non-dioxin-like (NDL)-PCBs, the three most common DL- and NDL-PCB congeners found in studies carried out in the 2000s (DL-PCB 105, 118,156 and NDL-PCB 138, 153, 180) (Consonni et al., 2012 Arrebola et al., 2012; Fernandez-Rodriguez et al., 2015; Magoni et al., 2016; Zong et al., 2015) were also evaluated individually.

The primary outcome was incidence or prevalence of hypertension or high blood pressure.

2.3. Information sources and search criteria

We systematically searched Embase, PubMed, and Web of Science databases for articles published up to March 23, 2020. The time span, the key words and the MESH terms of the search strategies for each database are described in Supplementary Table 1. We checked the reference lists of the eligible studies to look for other potentially relevant studies.

2.4. Study selection

The literature search was conducted independently by two reviewers (ER and SM) who searched the literature and selected potentially eligible studies based on title and abstract. Disagreements were resolved by consensus; if no agreement was reached, a third author (AC) was called to decide. All the eligible papers were examined in detail. The studies excluded according to title and abstract or full-article screening process were recorded specifying the reasons for the exclusion.

2.5. Data extraction and management

The following data were extracted independently by two investigators (AC and SM) from each study: title, first author, publication year, country, study design, PCB measurement, method for lipid adjustment, outcome assessment, age of subjects, proportion of males, sample size, cut-off values for categories of PCB levels, the variables by which the estimates were adjusted for, the risk estimates (OR, RR, HR) with 95% CI.

When the studies reported several models for estimating associations with different methods of adjustment, we extracted all of them for comparison. For the meta-analysis, we considered the risk estimates adjusted for the greatest number of potential confounders (full-adjusted model).

For some studies with data unsuitable for our analysis, we contacted the authors for providing further data on their studies.

2.6. Assessment of the level of evidence

We applied the GRADE methodology for environmental and occupational health studies to assess the quality of evidence (Morgan et al., 2016, 2018). The risk of bias for each study was evaluated through a modified version of ROBINS-I (Schunemann et al., 2019; Sterne et al., 2016), a recently proposed tool for the evaluation of non-randomized studies of exposures (Morgan et al., 2018). We defined the risk of bias according to the following seven domains: confounding, selection of participants into the study, classification of exposures, departures from intended exposures (change of exposure levels over time), missing data, measurement of outcomes and selection of the reported results. For each domain, each reviewer (ER, SM and AC) independently attributed a “low”, “moderate”, “serious” or “critical” risk of bias. Disagreements were resolved by consensus, and overall risk of bias was reported for each study based on the highest risk among the seven domains. The initial quality across the studies was defined as “high” (Morgan et al., 2018; Schunemann et al., 2019); subsequently, we evaluated the factors that may downgrade (overall risk of bias, inconsistency, indirectness, imprecision, publication bias) or upgrade (large effects, dose-response relationship) the level of evidence. According to the assessment of the risk of bias, we downgraded by one level for moderate risk of bias, by two levels for serious risk of bias and by three levels for critical risk of bias (Sterne et al., 2016). For all the other factors, we eventually downgraded or upgraded the initial quality by one level. The resulting quality of evidence was ranked as “high”, “moderate”, “low” or “very low”.

2.7. Statistical analysis

We performed separate meta-analyses for total PCBs, DL-PCBs, NDL-PCBs, and for the three most common DL- and NDL-PCB individual congeners including studies that measured PCBs in biological samples (blood or adipose tissue). Effect estimates were reported in different ways describing comparisons per unit change, between top and bottom tertiles or quartiles. To allow consistent comparison of study-specific estimates and interpretation of findings, the estimates of the association of PCB levels with hypertension were rescaled to represent the estimate for the top versus the bottom fourth of PCB concentration within a given study using standard statistical methods (Chene and Thompson, 1996). We used random-effects models to account for heterogeneity in study-specific results.

We performed sensitivity analyses evaluating the influence of each study on the overall effect size, repeating the meta-analysis after omitting one study in each turn.

Potential sources of heterogeneity due to the study design, the measurement method of PCBs and/or different levels of exposure, were evaluated using stratified analyses.

To quantify the magnitude of potential confounding (unmeasured, unknown or residual), an E-value was reported for total PCBs given an OR as the effect measure and an outcome prevalence higher than 15%. While a large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate, a small E-value implies little unmeasured confounding would be needed to explain away an effect estimate (Vanderweele and Ding, 2017).

A P-value < 0.1 for chi-square test was used to determine statistical significance for heterogeneity, and substantial heterogeneity was indicated by I^2 statistic >50%.

Funnel plots and regression asymmetry test (Egger et al., 1997) were used to provide a visual and statistical assessment of the associations between hypertension risk estimates, the study sample size, and the presence of publication bias.

Using meta-regression analysis we addressed the possible impact of the publication year, study design (cohort or cross-sectional design), level of exposure (general population or highly exposed workers/residents), adjustment for age, sex, tobacco smoking, BMI, alcohol consumption, physical activity, glucose intolerance, socioeconomic status, family history of cardiovascular diseases and ethnicity, on the overall association between total PCB and hypertension.

The statistical analyses were performed using the Stata 15 software (Stata Statistics/Data Analysis 15.0 - Stata Corporation, College Station, TX, USA).

We also performed a dose-response meta-analysis for total PCBs using inverse weighted least squares method (Orsini et al., 2006)

with the R package *"dosresmeta"* in the statistical software R (R Foundation for Statistical Computing, Vienna, Austria). The statistical tests were two-sided with a significance level of 0.05.

3. Results

3.1. Study acquisition

The results of the paper selection are shown in Fig. 1. Out of the 441 potentially relevant records, 67 were retrieved for the full-text screening and, after excluding the articles that did not meet the inclusion criteria, 17 articles were included.

3.2. Study characteristics

The characteristics of the included studies are summarized in Table 1. A total of 10 cross-sectional studies, 6 cohort studies and 1 nested case-control study were included in the systematic review. Four studies were conducted in the US, 3 in Spain, 2 in Japan, 2 in Sweden and 1 in each of the other six countries, setting a total of 29 153 individuals. Study populations were generally large, 11 studies included more than 400 individuals, and 6 studies exceeded 1000 subjects.

Ten of the studies analyzed the general population and 7 included highly exposed subgroups. While most of the studies measured the exposure as the sum of various PCB congeners; only 8 considered the sum of DL-PCB congeners and 5 the sum of NDL-PCB congeners.

Regarding the method of estimating exposure to PCB, 15 of the studies measured PCB concentration in serum or plasma, 1 study in adipose tissue and 1 estimated dietary PCB intake from a food frequency questionnaire.

Among the 15 studies measuring blood/serum PCBs, 6 expressed PCBs as ratio of serum levels of PCBs to total serum lipids (standardization) (Lind et al., 2014; Nakamoto et al., 2013; Pavuk et al., 2019; Valera et al., 2013a; Van Larebeke et al., 2015; Yamamoto et al., 2015), 4 in wet weight (ng/mL) but adjusting for serum lipids (total lipids or cholesterol) as covariates (Dusanov et al., 2018; Lee et al., 2014; Valera et al., 2013b; Yorita Christensen and White, 2011), 3 provided PCB in wet weight but not adjust for lipids (Henriquez-Hernandez et al., 2014; Raymond et al., 2016; Stehr-Green et al., 1986), and 2 used more than one approach (Donat-Vargas et al., 2018; Raffetti et al., 2020).

Almost all studies controlled for age (n = 15) and sex (n = 14), and most of them also adjusted for tobacco smoking (n = 12), body mass index (BMI, n = 12), alcohol consumption (n = 9) and physical activity (n = 6) (Supplementary Table 2). Some studies also adjusted for glucose intolerance (n = 4), socioeconomic status (n = 3), family history of cardiovascular diseases (n = 3), ethnicity (n = 2) and diet (n = 2).

3.3. Risk of bias

All the studies included in the review were at risk of bias. The overall risk of bias was considered "moderate" for 1, "serious" for 4 and "critical" for 12 studies (Supplementary Table 3). Most of the studies were at serious and critical risk of bias because of their cross-sectional nature and the lack of adjustment for confounders such as diet.

3.4. Meta-analysis: PCBs and hypertension

3.4.1. Total PCBs

Ten studies examined the association between total PCBs and

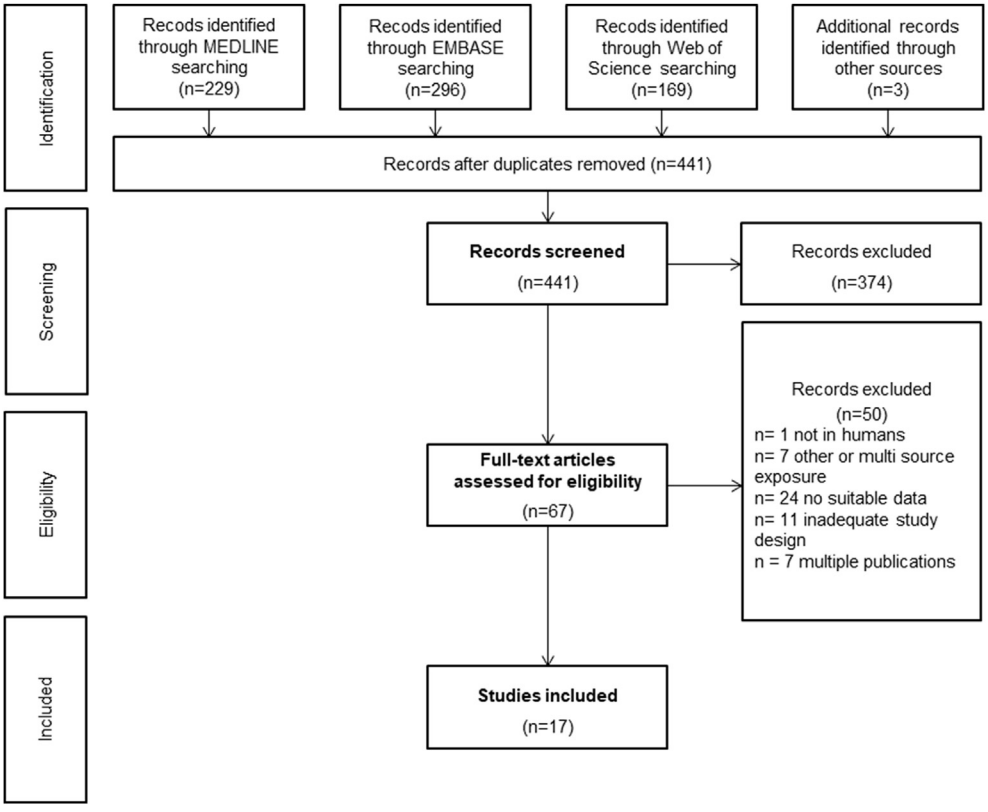

Fig. 1. Flow diagram of the systematic review.

Table 1
Main characteristics of studies included in the meta-analysis.

Study					Exposure			Outcome		ORs/RRs/HRs (95% CI) [a]	Lipid adjustment	Covariates adjusted for
First author and year	Country	Design	Study population	No. subjects (cases/controls) Males %, mean age (years)	Methods for detection	Evaluated PCBs	Measurement	Outcome	Methods for detection			
Arrebola et al., 2015	Spain	Cohort	Hospital-based population: patients undergoing non-cancer related surgery	297 Males 44.1% Age 48.0 years (median)	adipose tissues	∑PCBs, PCB 138, 153 and 180	Quartiles (ng/g lipid)	Hypertension	Blood pressure ≥140/90 or use of anti-hypertensive drugs	∑PCBs [b] HR = 1.12 (0.93 −1.35) PCB 138 HR = 2.21 (0.95 −5.13) PCB 153 HR = 1.61 (0.75 −3.45) PCB180 HR = 1.44 (0.67 −3.09)	Lipid-standardized PCBs	Age, BMI, tobacco smoking, alcohol consumption
Donat-Vargas et al., 2015	Spain	Cohort and cross-sectional	General population (The SUN Project)	14521 Males 36.6% Age 36.6 years	Indirect estimation from a Food Frequency Questionnaire and PCB concentrations in food samples	∑PCBs	Quintiles (means, ng/day) ∑PCBs [c] Q1 393.5 Q2 664.2 Q3 762.9 Q4 1077.7 Q5 1894.8	Hypertension	Self-reported hypertension	∑PCBs HR = 1.43 (1.09 −1.88)	No standardization	Age, sex, tobacco smoking, physical activity, sitting hours, hypercholesterolemia, family history of hypertension, aspirin and non-aspirin analgesics, and several nutritional variables including caffeine and alcohol.
Donat-Vargas et al., 2018	Sweden	Cohort	General population (VIP cohort)	1511 (repeated measures) Males 55.5%	Plasma samples	∑DL-PCBs, ∑NDL-PCBs	Tertiles (means (SE), ng/g lipids) ∑DL-PCBs T1 19.6 (5.3) T2 33.7 (8.6) T3 53.6 (23.8) ∑NDL-PCBs T1 251.6 (65.7) T2 398.5 (63.3) T3 635.8 (191.4)	Hypertension	Self-reported hypertension, blood pressure ≥140/90 or use of anti-hypertensive drugs	∑DL-PCBs [d] RR = 1.52 (1.08 −2.13 ∑NDL-PCBs RR = 1.08 (0.78 −1.49)	4 models 1. wet-weight (non-lipid standardized) 2.adjusted for total serum lipids 3.adjusted for total serum lipids plus BMI 4.lipid-standardized PCBs + adjusted for lipids	Gender, age, year, pre-diabetic status, total serum lipids and BMI
Dusanov et al., 2018	Norway	Cross-sectional	Hospital- based population: obese patients	431 Males 37.3%	Serum samples	∑DL-PCBs, ∑NDL-PCBs	Quartiles (pg/mL)	High systolic blood pressure	Blood pressure ≥130 or use of anti-hypertensive drugs	∑DL-PCBs [d] OR = 1.5 (0.8−2.8) ∑NDL-PCBs	Total cholesterol concentration as a model covariate	Age, gender, BMI, tobacco smoking, alcohol consumption and total cholesterol concentration

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Table 1 (*continued*)

Study					Exposure			Outcome		ORs/RRs/HRs (95% CI) [a]	Lipid adjustment	Covariates adjusted for
First author and year	Country	Design	Study population	No. subjects (cases/controls) Males %, mean age (years)	Methods for detection	Evaluated PCBs	Measurement	Outcome	Methods for detection			
										OR = 1.1 (0.6–2.1)		
Henriquez-Hernandez et al., 2014	Spain	Cross-sectional	General population (Canary Islands Nutrition Survey, ENCA)	428 Males 44.6% Age 47.2 years	Serum samples	PCB 153 and 180	Per 1 unit increase of PCB concentration (ng/mL)	Hypertension	Blood pressure ≥140/90 or use of anti-hypertensive drugs	PCB 153 OR = 1.42 (0.78–2.58) PCB 180 OR = 1.17 (0.14–10.04)	No standardization	None
Lee et al., 2014	Korea	Nested case control	General population (Uljin Korean cohort)	64/182 Males 31.9% controls, 35.9% cases Age Controls 54.7 years Cases 57.3 years	Serum samples	∑PCBs	Quartiles (pg/g lipid)	High blood pressure	Blood pressure ≥130/85 or use of anti-hypertensive drugs	∑PCBs OR = 1.1 (0.3–3.5)	Total cholesterol and triglycerides as model covariates	Age, gender, tobacco smoking, alcohol consumption, physical activity, triglycerides, total cholesterol, and BMI
Lind et al., 2014	Sweden	Cross-sectional	General population aged 70 years, (PIVUS study)	1016 Males 49.8% Age 70 years	Serum samples	PCB 105, 118, 138, 153, 156 and 180	Per 1 unit increase of log-transformed PCB concentration (ng/g lipid)	Hypertension	Blood pressure ≥140/90 or use of anti-hypertensive drugs	PCB 105 OR = 1.23 (0.96–1.6) PCB 118 OR = 1.26 (0.95–1.67) PCB 156 OR = 0.90 (0.63–1.3) PCB 138: OR = 1.25 (0.91–1.7) PCB 153 OR = 1.19 (0.85–1.67) PCB 180 OR = 0.94 (0.64–1.38)	Lipid-standardized PCBs	Gender, BMI, tobacco smoking, physical activity, and education
Nakamoto et al., 2013	Japan	Cross-sectional	General population	2232 Males 47.0%	Blood samples	∑DL-PCBs	Quartiles (pg TEQ/g lipid) Q1 0–3.2 Q2 3.2–5.6 Q3 5.6–10 Q4 >10	Hypertension	Blood pressure ≥140/90 or physician diagnosed hypertension	∑DL-PCBs OR = 2.4 (1.6–3.7)	Lipid-standardized PCBs	Age, gender, tobacco smoking, alcohol consumption, regional block, year, and BMI
Pavuk et al., 2019	US	Cohort	Population living in a highly polluted area (Anniston site)	145 Males 29.0% Age 57.4 years	Serum samples	∑PCBs	Per 1 unit increase of log-transformed PCB concentration (pg/g lipid)	Hypertension	Blood pressure ≥140/90 or use of anti-hypertensive drugs	∑PCBs HR = 1.89 (0.91–3.90)	Lipid-standardized PCBs + adjusted for lipids	Age, BMI, gender, ethnicity and family history of high blood pressure
Raffetti et al., 2020	Italy	Cohort	Population living in a highly polluted area	1031 Males 43.4%	Serum samples	∑PCBs	Tertiles (ng/g lipid) T1 0-208	Hypertension	Population based administrative data	∑PCBs RR = 2.30	3 models 1. wet-weight (non-lipid	Age, gender, education, BMI, tobacco smoking, alcohol consumption

				Age 45.3 years			T2 209-618 T3 619-34378			(1.26 −4.21)	standardized) 2.adjusted for total serum lipids 3. lipid-standardized PCBs + adjusted for lipids	and total lipids/ cholesterol
Raymond et al., 2016	US	Cross-sectional	Male anglers aged 50 years and older	154 Males 100% Age 61.7 years	Serum samples	∑PCBs, ∑DL-PCBs, PCB 180	Per 1 unit increase of PCB concentration (ng/mL)	High blood pressure	Self-reported hypertension	∑PCBs OR = 0 .99 (0.82 −1.18) ∑DL-PCBs OR = 1.10 (0.72 −1.66) PCB 180 OR = 1.51 (0.35 −6.19)	No standardization	Age, BMI, employment status, and alcohol consumption
Stehr-Green et al., 1986	US	Cross-sectional	Population living in a highly polluted area (chemical waste sites)	106	Serum samples	∑PCBs	Two categories (ng/mL) ≥20 vs < 20	High blood pressure	Self-reported hypertension or physician-diagnosed hypertension	∑PCBs OR = 1.63 (0.63 −3.85)	No standardization	None
Valera et al., 2013a	Denmark (Greenland)	Cross-sectional	Arctic population, Inuit from Greenland	1614 Males 43.9% Age 44.6 years	Plasma samples	∑DL-PCBs, ∑NDL-PCBs, PCB 105, 118, 138, 153, 156 and 180	Per 1 unit increase of log-transformed PCB concentration (ng/g lipid)	Hypertension	Blood pressure ≥140/90 or use of anti-hypertensive drugs	∑DL-PCBs[d] OR = 1.04 (0.89 −1.21) PCB 105 OR = 1.07 (0.93 −1.22) PCB 118 OR = 1.07 (0.93 −1.23) PCB 156 OR = 0.93 (0.80 −1.09) PCB 138 OR = 0.97 (0.84 −1.12) PCB 153 OR = 0.96 (0.83 −1.11) PCB 180 OR = 0.90 (0.78 −1.04) ∑NDL-PCBs OR = 0.95 (0.81 −1.11)	Lipid-standardized PCBs	Age, gender, BMI, diabetes, physical activity, and tobacco smoking
Valera et al., 2013b	Canada	Cross-sectional	Arctic population, Inuit from Nunavik	315 Males 42.5%	Plasma samples	∑PCBs, ∑DL-PCBs, ∑NDL-PCBs, PCB	Per 1 unit increase of log-transformed PCB	Hypertension	Blood pressure ≥140/90 or use of anti-	∑PCBs OR = 1.50 (1.12	Total lipids as a model covariate	Age, gender, fasting glucose, total lipids, waist circumference,

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Table 1 (*continued*)

Study					Exposure			Outcome		ORs/RRs/HRs (95% CI) [a]	Lipid adjustment	Covariates adjusted for
First author and year	Country	Design	Study population	No. subjects (cases/controls) Males %, mean age (years)	Methods for detection	Evaluated PCBs	Measurement	Outcome	Methods for detection			
				Age 32.7 years		105, 118, 156, 138, 153, 180	concentration (ng/mL)		hypertensive drugs	−2.02) ∑DL-PCBs [d] OR = 1.16 (0.88 −1.53) ∑NDL-PCBs OR = 1.47 (1.10 −1.97) PCB 105 OR = 1.44 (1.11 −1.86) PCB 118 OR = 1.27 (0.98 −1.65) PCB 156 OR = 0.84 (0.67 −1.06) PCB 138 OR = 1.38 (1.05 −1.82) PCB 153 OR = 1.23 (0.95 −1.60) PCB 180 OR = 1.08 (0.86 −1.37)		acid + docosahexaenoic acid), lead, and mercury
Van Larebeke et al., 2015	Belgium	Cohort	General population (FLEHS cohort)	970 Males 48.2% Age 57.4 years (geometric mean)	Serum samples	∑PCBs	Doubling of exposure (ng/g lipid)	Hypertension	Self -reported hypertension	∑PCBs [b] OR = 0.39 (0.26 −0.58)	Lipid-standardized PCBs	Age, gender, tobacco smoking and correlated exposures (toxic chemicals)
Yamamoto et al., 2015	Japan	Cross-sectional	Waste incinerator male workers	678 Males 100% Age 43.1 years	Serum samples	∑PCBs	Quartiles (pg TEQ/g lipid) Q1 <2.60 Q2 2.60−4.44	Hypertension	Self-reported hypertension or blood pressure ≥140/90	∑PCBs OR = 2.31 (1.33 −4.02)	Lipid-standardized PCBs	Age, survey year, BMI, tobacco smoking, alcohol consumption

							Q3 4.45−7.29 Q4 ≥7.30					
Yorita Christensen and White, 2011	US	Cross-sectional	General population (NHANES study)	4119 Males 47.2%	Serum samples	∑PCBs, ∑DL-PCBs, PCB 105, 118, 156, 153, 180	Quartiles (ng/ml) ∑PCBs Q1 <0.66 Q2 0.66−1.09 Q3 1.10-1.93 Q4>1.94 ∑DL-PCBs Q1 <0.20 Q2 0.20 -0.39 Q3 0.39-0.72 Q4≥0.72	Hypertension	Self-reported hypertension, blood pressure ≥140/90 or use of anti-hypertensive drugs	∑PCBs OR = 1.38 (1.02 −1.87) ∑DL-PCBs OR = 1.26 (0.91 −1.74) PCB 105 OR = 1.25 (0.97 −1.62) PCB 118 OR = 1.63 (1.23 −2.17) PCB 156 OR = 1.24 (0.94 −1.62) PCB 153 OR = 1.42 (1.03 −1.95) PCB 180 OR = 1.22 (0.86 −1.72)	Total cholesterol and serum lipid concentration as model covariates	Age gender, BMI, ethnicity, tobacco smoking, physical activity, family history of cardiovascular disease, total cholesterol and total lipid concentration.

[a] The estimation is presented for the highest category compared with the lowest for the most adjusted model.
[b] Less than 10 PCBs included in the total.
[c] Estimated full intake.
[d] Less than five PCBs included in the total.

hypertension (Arrebola et al., 2015; Lee et al., 2014; Pavuk et al., 2019; Raffetti et al., 2020; Raymond et al., 2016; Stehr-Green et al., 1986; Valera et al., 2013b; Van Larebeke et al., 2015; Yamamoto et al., 2015; Yorita Christensen and White, 2011). Significantly positive associations were found in 4 studies (Raffetti et al., 2020; Valera et al., 2013b; Yamamoto et al., 2015; Yorita Christensen and White, 2011), non-significantly positive in 3 (Arrebola et al., 2015; Pavuk et al., 2019; Stehr-Green et al., 1986), null in 2 (Raymond et al., 2016; Lee et al., 2014) and negative in one (Van Larebeke et al., 2015). The strong negative association found in the study by Van Larebeke et al., 2015 was inconsistent with all the other studies and may have been caused by an over-adjustment for correlated exposures, and therefore it was excluded from the computation of summary estimates. The pooled OR of hypertension for the highest versus lowest quartile of the total PCB distribution was 1.70 ($I^2 = 38.3\%$) (Fig. 2). The corresponding E-value, that could explain away the association, was 1.93 for the estimated risk ratio and 1.51 for the lower confidence limit. According to the dose-response meta-analysis of 3 studies (Arrebola et al., 2015; Raffetti et al., 2020; Yorita Christensen and White, 2011), there was a linear dose-effect relationship between total PCB levels and the risk of hypertension [OR 2.23 (95% CI: 1.59−3.14 $p < 0.001$, $I^2 = 0.0\%$) per 1000 ng PCB/g lipid increase, data not shown in table].

Stratifying the analysis by study design, the ORs were 2.12 (95% CI 1.32-3.42 $p = 002$, $I^2 = 0.0\%$) for cohort and nested case-control studies grouped together (Arrebola et al., 2015; Lee et al., 2014; Pavuk et al., 2019; Raffetti et al., 2020) and 1.59 (1.11-2.27 $p = 0.011$, $I^2 = 53.8\%$) for the cross-sectional ones (Raymond et al., 2016; Stehr-Green et al., 1986; Valera et al., 2013b; Yamamoto et al., 2015; Yorita Christensen and White, 2011). In the analysis by population, the ORs were 1.40 (1.06-1.85 $p = 0.018$, $I^2 = 0.0\%$) for studies conducted in the general population (Arrebola et al., 2015; Lee et al., 2014; Yorita Christensen and White, 2011) and 1.96 (1.25-3.07 $p = 0.003$ $I^2 = 55.4\%$) for those on highly exposed subjects (Pavuk et al., 2019; Raffetti et al., 2020; Raymond et al., 2016; Stehr-Green et al., 1986; Valera et al., 2013b; Yamamoto et al., 2015). According to geographic area, the relationship was confirmed in both North America, OR =1.46 (1.03-2.06 $p = 0.031$, $I^2 = 35.4\%$), and Europe-Asia, OR = 2.28 (1.54-3.35 $p < 0.001$, $I^2 = 0.0\%$).

3.4.2. DL-PCBs

Eight studies examined the relationship between total DL-PCBs or the individual DL-PCB congeners 105,118 and 156 (Donat-Vargas et al., 2018; Dusanov et al., 2018; Nakamoto et al., 2013; Raymond et al., 2016; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011·Lind et al., 2014). For total DL-PCB exposure (Donat-Vargas et al., 2018; Dusanov et al., 2018; Nakamoto et al., 2013; Raymond et al., 2016; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011), there was a 46% increased odds of hypertension (OR = 1.46, $I^2 = 32.4\%$), comparing the highest versus lowest quartile (Fig. 3). For individual DL-PCB congeners, the pooled estimate was in the same direction for PCB-105 (Lind et al., 2014; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011) (OR = 1.41, $I^2 = 37.8\%$) and PCB-118 (Lind et al., 2014; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011) (OR = 1.50, $I^2 = 0.0\%$), but not for PCB 156 (Lind et al., 2014; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011) (OR = 0.92, $I^2 = 48.6\%$).

3.4.3. NDL-PCBs

Total NDL-PCBs (Donat-Vargas et al., 2018; Dusanov et al., 2018; Valera et al., 2013a, Valera et al., 2013b) were not associated with risk of hypertension (OR = 1.19, $I^2 = 54.9\%$) (Fig. 4). For individual NDL-PCB congeners, moderate OR estimates, statistically significant, were found for the NDL-PCB138 (Arrebola et al., 2015; Lind et al., 2014; Raffetti et al., 2020; Valera et al., 2013a, Valera et al., 2013b) (OR = 1.67, $I^2 = 59.3\%$) and 153 (Arrebola et al., 2015; Henriquez-Hernandez et al., 2014; Lind et al., 2014; Raffetti et al., 2020; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011) (OR = 1.41, $I^2 = 27.7\%$), but not for the NDL-PCB-180 (Arrebola et al., 2015; Henriquez-Hernandez et al., 2014; Lind et al., 2014; Raffetti et al., 2020; Raymond et al., 2016; Valera et al., 2013a, Valera et al., 2013b; Yorita Christensen and White, 2011) (OR = 1.12, $I^2 = 12.0\%$).

3.4.4. Sensitivity analyses and quality of evidence

When removing one study at a time no substantial changes in the summary estimates were evidenced. Although Egger's

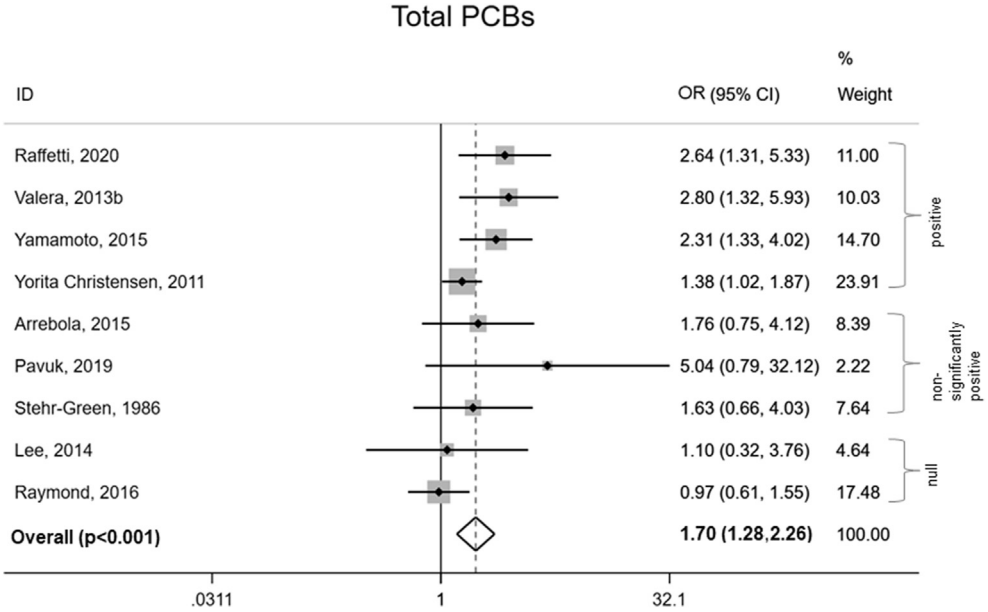

Fig. 2. Risk of hypertension comparing the highest with the lowest quartile of total PCB distribution. Meta-analyses with random-effects models. Abbreviations: OR, odds ratio; CI, confidence interval.

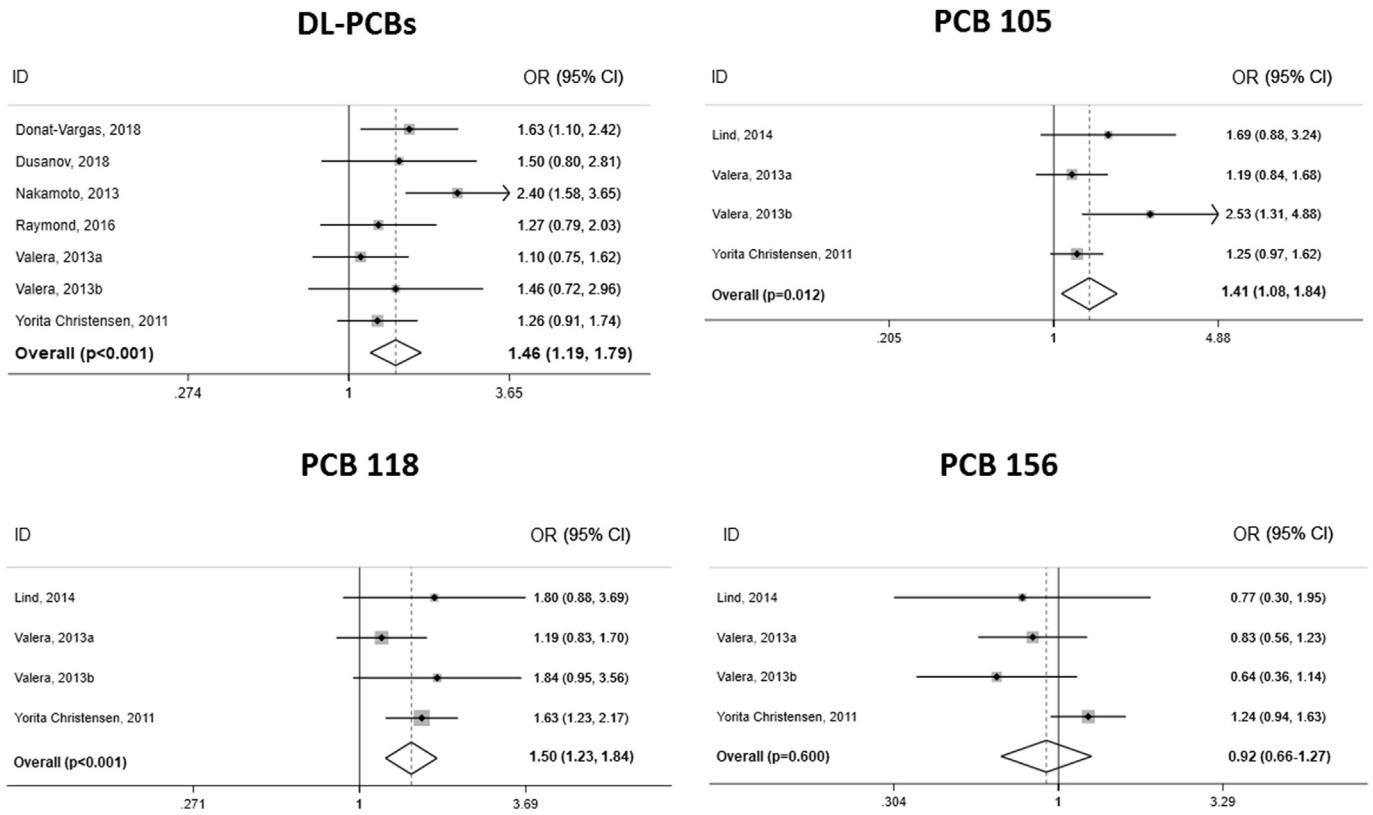

Fig. 3. Risk of hypertension according to DL-PCBs. PCB105, 118 and 156. Meta-analyses with random-effects models. Abbreviations: OR, odds ratio; CI, confidence interval.

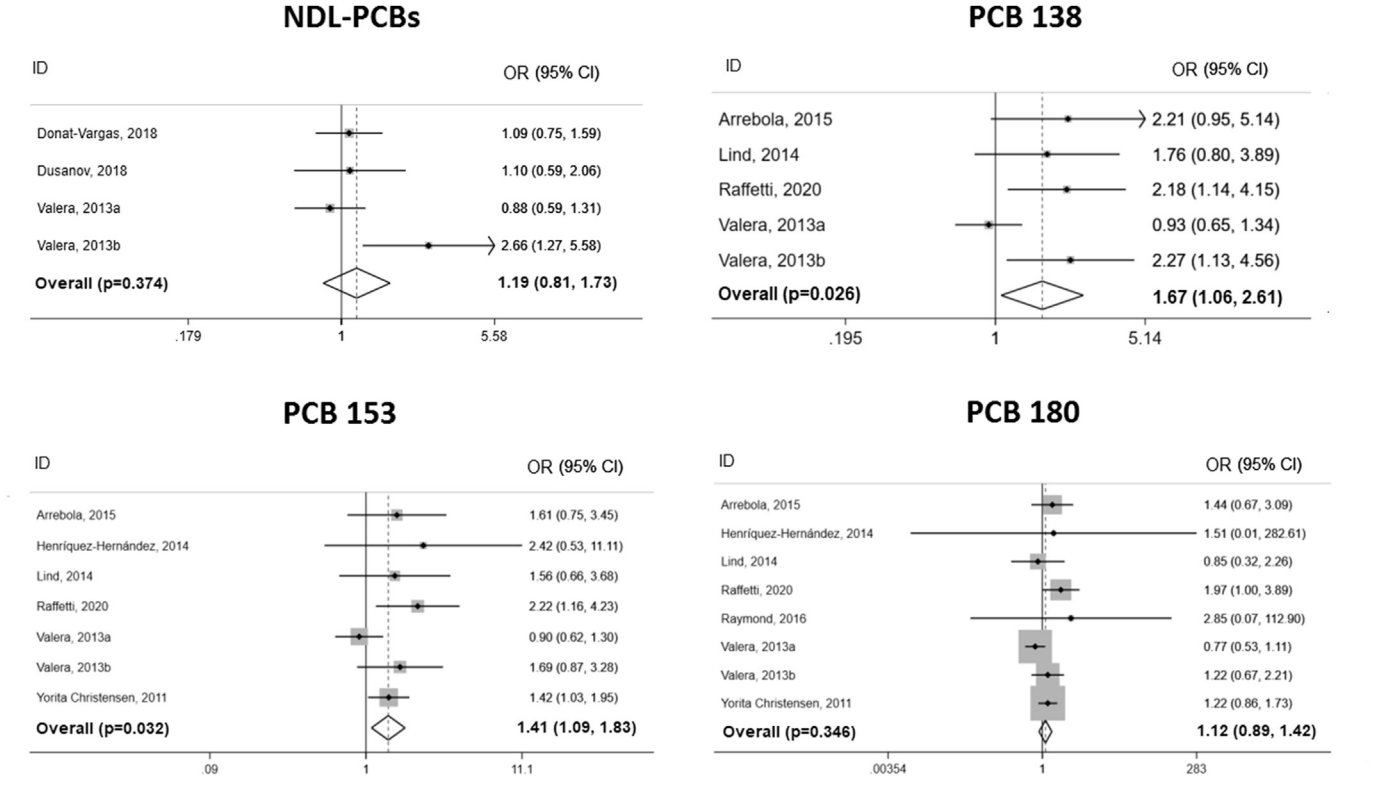

Fig. 4. Risk of hypertension according to NDL-PCBs. PCB-138, 153 and 180. Meta-analyses with random-effects models. Abbreviations: OR, odds ratio; CI, confidence interval.

regression tests indicated no evidence of publication bias, the Begg's funnel plots showed a slight asymmetry only for total PCBs, with lack of small studies with null association (Supplementary Fig. 1).

The meta-regression analysis showed that the year of publication, the study design, the level of exposure and the adjustment for different confounders did not significantly influence the magnitude of the overall association between total PCBs and hypertension (data not shown).

Finally, when we compared PCB estimates within studies that used more than one lipid adjustment approach (Donat-Vargas et al., 2018; Raffetti et al., 2020) (Supplementary Table 4), we found that different approaches did not impact significantly on the estimates (±10-15% fluctuation), although lipid-standardized estimations showed a slightly lower magnitude of results compared to those lipid-adjusted.

The quality of the currently available evidence, according to the GRADE approach, was rating as low due to an overall critical risk of bias across studies which was partially offset by a dose-response effect.

4. Discussion

We performed a systematic review and meta-analysis of the association between PCB exposure and hypertension. Considering the available literature up to March 23, 2020 including 17 epidemiological studies, we conclude that total PCBs, especially DL-PCBs, are associated with an increased risk of hypertension. However, this conclusion is based on a "low" level of evidence, according to the GRADE approach. Nevertheless, the causality of the potential PCB-hypertension association is supported by the strength of associations and other Bradford Hill's criteria such as consistency, temporality, dose-response, analogy, coherence, and biological plausibility.

The direction of the associations and the magnitude of the point estimates were consistent across populations, type of study design and different contexts. Furthermore, results from prospective studies described a *temporal relationship* with PCB exposure preceding the onset of hypertension (Donat-Vargas et al., 2018; Raffetti et al., 2020), and a linear *dose-response relationship*, with the risk of hypertension increasing from low to high PCB concentration values.

Previous studies have investigated the biological mechanisms that might be involved in the association between DL-PCBs and hypertension. Blood pressure is regulated by a combination of vessel vascular resistance, neurotransmitters and hormonal control. Evidence from in vitro (Andersson et al., 2011;Eske et al., 2014; Helyar et al., 2009; Liu et al., 2015) and animal studies (Arsenescu et al., 2011;Dalton et al., 2001;Kopf et al., 2008; Lind et al., 2004) have shown that DL- PCBs induce chronic inflammation, dysfunction in the vascular endothelium and may disturb lipid metabolism (Dalton et al., 2001), and lead to the formation of atherosclerotic plaques (Hennig et al., 2007), through different aryl hydrocarbon receptor (AhR)-mediated pathways such as via expression of several inflammatory markers (Eske et al., 2014; Liu et al., 2015) or increasing cellular oxidative stress (Kopf et al., 2008). The DL- PCB congener 126 showed to stimulate the production of vasoconstriction factors, including cyclooxygenase (COX-2), prostaglandins and reactive oxygen species (ROS), as well as to inhibit the release of the vasodilator nitric oxide (NO) (Andersson et al., 2011; Helyar et al., 2009). Our findings are consistent with the literature on dioxins and other dioxin-like compounds such as dichlorodiphenyldichloroethylene, which share the same biological pathways as DL- PCBs – via AhR – to exert *analogue* effects (Donat-Vargas et al., 2018; Valera et al., 2013b). Moreover, given their toxic effects on both endocrine and central nervous systems, PCBs might dysregulate the pressure control also through an alteration of the sympathetic nervous system and the mineralocorticoid response (Fommei et al., 2017). Experimental and animal studies evaluating the potential effect of NDL-PCB on the cardiovascular system are still lacking. Likewise, the present meta-analysis could not show if there was an association between NDL-PCB and hypertension. PCB congeners are found in both food and human blood, showing very high correlations between all of them; so, it is very difficult, outside the lab, to isolate the effect of some congeners independently of the others. Thus, the positive association found for the NDL-PCB153 may be due to the high correlation with the other DL congeners or, by contrast, the lack of significant positive association for the other NDL congeners may be due to low statistical power. From the public health point of view, the interest is not the effect on human health of the 208 individual PCB congeners, but the total effect of their mixture.

Three aspects of the PCB-hypertension relationship should be taken into account: the intensity of exposure, the duration of exposure, and the sensitive lifetime period of exposure. In the last century, the world population has been constantly exposed to background environmental PCB contamination due to the global diffusion and persistence of these chemicals. PCBs accumulate in the lipid tissue, particularly in subcutaneous fat, are poorly metabolized and there is an equilibrium between their levels in tissues and blood.

Blood PCB concentration reflects accurately the body burden accumulated during a lifetime, which is approximately the product of the intensity by the duration of exposure over time and, therefore, is age dependent. Growing evidence shows that toxic exposures during early life years can determine a higher risk of developing chronic diseases than exposure in older ages. The Donat-Vargas et al. study (Donat-Vargas et al., 2018) showed an effect modification of birth year and age on PCBs-hypertension association, suggesting that those individuals that experienced an additional pre- and/or post-neonatal early-life exposure may be at elevated hypertension risk.

In human studies on PCB serum levels, handling lipid profiles is an important methodological issue. PCBs are predominantly carried in the lipid component of the blood, thus, lipid-standardized concentrations (i.e. the concentrations of serum POPs divided by total serum lipid content) have been widely used as a measure that reflects POP body burden better than wet-weight concentrations. However, lipid-standardized concentrations would underestimate the true associations between PCBs and certain outcomes if lipid levels were in the causal pathway. Various alternative approaches have been suggested, but there is no agreement on what the best method is (Schisterman et al., 2005; O'Brien et al., 2016). There is substantial disparity in the lipid adjustment approaches used across the studies included in this review: wet-weight concentrations ($n = 3$), standardization for total lipids ($n = 6$), adjustment for total lipids as a covariate ($n = 4$), and more than one approach ($n = 2$). Considering studies that used more than one lipid adjustment approach (Donat-Vargas et al., 2018; Raffetti et al., 2020), lipid-standardized compared to lipid-adjusted models showed a slightly lower magnitude of the estimates (10-15% reduction), suggesting a minor role of the lipid adjustment to estimate the true value. The "potential problem" with lipid standardization is that small errors in the lipid measurements may lead to bigger errors in the PCB estimates. However, as PCBs are usually categoried by tertiles or quartiles comparing extreme categories; no important differences in the risks estimated among the different approaches are identified.

The overall effect estimate should be interpreted in terms of the direction of the effect. To allow consistent comparisons, effect estimates were harmonized and transformed with the comparison

between top and bottom quartile according to established methods (Chene and Thompson, 1996). This scaling method assumes that the exposure variable is normally distributed, and a log-linear association exists between exposure and outcome. We also applied a dose-response meta-analysis showing a 2-fold increase in the risk of hypertension per 1000 ng PCB/g lipid. This approach allows different categorization of exposure and may be interpreted in terms of the magnitude of the effect.

The "low" level of evidence according to the GRADE evaluation depends on some limitations of the included studies. First, as most of the studies were cross-sectional (n = 10 out of 17), the possibility of reverse causation cannot be ruled out. However, it is biologically improbable that reverse causality could occur in the relationship of PCB serum levels with hypertension. Moreover, the magnitude as well as the direction of the effect are consistent between prospective and cross-sectional studies. Second, large differences in factors controlled for in data analysis were observed among the studies. Most of the studies adjusted for the main confounders such as age, sex, BMI, socioeconomic status and lifestyle factors, but not for diet and weight changes. Fatty fish is the primary source of PCBs in the general population, but it is also the primary source of polyunsaturated essential fatty acids that have a well-known protective role on hypertension risk. Along the same lines, weight loss might temporarily increase PCB blood levels (lipolysis of adipose tissue where PCBs accumulate) and reduce the risk of hypertension. Results from the meta-regression analysis highlight that adjustment for specific confounders did not impact the overall effect size, supporting marginal role of confounding adjustment on heterogeneity among studies.

Residual confounding could have led to a bias estimation of the true association between PCB levels and hypertension. However, we performed a sensitivity analysis to assess confounding. With a pooled OR of hypertension of 1.70 for total PCBs, an unmeasured confounder associated with both the outcome and the exposure by a risk ratio of 1.93 each could explain away the estimate; to move the confidence interval to include the null, a confounder that was associated with PCB exposure and hypertension by a risk ratio of 1.51 each could do so, but weaker confounding could not.

PCB contamination is still and will probably remain a global environmental issue in the near future. For a more comprehensive and accurate evaluation of its health impact, additional prospective cohort studies should be performed in populations using repeated measures over time. Simultaneously, further experimental studies to disentangle mechanisms of PCBs causing hypertension are also warranted.

In conclusion, results from this meta-analysis suggest that exposure to PCBs, mainly DL-PCBs, may be positively associated with risk of hypertension. Current human evidence linking total PCBs and DL-PCBs to hypertension is substantial and consistent, although more longitudinal studies overcoming the limitations of the previous ones are needed in order to establish a causal association.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2020.126984.

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