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Review article

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ABSTRACT

Background: Endometriosis is a gynaecological disease characterized by the presence of ectopic endometrial tissue that affects women during their reproductive years, having a strong impact on their lives, fertility and healthcare costs. The aetiology remains largely unknown, but current evidence suggests that it is multi-causal and oestrogen-dependent. Many epidemiologic studies have explored associations between organochlorine chemicals (OCCs) and endometriosis, but the findings are inconsistent.

Objectives: A systematic review (SR) and meta-analysis were conducted to gather and synthesize all the available evidence from human epidemiological studies about the associations between OCCs and endometriosis.

Data sources: The searches were conducted in PubMed and Web of Science in June 2016 with a final follow-up in August 2018.

Study eligibility criteria: Only human epidemiological studies were considered, independent of participant age, body mass index or life-stage. Studies reporting individual measures of exposure to OCCs were included, considering but not limited to polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), or organochlorine pesticides (OCPs). The primary health outcome was presence of endometriosis, including all sub-types. Eligibility criteria excluded articles not written in English, conference papers, reviews and studies with overlapping information.

Study appraisal and synthesis methods: A SR protocol pre-registered at PROSPERO was applied in duplicate to gather and extract all eligible original papers from PUBMED and Web of Science databases. Odds ratios were pooled using the inverse variance method for random effects meta-analysis for each group of OCCs. Risk of bias was assessed using the National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT) Risk of Bias Rating Tool for Human and Animal Studies adapted to the review question. The confidence in the body of evidence and related level of evidence was measured by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) based NTP/OHAT framework. The results were structured and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: Of the 51 studies retained for the full-text screening, 17 provided effect sizes and metrics sufficient for pooling estimates through meta-analysis. The overall odds ratios and 95% confidence intervals were 1.65 (1.14; 2.39) for dioxins (n = 10), 1.70 (1.20; 2.39) for PCBs (n = 9), and 1.23 (1.13; 1.36) for OCPs (n = 5). Despite being statistically significant, these estimates should be considered with caution given the notable heterogeneity and small estimated effect size. Misclassification of exposure, due to varying laboratory detection rate

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capabilities, and disease status, due to varying definitions of endometriosis, were identified as major sources of uncertainty.

Limitations, conclusions, and implications of key findings: The level of evidence was considered to be "moderate" with "serious" risk of bias according the NTP/OHAT criteria, supporting the need for further well-designed epidemiological research to fill lingering data gaps. Given the complexity of endometriosis and lack of known biomarkers suitable for population-based research, carefully designed observational studies play an important role in better understanding the aetiology of endometriosis, as will evolving mixture modeling approaches capable of handling various environmental chemical exposures. Attention to critical windows of exposure will shed further light on the possible developmental origin of endometriosis. Considering the high economic and societal cost associated with endometriosis, further research on this field is urged.

Systematic review registration number: CRD42018080956

1. Introduction

Endometriosis is a gynaecological disease characterized by the presence of endometrial glands and stroma outside the uterus and may present multiple non-specific symptoms such as chronic pelvic pain, dysmenorrhea, dyspareunia, dyschesia, and infertility (Eskenazi et al., 2002; Giudice, 2010; Sampson, 1927). The population prevalence is unknown but is believed to be around 5–15% for women of reproductive age, strongly impacting their lives, fertility and healthcare costs (Buck Louis et al., 2011; Parazzini et al., 2017). Three sub-types of endometriosis have been identified histologically: peritoneal endometriosis, ovarian endometrioma (OMA) and deep endometriosis (DE) (Nisolle and Donnez, 1997; Zondervan et al., 2002), each associated with various individual genetic susceptibilities (Borghese et al., 2015).

Although the aetiology remains largely unknown, current evidence suggests that endometriosis is a multi-causal, oestrogen-dependent disease and is responsive to the suppression of ovarian hormonal production (Giudice, 2010). In addition to retrograde menstruation, which has been the most frequently proposed mechanical factor to explain the ectopic dissemination and implantation of endometrial cells (Sampson, 1927), a list of other factors has been suggested to account for the proliferation and adhesion processes, including dysfunctional immune responses, pro-inflammatory milieus, genetic predispositions, as well as epigenetics (Baranov et al., 2015; de Ziegler et al., 2010; Greene et al., 2016). During the last few decades, the evidence supporting the association between exposure to chemicals with endocrine disruption potential and hormone-related gynaecological diseases has steadily increased (Caserta et al., 2008; Gore et al., 2015; Smarr et al., 2016). Some primate and rodent studies suggest that exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is associated with endometriosis, but such associations are inconsistent in human studies and for other organochlorine exposures (Bruner-Tran and Osteen, 2010; Cummings et al., 1999; Cummings et al., 1996; Rier et al., 1993; Smarr et al., 2016). Inconsistency of epidemiological studies is likely due to methodological and population heterogeneity (Heilier et al., 2008; Smarr et al., 2016) and laboratory differences in quantifying and reporting chemical concentrations (Louis, 2012). The disruption of oestrogen and progesterone action related to the matrix metalloproteinase system regulation has been proposed as a putative mechanism underlying the associations between environmental chemicals and endometriosis invasiveness (Bruner-Tran and Osteen, 2010).

Systematic-review principles applied to environmental epidemiology have emerged as a novel discipline to ensure objectivity, rigor, transparency and reproducibility in evidence-based evaluations for questions related to the health-environment interface (Rooney et al., 2014). Risk of bias tools, specifically designed for environmental epidemiology, substantially improve the process of rating the confidence and level of evidence (Cano-Sancho et al., 2017; Morgan et al., 2016). During the last decade, different guidelines and systematic-review frameworks have been proposed (e.g. Navigation Guide, NTP/OHAT), allowing a more extended implementation by the scientific community and risk assessors (Beronius and Vandenberg, 2015; Rooney et al., 2014).

Considering the divergence of published studies in the field, the overall objective of the present work is to apply a systematic review approach to gather all the evidence available from human epidemiological studies on the association between organochlorine chemicals (OCCs) and endometriosis. We aim to identify major sources of methodological heterogeneity that may help in future study design. For the first time, the level of evidence will be established using a systematic and transparent approach.

2. Materials and methods

2.1. Review framework

This systematic-review with meta-analysis was conducted following the guidelines established in the National Toxicology Program Office of Health Assessment and Translation's (NTP/OHAT) Handbook for Conducting a Literature-Based Health Assessment, which provides a standardized methodology to implement the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health assessments (NTP/OHAT, 2015a; Rooney et al., 2014). On that basis, we developed a protocol iteratively improved to efficiently answer the study question (Supplemental material Section 1). The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018080956 on 03 January 2018. Protocol modifications were conducted in August 2018 to extend the search strings ensuring a more comprehensive search and also to incorporate a new member in the team of reviewers. The review panel came forth from an international collaboration of research groups from France, Belgium, United States and Spain, which focused on the environmental risks affecting female reproductive health as a core partnership. Screening, data extraction, and data synthesis were performed in duplicate by two reviewers (GCS and SP). Assessment of risk of bias was also performed in duplicate by two independent teams (CGS, JM and EA) with supportive instructions and without prior consensus on risk of bias classification to avoid prejudgments and misclassifications. Discrepancies were discussed with external expert advisors solicited for their critical analysis and consolidated expertise in the field. The results were structured and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines for Meta-analyses and Systematic reviews of Observational Studies (Stroup et al., 2000).

2.2. Study question

The search question was: "Does the current human epidemiological evidence support a potential role of organochlorine environmental pollutants in the pathogenesis of endometriosis?"

2.3. Search strategy

The search terms were extracted from published reviews and primary studies identified in a preliminary search. No filters were implemented during the search to limit publication date. The search string was initially built by combining major keywords representative of the Exposure and Outcome components identified in the PECO statement, i.e. ("endocrine-disrupting chemicals" or pesticide* or "Polychlorinated Biphenyl*" or "Halogenated Diphenyl Ether*" or "Polybrominated Biphenyl*" or "organochlorine pollutants" or dioxin* or "flame retardant*" or "persistent organic pollutant*") AND endomet*. The search string was applied to the electronic literature databases MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) and WEB of SCIENCE (https://apps.webofknowledge.com), in June 2016, and follow-up searches were performed June 2017 and December 2017. An extended search string including further synonyms and MESH terms (Supplemental Table S1) was run August 2018.

2.4. Selection of studies and eligibility criteria

Eligibility criteria for the key PECO elements (population, exposure, comparators and outcomes) were defined and summarized in the PECO statement (Table 1).

Relevant exposure was limited to individual measures of OCCs, their metabolites and combinations, considering all PCDD/Fs, PCBs and OCPs such as dichlorodiphenyltrichloroethane (DDT), aldrin, chlordane, dieldrin, endrine, heptachlor, hexaclorobenzene, mirex, toxophene, chlordecone, alpha hexachlorocyclohexane (HCH), γ-HCH, pentachlorobenzene or endosulfans. Primary outcome was endometriosis, including all sub-types and diagnostic methods (e.g. laparoscopy, ultrasound, medical history records and self-reported questionnaires). Exclusion criteria accounted for: a) articles not written in English, b) conference papers and reviews, c) studies with information overlapping another publication (unless the overlapping study provided additional information useful for sensitivity analysis), and d) studies without quantitative exposures. We considered epidemiological studies as the unit of analysis, so study dates and participant numbers were used to identify multiple records of the same study. In the event of overlapping studies, we selected the most recent and/or most comprehensive manuscript.

Study selection was a two-part process, wherein an initial screening of title and abstract was performed, retaining all studies that met the eligibility criteria or did not provide enough information to decide for a second screening based on the full-text.

2.5. Data extraction

Data from included records were extracted using a predefined form, considering the following items: authors, publication year, funding source, conflicts of interest, study population name/description, dates of study and sampling time frame, geography (country, region), demographics (age, race), number of participants (cases/controls), recruitment strategy, inclusion/exclusion criteria, study design, health outcome, diagnostic or methods used to measure health outcome, confounding or modifying factors, substance name, exposure assessment (biological matrix), units, methodological details for exposure assessment, statistical methods, exposure levels, and statistical findings.

Relative risk was considered for effect size (e.g. odds ratios or risk ratios). For studies with overlapping information, the criteria for selecting effect size estimates were as follows: the publication reporting "the most representative population" AND/OR "more comprehensive publication" AND/OR "latest publication date" was retained. Data from plots were extracted using the WebPlotDigitizer (version 4.0 PLOTCON 2017 - Oakland, CA), a semi-automated web-based tool.

2.6. Data synthesis and meta-analysis

Odds ratios and risk ratios were pooled using the inverse variance method for random effects meta-analysis (DerSimonian and Laird, 1986) for each group of OCCs (dioxins/furans, PCBs, pesticides) whenever the metrics allowed for combination. We considered the high versus low percentile approach for studies with categorical exposures. Between-study variance in the random-effects meta-analysis was represented by tau-squared (τ^2). Heterogeneity was assessed with the I^2 statistic, which quantifies the heterogeneity and degree of inconsistency among studies. The results were interpreted using Cochrane criteria: I^2 between 0% and 40% percent: heterogeneity might not be important, between 30% and 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. Potential small study bias was evaluated by funnel plots and Egger's test (Harbord et al., 2006). Publication bias was addressed with the "trim-and-fill" method, which trims asymmetrical studies to estimate the true centre of the funnel plot, then fills the assumed missing studies (mirror image), allowing the estimation of adjusted overall confidence intervals (Duval and Tweedie, 2000). Given the tendency of the trim-and-fill method to underperform when between-study heterogeneity is moderate to high (likely in observational studies), we considered adjustments to evaluate the consistency and robustness of the estimates (Peters et al., 2007). The influence of each individual study was investigated by omitting one study at a time, and re-calculating summary estimates (leave-one-out method). Meta-analysis was performed in R (v.3.3.1.) using the 'meta' and 'metafor' packages. Studies not eligible for meta-analysis were evaluated and synthesized narratively with focus on the direction and magnitude of effects to evaluate potential selection bias of meta-analysis.

2.7. Assessment of risk of bias

Risk of bias was evaluated for the main body of evidence (studies included in the meta-analysis) to support the final conclusions. The NTP/OHAT Risk of Bias Rating Tool for Human and Animal Studies' was adapted to the review question and used to classify each individual

Table 1
PECO statement.

Population	Exposure	Comparators	Outcomes
All ages, body mass index, and/or life-stage at exposure or outcome assessment will be included.	Exposure to organochlorine chemicals (OCCs) and derivatives or isoforms based on administered dose or concentrations, environmental measures or indirect measures. The exposure must be measured individually using direct validated biomonitoring methods including activity-based assays like CALUX. All biological matrices will be considered.	Reference groups of population exposed at lower levels of OCCs than the rest of population groups.	Primary outcome: endometriosis, including different sub-types and severity stages. Secondary outcome: not considered.

study in a tier (1 to 3) for risk of bias (Rooney et al., 2014; NTP/OHAT, 2015a,b). This tiered approach highlights several key elements of bias relevant to each individual study to establish classification criteria. For observational human studies, key elements include exposure assessment, outcome assessment, and confounding/selection. The following bias domains and questions were considered:

1. *Confounding Bias [Key element]* Did the study design or analysis account for important confounding and modifying variables?
2. *Attrition/Exclusion Bias.* Were outcome data incomplete due to attrition or exclusion from analysis?
3. *Detection Bias [Key element].* Can we be confident in the exposure characterization?
4. *Detection Bias [Key element].* Can we be confident in the outcome assessment?
5. *Selective Reporting Bias.* Were all measured outcomes reported?
6. *Selection bias.* Did selection of study participants result in appropriate comparison groups?
7. *Conflict of Interest.* Was the study free of support from a company, study author, or other entity having a financial interest in any of the treatments studied?

Specific details and instructions for each question are expanded upon in the protocol (Supplemental material Appendix 1). Risk of bias was evaluated in duplicate by GCS and JM, after piloting the instructions in a study sample. Disagreements were discussed to reach consensus, and external expert advice was sought when required. The overall body of evidence was classified as having "Not likely", "Serious" or "Very serious" risk of bias, based on the classification tiers for most of the evidence (Details at Supplemental material Section 1.4).

2.8. Confidence in the body of evidence and level of evidence

Confidence in the body of evidence and related level of evidence was evaluated using the NTP/OHAT framework (Rooney et al., 2014), based on the GRADE approach (Morgan et al., 2016; Schunemann et al., 2011). The framework describes criteria for assessing both the quality and strength of research evidence reflecting the Bradford Hill criteria for causation. In brief, the body of evidence is given an initial classification based on the ability of the study design to address causality, with observational studies receiving moderate to low confidence due to the lack of control in the allocation of exposures. Subsequently, the body of evidence is subjected to a critical evaluation of factors that may downgrade the initial confidence rating (i.e. risk of bias, unexplained inconsistency, indirectness, imprecision and publication bias) or factors that may upgrade it (i.e. large magnitude of effects, dose-response, residual confounding, cross-population/study consistency). The final confidence rating will fall in one of the four main descriptors: "high", "moderate", "low" or "very low" confidence (Rooney et al., 2014).

This final "confidence in the body of evidence" is subsequently translated into a "level of evidence for the health effect." In the absence of support in the literature for a health effect, the level of evidence will be considered "low". If the overall study results support the presence of a health effect, the strength of this association will be classified as either "high", "moderate" or "low" (Details are provided in the Supplemental material Section 1.4.)

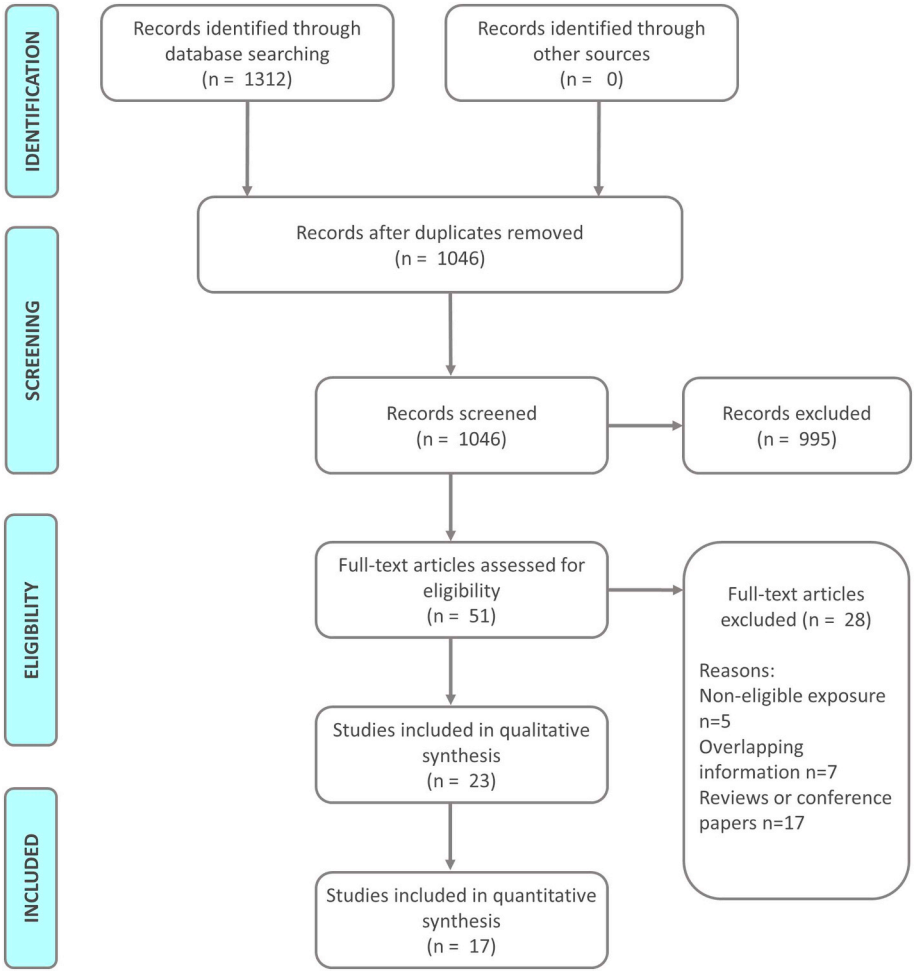

Fig. 1. PRISMA flow diagram representing the identification, screening and selection process performed in the current systematic review and meta-analysis.

Table 2

Study characteristics of those studies included in the meta-analysis. Abbreviations: AGE-M, age at menarche; AT, adipose tissue; BE, Belgium; BFRs; brominated flame retardants; BMI, body mass index; BRF|PAR, breastfeeding conditional on parity; Ca: Cases; CAF, caffeine consumption; Co: Controls; DE, deep endometriosis; DLC, dioxin-like compounds; ENDO, total endometriosis; EMP, employment status; ETH, ethnicity; FH, familial history; GRV, gravidity; HCC, hospital-based case-control; IL, Israel; IT, Italy; INC, income; INS, health insurance status; JP; Japan; LAP, diagnose based on laparoscopy; LW, units in lipid weight; MC, menstrual cycle; MCD, menstrual cycle dysregulation; MEN, menarche status; MER, menstrual regularity; MR, medical record; MRI, magnetic resonance imaging; NCC, nested-case-control; NS, no specified; OCs, oral contraceptives; OCPs, organochlorinated pesticides; OMA, ovarian endometrioma; PAR, parity; PBB, polybrominated biphenyls; PBDE, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCC, population-based case-control; PES, phthalates esters; Ppt, parts per trillion; RC, retrospective cohort; Sev ASRM, Revised American Society for Reproductive Medicine classification; Sev rAFS, Severity of endometriosis was staged according to the American Fertility Society's revised definition; SR, self-reported; RecLAP, recorded diagnose based on laparoscopy; RB, random biopsies; SMO, smoking; SP, Spain; TAM, tampon use; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, dioxin toxic equivalents; US, United States; WL, weight loss; WM, weight modification; WWA, units in wet basis and total lipid adjusted as covariates; ¥, control group infertile women.

Reference	Cohort name	Dates[a]	Geo[b]	Study design	Age[c] range	N[d]	Outcome assessment		Confounders[e]	Exposure assessment		
					(mean ± SD)	(Ca/Co)	Outcome	Diagnose		Chemicals	Matrix	Units
Buck Louis et al., 2012	ENDO	07-09	US	HCC PCC	18–44 (32–34 ± 8)	190/28314/113	ENDO (Sev ASRM)	Ca: LAP + Hist/MRI Co: LAP/MRI	Age, BRF|PAR, BMI, cotinine, TSL	PCBs, OCPs, PBDEs	AT Serum	WWA
Cai et al., 2011	NS	04-09	JP	HCC (¥)	(36.4 ± 5.9)	10/7	ENDO (Sev ASRM)	Ca: LAP Co: LAP	Matched: AGE, BMI, PAR, SMO	Dioxins, PCBs	Serum	TEQ-LW
Cooney et al., 2010	NS	99-00	US	HCC	18–40 (31–32 ± 5)	32/82	ENDO (Sev rAFS)	Ca: LAP Co: LAP	SMO, TSL, OCPs	OCPs	Serum	WWA
Eskenazi et al., 2002	SWHS	76-80	IT	NCC	Exposure ≤ 30	19/277 (19/582)	Incident ENDO	Ca: MR (LAP) Co1: MR (LAP) Co2: Uncertain	Age [EDU, SMO,ALC, EMP, BMI, GRAV, OC, MEN]	TCDD	Serum	LW
Heilier et al., 2005	NS	NS	BE	HCC	30–32 ± 7	50/21	ENDO DE	Ca: LAP + Hist Co: No symptoms	Age, BMI, AGE-M, OCs, FH, MCD	Dioxins, PCBs	Fasting serum	LW/TEQ–LW
Hoffman et al., 2007	MFHS	76-81	US	RC	Exposure 22 ± 14 Diagnose 45 ± 14	79/964	Incident ENDO	Ca: SR/MR Co: No symptoms	BMI, Men; SMO [AGE, EDU, INC, INS]	PBB153, Aroclor	Serum	WW
Louis et al., 2005	NS	99-00	US	HCC	18–40	32/52	ENDO (Sev rAFS)	Ca: LAP Co: LAP	GRV, PAR, BMI, SMO.	PCBs	Serum	WWA
Martinez-Zamora et al., 2015	NS	NS	SP	HCC	18–40 (31–32 ± 4)	30/30	DE	Ca: LAP + Hist Co: LAP	AGE, SMO, BMI	Dioxins, PCBs	Fasting AT	LW
Mayani et al., 1997	NS	91-95	IL	HCC (¥)	(34 ± 6)	44/35	ENDO (Sev AFS)	Ca: LAP Co: LAP	ETH	TCDD	Blood	ppt
Niskar et al., 2009	NS	NS	US	HCC	23–45	64/60	ENDO (Sev ASRM)	Ca: LAP Co: LAP	AGE, GRV, INC, SMO, TAM	Dioxins, PCBs, DDE	Serum	TEQs LW WW
Pauwels et al., 2001	NS	96-98	BE	HCC (¥)	24–42 (31–32)	42/27	ENDO (Sev rAFS)	Ca: LAP Co: LAP	AGE, BMI, MCD, SMO, ALC, CAF;	PCBs	Blood	CALUX TEQ-LW
Ploteau et al., 2017	ENDOTOX	13-14	FR	HCC	18–45 (33–37 ± 5–6)	44/49	DE – OMA (Sev rAFS)	Ca: LAP Co: No symptoms	BMI, AGE [BRF|PAR, GRV]	Dioxins, PCBs, OCPs, BFRs	AT/Serum	LW
Porpora et al., 2009	NS	02-05	IT	HCC	18–45	80/80	ENDO (Sev ASRM)	Ca: LAP + Hist Co: LAP	AGE, BMI, SMO, WM	PCBs	Serum	CALUX TEQ-LW
Simsa et al., 2010	NS	01-05	BE	HCC (¥)	20–46 (31–32)	96/106	ENDO (Sev rAFS)	Ca: LAP + Hist Co: LAP	AGE	DLC	Plasma	CALUX-TEQ/LW
Tsukino et al., 2005	NS	99-00	JP	HCC (¥)	20–45 (32–33 ± 3–4)	58/81	ENDO (Sev rAFS)	Ca: LAP Co: LAP	MER, MC	Dioxins, PCBs	Fasting serum	LW
Trabert et al., 2010	WREN	96-01	US	PCC	18–49	251/538	ENDO OMA/PE	Ca: MR/SR Co: MR/SR No symptoms	ALC, INC, DDE, TSL	PCBs	Serum	WWA
Upson et al., 2013	WREN	96-01	US	PCC	18–49	248/538	ENDO	Ca: MR/SR Co: MR/SR No symptoms	ALC, INC, DDE, TSL [BRF|PAR[f]]	OCPs	Serum	WWA

[a] Enrolment dates.
[b] Geo, geographical region/country.
[c] Age represented as range at inclusion. Mean ranges cases-controls ± standard deviation in parentheses.
[d] N, number of participants. Ca: cases/Co: controls.
[e] Confounders in brackets means the variables were considered in exploratory analysis.
[f] Composite variable: nulliparous women, parous women with lifetime history of breastfeeding ≤6 months, parous women with lifetime history of breastfeeding > 6 months.

3. Results

3.1. Study acquisition

The study selection is summarized in Fig. 1. Of the 51 studies retained for the full-text screening, 23 studies were eligible for data extraction and synthesis, 17 of which provided effect sizes and metrics for estimate-pooling in meta-analysis. The remaining 6 studies were synthesized narratively. Manual searches did not contribute additional manuscripts to be included.

3.2. Study characteristics

The characteristics of included studies are summarized in Table 2, and all extracted data are available in Supplemental material Section 1.3 (Extraction data forms). Studies excluded from meta-analysis and their characteristics are summarized in Table S10. To maintain scientific relevance, we designated the main body of evidence as studies included in the meta-analysis, and provided a brief description and narrative synthesis for the remaining studies.

Studies included in the meta-analysis comprised three studies performed with a two population-base case-control study (WREN and ENDO) based in US (Buck Louis et al., 2012; Trabert et al., 2010; Upson et al., 2013), one nested case-control study based in the Seveso area following dioxin exposure (Eskenazi et al., 2002), and one retrospective cohort study in Michigan following a PBB incident (Hoffman et al., 2007). The remaining twelve studies were hospital-based case-control studies (Cai et al., 2011; Cooney et al., 2010; Heilier et al., 2005; Louis et al., 2005; Martinez-Zamora et al., 2015; Mayani et al., 1997; Niskar et al., 2009; Pauwels et al., 2001; Ploteau et al., 2017; Porpora et al., 2009; Simsa et al., 2010; Tsukino et al., 2005). Taking into account that two records focused on the same (WREN) population (Trabert et al., 2010; Upson et al., 2013), this meta-analysis covered a total of 3331 individuals and 1135 cases of endometriosis. Study populations were generally modest in size, with 12 studies including < 200 individuals, and 5 studies exceeding 500 participants. Seven out of the 17 studies were conducted in the United States, two in Japan, two in Italy, three in Belgium, one in Israel, one in Spain, and one in France. Outcome ascertainment based on medical records and/or self-report was considered in 4 studies, whereas the remainder of studies relied upon laparoscopically-confirmed disease. Laparoscopic-confirmation of no endometriosis in control women was reported by 11 studies.

Concerning the class of organochlorines, we retained for the meta-analysis 10 studies reporting ORs or RRs for dioxins, 9 for PCBs and 5 for OCPs. Seven studies provided results of different groups simultaneously. As part of the eligibility criteria, we included only studies that used individual internal exposure data, determined in most cases by gas chromatography coupled to high resolution mass spectrometry detection with some minor exceptions (2 studies used the CALUX assay, based on the binding affinity of dioxin-like compounds to the aryl hydrocarbon receptor). The majority of studies used serum or plasma as biological matrix to analyse the proxy internal levels of organochlorines; three studies directly analysed the compounds on adipose tissue and one in peritoneal fluid. Circulating levels of OCCs were mostly expressed on lipid basis (i.e. ratio of chemicals in serum per concentration of total serum lipids), although 5 studies modelled the organochlorines in a fresh weight basis (i.e. ratio of chemicals in serum per mL of serum) adjusting by the serum lipids as covariates, and one study did not analyse serum lipid levels and only provided the results through models with raw values (fresh weight basis).

3.3. Meta-analysis: endometriosis and dioxins

Ten studies reported risk measures for endometriosis in relation to exposure to dioxins or dioxin-like activity. We combined studies reporting the individual TCDD activity or the activity of a sum of dioxins, expressed as toxic equivalent factors (TEFs). Results of the meta-analysis are shown in a forest plot in Fig. 2. The summary risk estimate using the random effect model for the inverse variance method was log OR (95% CI) of 0.50 (0.13; 0.87) back-transformed to an OR of 1.65 (1.14; 2.39), with a substantial heterogeneity (I^2 = 72%). We further stratified this analysis to explore sources of heterogeneity like study design variables (i.e. analytical method, geographical region, outcome definition, exposure biological matrix or risk of bias), see Table 3. Although this stratification did not reveal significant differences on the meta-estimates, there was a decrease in heterogeneity in studies based in Europe, studies based on exposure markers determined in adipose tissue, and studies using the CALUX assay to determine dioxin-like activity. The asymmetry of the funnel plot (Fig. 3) revealed possibility of publication bias (Egger's test, p = 0.007), which we adjusted by using the trim-and-fill method for the four missing studies, decreasing meta-estimates to 1.18 (0.81; 1.7). The influence analysis, leaving one study out at the time, did not reveal major changes triggered by individual studies (Supplemental material Section 2).

3.4. Meta-analysis: endometriosis and polychlorinated biphenyls

Nine studies reported risk measures of endometriosis in relation to PCB exposures. The pooled estimate comparing high vs low percentiles of PCBs was a log OR (95% CI) of 0.53 (0.18; 0.57) corresponding to an OR of 1.70 (1.20; 2.39) (Fig. 4). The heterogeneity was considerable according the Cochrane criteria (I^2 = 78%), and the funnel plot also

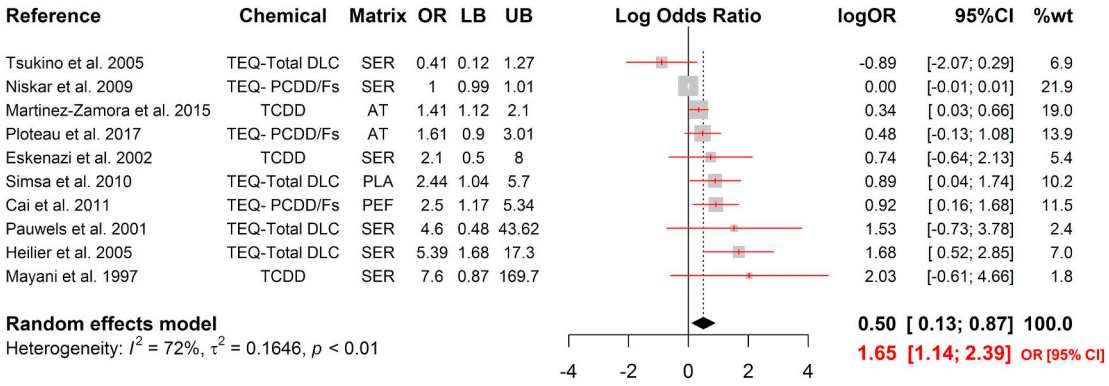

Fig. 2. Forest plot of the risk estimates, log odds ratios (OR) and 95% confidence intervals (CI) from the studies included in the meta-analysis of the associations between exposure to dioxins and endometriosis (n = 10). Abbreviations: AT, adipose tissue; DLC, dioxin-like compounds; LB, confidence interval lower bound; PEF, peritoneal fluid; PLA, plasma; SER, serum; UB, confidence interval upper bound, %wt, percentage of study weight in the meta-analysis. Meta-estimates are represented with a black diamond, 95% confidence intervals with a red line and the grey box around the log OR represents the relative weight of each study in the meta-analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Stratification analysis of meta-estimates for the studies on dioxins, polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs). The table summarizes the odds ratio (OR) and 95% confidence intervals (95% CI) for sub-group meta-estimates. Heterogeneity is measured with I^2 statistic. N indicates the number of studies in each sub-group.

	Dioxins				Polychlorinated biphenyls				Organochlorine pesticides			
	N	OR	95%CI	I^2 (%)	N	OR	95%CI	I^2 (%)	N	OR	95%CI	I^2 (%)
Analytical method												
Calux assay	2	2.64	(1.19; 5.85)	0								
Mass spectrometry	8	1.52	(1.03; 2.23)	73								
Geographical region[a]												
Europe	6	1.86	(1.30; 2.67)	25	4	2.35	(1.44; 3.82)	63				
Other (US)	4	1.25	(0.58; 2.68)	70	5	1.08	(0.93; 1.26)	7				
Study type												
Population-based	1	2.10	(0.53; 8.40)		3	1.14	(0.88; 1.48)	32	1	1.27	(1.01; 1.59)	
Operative case-control	9	1.63	(1.11; 2.39)	74	6	2.08	(1.40; 3.08)	48	4	2.39	(1.47; 3.91)	36
Outcome												
Deep endometriosis	3	1.92	(1.03; 3.58)	65	2	1.76	(1.35; 2.28)	0				
Total endometriosis	8	1.90	(1.03; 3.52)	72	7	1.73	(1.08; 2.76)	72				
Matrix analysed												
Adipose tissue	2	1.45	(1.10; 1.92)	0	3	1.42	(0.91; 2.21)	87	2	2.44	(0.60; 9.92)	89
Serum	6	1.75	(0.77 3.97)	67	6	2.02	(1.20; 3.40)	52	3	1.88	(1.26; 2.81)	0
Peritoneal fluid	1	2.50	(1.17; 5.34)									
Plasma	1	2.44	(1.04; 5.71)									
Exposure contrast												
Continuous	7	1.68	(1.13; 2.51)	75	4	1.51	(0.89; 2.57)	82	3	2.32	(0.92; 5.85)	80
Categorical	3	1.46	(0.36; 5.90)	71	5	1.86	(1.21; 2.86)	50	2	1.81	(1.17; 2.81)	0
Risk of bias												
Tier 2	8	2.09	(1.25; 3.50)	43	4	1.57	(1.18; 2.09)	0	3	2.59	(1.28; 5.21)	57
Tier 1	2	1.14	(0.82; 1.59)	78	5	1.78	(1.02; 3.12)	85	2	1.40	(0.94; 2.10)	29
Infertility among control												
Combined	5	1.47	(1.00; 2.18)	75								
Only infertile control	5	1.92	(0.83; 4.46)	55								
Laparoscopy among controls												
Laparoscopy	8	1.46	(0.99; 2.15)	68	5	1.78	(1.02; 3.13)	85	3	1.47	(1.03; 2.08)	20
No laparoscopy	2	2.65	(0.83; 8.49)	69	4	1.57	(1.18; 2.09)	0	2	2.84	(0.93; 8.68)	79

[a] Other geographical regions limit to United States (US) for PCBs and OCPs.

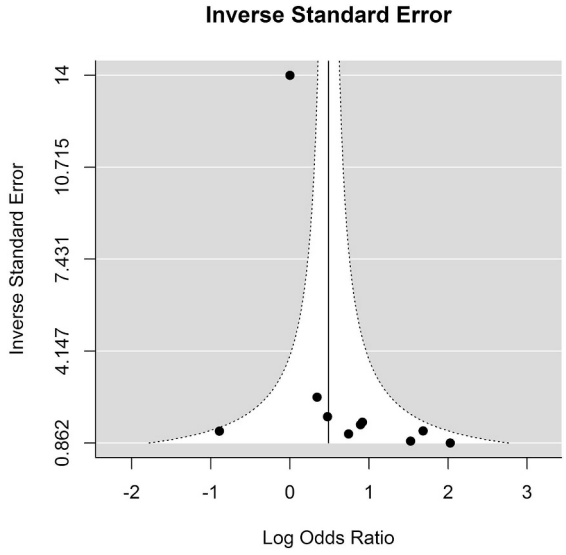

Fig. 3. Funnel plot of the risk estimates from the studies included in the meta-analysis of the associations between dioxins and endometriosis.

revealed an asymmetric trend (Fig. 5) that was addressed with the trim-and-fill method for the five missing studies. The meta-estimate adjusted for the small-studies effect was an OR of 1.0 (0.80; 1.51). The influence analysis did not reveal any studies with major effects on the pooled estimates (Supplemental material Section 2). Stratification analysis showed larger meta-estimates from European studies and operative case-control study designs, which are coincident (Table 3). Both geographical region and study type were thus identified as relevant sources of heterogeneity.

3.5. Meta-analysis: endometriosis and organochlorinated pesticides

Five studies reported risk measures for endometriosis and OCP exposures. Considering most studies provided individual estimates for each type of OCP, we performed the meta-analysis under two different scenarios. In the first ('worst case') scenario the individual OCP that exhibited the highest risk estimate from each study was selected for meta-analysis. In the second scenario, all estimates for all OCPs from the different studies were pooled together through a random effect model. The results are summarized in forest plots in Figs. 6 and 7 for scenarios 1 and 2, respectively. The pooled log OR (95% CI) for the first scenario was 0.68 (0.22; 1.14) corresponding to an OR of 1.97 (1.25; 3.13) and for the second, a log OR of 0.21 (0.12; 0.31), with an OR of 1.23 (1.13; 1.36). Heterogeneity was considered substantial (I^2 = 65%) in the first case and moderate (I^2 = 50%) in the second. The funnel plots from the first (Fig. 8A) and second (Fig. 8B) scenarios exhibited an asymmetric trend, confirmed by a statistically significant Egger's test for the second scenario ($p < 0.01$). The trimmed model adjusted by imputing 3 missing studies and resulted in a random-effects model OR of 1.37 (0.88; 2.14) for the first scenario and 1.09 (0.98; 1.21) for the second, after the imputation of 14 studies. When we stratified the analysis from the second scenario for OCPs subtypes, we found substantial differences in terms of magnitude and direction of the effect for the group of DDTs with OR 0.95 (0.83; 1.09). Stratification also showed larger meta-estimates for studies without laparoscopically confirmed controls (Table 3). Heterogeneity was substantially lower for DDTs, HCH and other pesticides including Mirex, aldrin or dieldrin (Supplemental material Section 2).

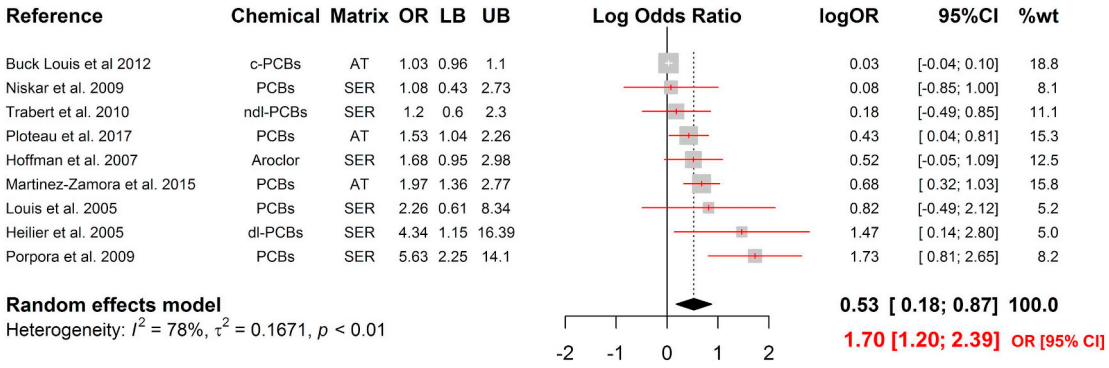

Fig. 4. Forest plot of the risk estimates, log odds ratios (OR) and 95% confidence intervals (CI) from the studies included in the meta-analysis of the associations between exposure to polychlorinated biphenyls (PCBs) and endometriosis (n = 9). Abbreviations: AT, adipose tissue; c-PCBs, coplanar PCBs; dl-PCBs, dioxin-like PCBs; ndl-PCBs, non-dioxin-like PCBs; %wt, percentage of study weight in the meta-analysis. Meta-estimates are represented with a black diamond, 95% confidence intervals with a red line and the grey box around the log OR represents the relative weight of each study in the meta-analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

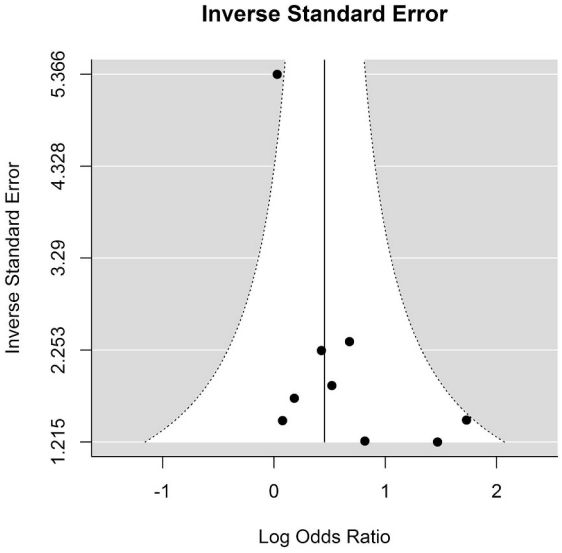

Fig. 5. Funnel plot of the risk estimates from the studies included in the meta-analysis of the associations between polychlorinated biphenyls and endometriosis.

3.6. Risk of bias

Results from the risk of bias assessment are summarized in Table 4 and the rationale for each evaluation can be found in the Supplemental material (Section 2.1. Risk of bias results). The NTP/OHAT risk of bias tool classifies each study by key domains of bias. Confounding bias and detection bias (both exposure and outcome assessment) were considered the most pertinent domains for this review question. Attrition/exclusion bias, conflict of interest and selective reporting bias did not contribute as much influence in the risk of bias analysis. Most study authors declared receiving public funding and/or having no conflict of interest, and only three study were classified as "probably high" for conflict of interest due to lack of reporting financial sources or other potential conflicts of interest (Cai et al., 2011; Mayani et al., 1997; Tsukino et al., 2005). Overall, we ruled out financial influence from private sectors. Confounding bias was identified at "probably high" in six studies where statistical models did not include key confounding variables like age and body mass index (BMI) which may be directly related to exposure levels of OCCs and endometriosis. Due to the uncertain relationship between parity and breastfeeding with endometriosis, we did not consider them as key confounding variables. With one exception, all studies were classified as "probably low" risk of detection bias concerning the confidence with the exposure assessment method, reporting reliable and accurate methods for detection of OCCs. As detailed in the "Study characteristics" section, the use of biomarker-based individual internal levels strengthens the reliability of the measurements. One study failed to assess serum lipids (Hoffman et al., 2007), required for normalization and/or covariate adjustment of lipophilic chemicals. Five studies were classified as "probably high" risk of detection bias of outcomes because the disease definition were based on self-reports, medical records and/or without clinical confirmation of control groups. Eight hospital-based case-control studies were classified as "probably high" risk of selection bias because the limitation of the setting to recruit controls with exposure profiles representative of the general population. Five studies considered only infertile women as control population, a condition that has already associated with higher levels of certain environmental exposures (Gore et al., 2015), and thus those studies were classified as "definitively high" risk of selection bias.

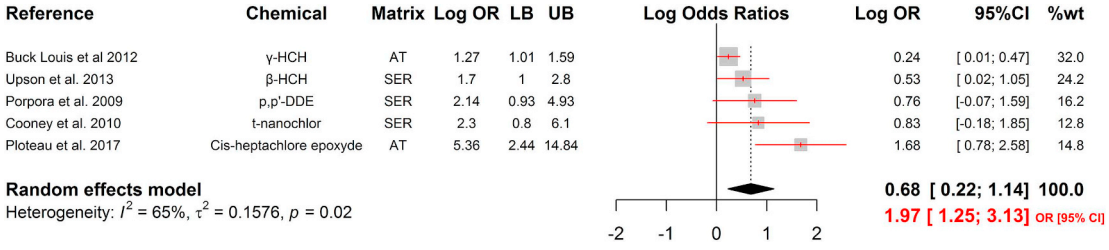

Fig. 6. Forest plot of the risk estimates, odds ratios (OR) and 95% confidence intervals (CI) from the studies included in the meta-analysis of the associations between exposure to organochlorine pesticides (OCPs) and endometriosis (n = 5) for the scenario 1 where an OCP was selected from each study on the basis of the highest effect estimate. Abbreviations: AT, adipose tissue; HCH, hexachlorocyclohexane; SER, serum; %wt, percentage of study weight in the meta-analysis. Meta-estimates are represented with a black diamond, 95% confidence intervals with a red line and the grey box around the log OR represents the relative weight of each study in the meta-analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

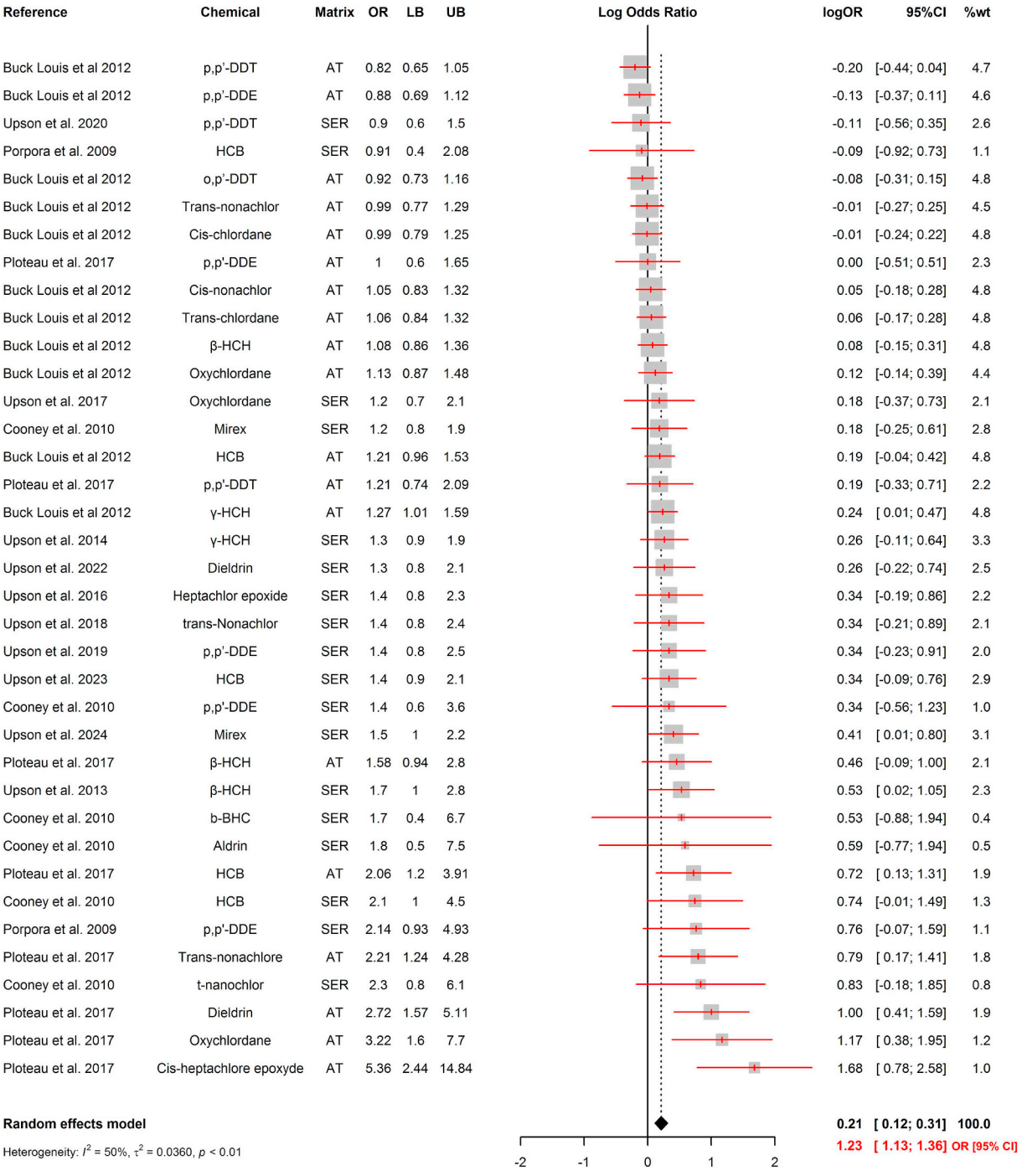

Fig. 7. Forest plot of the risk estimates, odds ratios (OR) and 95% confidence intervals (CI) from the studies included in the meta-analysis of the associations between exposure to organochlorine pesticides (OCPs) and endometriosis (n = 37) for the scenario 2 where all OCPs were selected from each study and pooled together in the meta-analysis. Abbreviations: AT, adipose tissue; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; SER, serum; %wt, percentage of study weight in the meta-analysis. Meta-estimates are represented with a black diamond, 95% confidence intervals with a red line and the grey box around the log OR represents the relative weight of each study in the meta-analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Other sources of bias related to the specific methodological issues inherent in observational studies on endometriosis were further considered. For instance, the use of lipid-normalized levels of circulating POPs may bias estimates if circulating lipids are in the causal pathway or if they are not associated with the disease, resulting in an attenuation of point estimates (Schisterman et al., 2005). Considering the influence of body composition and lipid metabolism on endometriosis, some residual bias may arise due to model misspecification as most studies used a lipid-normalized model. Overall, most studies were classified as either Tier 2 (n = 11) or Tier 1 (n = 6) for risk of bias according the NTP/OHAT criteria, indicating the presence of plausible bias that may raise some doubt about the results. The overall risk of bias was less concerning for the sub-group of studies focusing on PCBs because 56% of studies were classified at Tier 1.

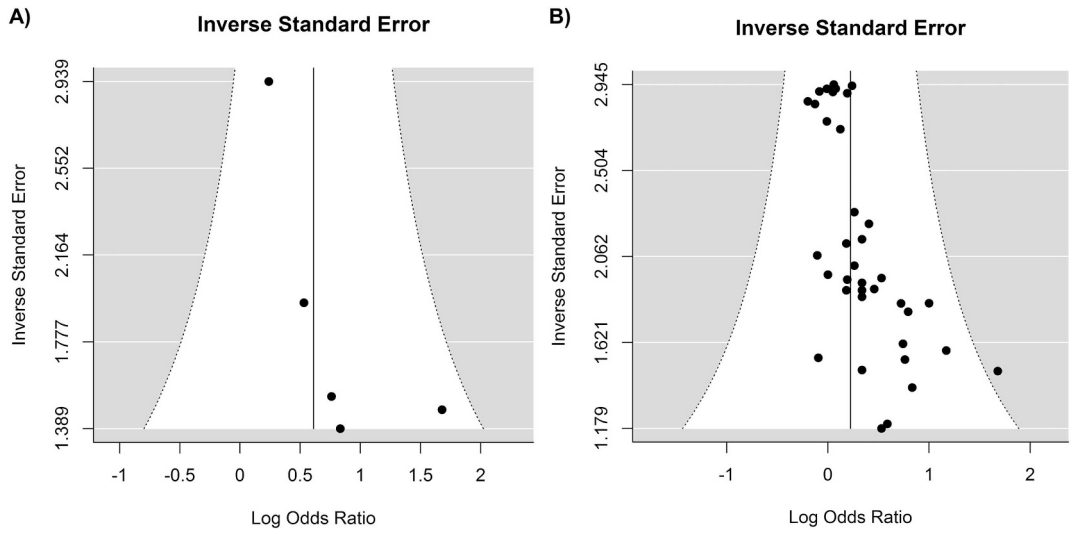

Fig. 8. Funnel plots of the risk estimates from the studies included in the meta-analysis of the associations between organochlorine pesticides and endometriosis for the scenario 1 (Panel A) and 2 (Panel B).

3.7. Studies excluded from the meta-analysis

Six studies were excluded from the meta-analysis. Study characteristics can be found in the Supplemental Table S10. Four studies did not present the results with ORs or RRs for statistical pooling (De Felip et al., 2004; Fierens et al., 2003; Lebel et al., 1998; Reddy et al., 2006), and two studies provided potentially overlapping information with other included studies (Heilier et al., 2004; Porpora et al., 2006). The excluded studies represented 261 cases and 404 controls, of which 57 cases and 50 controls provided overlapping data. Four out of the six excluded studies exhibited null results, and two showed statistically significant associations: OR 4.0 (1.3–13) comparing highest versus lowest tertiles of dioxin and non-dioxin like PCBs (Porpora et al., 2006) or increased levels of PCBs among cases respective to the controls ($p < 0.05$, ANOVA) (Reddy et al., 2006).

3.8. Confidence in the body of evidence and level of evidence

Confidence rating summaries are displayed in the Table 5. According to the NTP/OHAT framework, only experimental and controlled studies receive an initial rating of "high confidence," precluding random allocation bias and ensuring that exposure precedes the outcome onset. Considering that all studies included in this review were observational case-control or retrospective cohort studies, we established an initial rating of "moderate confidence".

- *Downgrading factors*
  A set of factors were evaluated to potentially downgrade the initial confidence rating, including risk of bias or unexplained inconsistency. The NTP/OHAT guidance states that downgrading due to risk of bias should be reserved for those cases where the risk is

Table 4
Tier 1 (T1) and Tier 2 (T2) according the NTP/OHAT tiered approach risk of bias tool approach (NTP/OHAT, 2015a,b). Full instructions at "Section 6, Instructions to assess the risk of bias of human epidemiological studies".

RESPONSE LEVELS

++	Definitively low risk of bias
+	Probably low risk of bias
-	Probably high risk of bias
--	Definitively high risk of bias

BIAS DOMAIN	Buck Louis et al. 2012	Cai et al. 2011	Cooney et al. 2010	Eskenazi et al. 2002	Heilie et al. 2005	Hoffman et al. 2007	Louis et al. 2005	Martinez-Zamora et al. 2015	Mayani et al. 1997	Niskar et al. 2009	Pauwels et al. 2001	Ploteau et al. 2017	Porpora et al. 2009	Simsa et al. 2010	Trabert et al. 2010	Tsukino et al. 2005	Upson et al. 2013
CONFOUNDING BIAS. [Key domain] Did the study design or analysis account for important confounding and modifying variables?	+	+	-	-	+	-	+	+	-	+	+	+	+	-	+	-	+
ATTRITION/EXCLUSION BIAS Were outcome data incomplete due to attrition or exclusion from analysis?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DETECTION BIAS Can we be confident in the exposure characterization? **[Key domain]**	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
Can we be confident in the outcome assessment? **[Key domain]**	+	+	+	-	-	-	+	+	+	+	+	+	+	+	-	+	-
SELECTIVE REPORTING BIAS Were all measured outcomes reported?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SELECTION BIAS Did selection of study participants result in appropriate comparison groups?	+	--	-	+	-	+	-	-	--	-	--	-	-	--	+	--	+
CONFLICT OF INTEREST	+	-	+	+	-	+	+	+	-	+	-	+	+	+	+	-	-
SUMMARY TIERED CLASSIFICATION	T1	T2	T2	T2	T2	T2	T1	T1	T2	T1	T2	T1	T1	T2	T2	T2	T2

Table 5
Summary of results from the evaluation of the confidence and level of evidence from epidemiological studies reporting associations between organochlorine pollutants and endometriosis.

		Rate	Comments
Initial rate of confidence		Moderate confidence	The majority of studies were performed with case-control designs and five of them under cohort or nested case-control settings.
Downgrading factors	Risk of bias	No downgrade	Most individual studies were classified in the Tier 1 (n = 6) and Tier 2 (n = 11). None of studies was classified in Tier 3.
	Unexplained inconsistency	No downgrade	Heterogeneity in the meta-analyses ranged from 50 to 75%. The stratification analysis revealed some sources of inconsistency such as the biological matrix or the analytical methods.
	Indirectness	No downgrade	No evidence of lack of applicability of populations or study design was found across studies.
	Imprecision	No downgrade	The confidence intervals were not considered especially concerning to penalize the confidence. Largest ratio UB/LB 95%CI was 2.5
	Publication bias	No downgrade	Despite asymmetrical funnel plots, no additional evidence of publication bias was found (e.g. private sponsorship, unpublished studies)
Upgrading factors	Large magnitude	No upgrade	The magnitude was considered to be modest in general
	Dose-response	No upgrade	No evidence of dose-response across the studies
	Residual confounding	No upgrade	Evidence of confounding that would bias toward null but the extent of its effect remain uncertain to justify the upgrading
	Consistency	No upgrade	The consistency was considered to be moderate and insufficient to upgrade the rating
Final rate of confidence		Moderate confidence	No upgrading nor downgrading factor modifying the initial rating
Level of evidence		Moderate	There is moderate confidence in the body of evidence for an association between exposure to OCCs and endometriosis

substantial across most studies composing the body of evidence. Considering that most of evidence was categorized as Tier 2 and Tier 1, without studies at Tier 3, we judged that risk of bias was insufficient to weaken the confidence in the results (See Table S4 at Supplemental material). Despite that heterogeneity ranged from 50 to 75%, unexplained inconsistency was not considered a concerning factor because stratification analysis revealed sources of heterogeneity were related to the analytical methods, biological matrices or population origin. In turn, confidence intervals did not penalize the confidence rating because the largest ratio upper to lower 95% CI was estimated at 2.5 in the meta-analysis of OCPs. This ratio is far from the threshold of 10 proposed by the guidance to consider a penalization of confidence. Publication bias was notable in the obvious asymmetry of funnel plots and statistically significant test for small study effects. However; it is well acknowledged that statistical and graphical methods are not accurate in evaluating publication bias with a small number of studies. Furthermore, the NTP/OHAT handbook suggests a more extended evaluation to also account for industrial sponsors, early positive studies, and the presence of abstracts of unpublished studies and conference papers. Overall, we thus considered publication bias not concerning because most studies were supported by public funding, and we failed to find abstracts, theses or conference papers for non-published studies.

Other uncertainties included misclassification for both exposure and outcome, due to varying laboratory capabilities in detection rates, and disease, as reflected in varying definitions of endometriosis (e.g., from self-reports to the clinical gold standard of laparoscopy). We recognize that model specification remains a consideration in weighting all evidence, as the right choice of biospecimens for exposure assessment, but we did not downgrade the final confidence because the influence of these factors on the final estimates remains unknown.

- *Upgrading factors*

Several factors were also considered to potentially upgrade the confidence rating. Residual bias was considered the most relevant of these factors given the methodological differences previously noted across studies that may limit estimating absolute risk. However, we considered that this factor was insufficient to support upgrading. Dose-response, within the individual or across studies, was not considered a factor supporting upgrading the confidence, because the absence of clear monotonic or non-monotonic responses. Also, the available data did not allow proper dose-response meta-analysis.

Overall, no compelling factors were identified to modify the initial confidence rating, and the final rating was “moderate” (See details at Table 5). Considering the presence of positive associations between the OCCs and the endometriosis, the moderate confidence rating was translated a “moderate level” of epidemiological evidence according the NTP/OHAT Handbook.

4. Discussion

During the past decades, a growing body of human epidemiological evidence has suggested an association between environmental pollutants and endometriosis. Differences in study design, population, and laboratory and analytical methodologies may explain some of the equivocal findings reported to date as summarized in recent narrative reviews on endocrine disrupting chemicals (Smarr et al., 2016), dioxins (Guo et al., 2009), PCBs (Yao et al., 2017), dioxin-like PCBs (Bruner-Tran and Osteen, 2010) or organochlorines in general (Heilier et al., 2008). To our knowledge this is the first study attempting to systematically and quantitatively assemble, integrate and evaluate the available epidemiological evidence on the association between OCCs and endometriosis. To this end, we have applied a valuable framework developed by the NTP/OHAT (2015a) for searching, selecting, extracting, synthesizing the evidence and rating the level of confidence in the evidence. Despite the publication of different guidance and tools tailored to support the development of protocols and execution of SRs (e.g. NTP/OHAT), there is no consensus as how evaluations should be done. The online platforms such as Health Assessment Workspace Collaborative (*HAWC, hawcproject.org*) supporting the development of SR and GRADE evaluations in environmental health, orchestrated with PROSPERO register may be instrumental in centralizing evaluations and avoiding multiplicative efforts.

These approaches become an essential step forward toward a more robust evidence-based environmental health science supporting decisions on state-of-science or regulatory evaluations. Specifically, such evaluations can help reliably quantify economic costs attributable to exposure to chemicals with endocrine disruption potential. An example of quantification has been published in the past for evaluating phthalate-attributable endometriosis in Europe (Hunt et al., 2016). The resulting cost estimate of €1.25 billion was based on a low rating for strength of epidemiological evidence and moderate for toxicological evidence assuming a probability of causation of 20%–39%. The evidence was integrated and evaluated by a panel of experts instead of

using a systematic-review approach, that could help to increase the transparency, rigor and certainty of estimates. Hence, we believe that the present study will stimulate further estimations of OCCs-attributable costs of endometriosis through more systematic approaches.

4.1. Limitations of the meta-analysis

We analysed the major organochlorine chemical families using effect sizes of each group (e.g. dioxins) when such data was reported. First, in each study we selected the chemical with the highest risk estimate to avoid overrepresentation of the studies. Secondly, we included all effect size estimates reported for all included studies, assuming the model was substantially unbalanced. While beyond the scope of this review, bootstrapping with resampling may help generate a range of scenarios and risk estimates to aid in the interpretation of findings (Bonde et al., 2016).

Summary estimates based on pooling the highest versus lowest percentiles do not provide an accurate measure of dose-response relationships, resulting in substantial heterogeneity and semi-quantitative estimates. Pooling ORs from different studies resulted in a range of dose-response estimates; this may have been due to differences in comparisons groups by time and/or geographical location. There was insufficient evidence to perform a fully quantitative dose-response analysis (Berlin et al., 1993). Nonetheless, we considered this semi-quantitative synthesis to be more advantageous than a narrative synthesis in our systematic analysis.

4.2. Study design

Study design has often been identified as a critical issue in accurately assessing endometriosis in epidemiological settings (Zondervan et al., 2002). The majority of included studies utilized hospital-based case-control designs (n = 12), whereas five relied on population-based designs. For both, cases and controls should be recruited from the same population for comparability of background exposures and concomitant unmeasured risk factors. To this end, population-based designs are preferred over the hospital-based settings to identify the most representative comparative controls and better reflecting background exposure profiles of the study population. Furthermore, misclassification of controls in population-based cohorts is believed to be alleviated by dilution (Zondervan et al., 2002); however, the presence of asymptomatic and undiagnosed forms of endometriosis remains a limitation. About 11% of asymptomatic women from the ENDO study presented some form of stage 3 or 4 of endometriosis revealed by MRI, a prevalence that may largely underestimate mild forms (Buck Louis et al., 2011). The design implemented by Buck Louis et al. (2012) matching a hospital-based cohort to a population-based cohort revealed inconsistent risk estimates among various methodological approaches, designs and matrices. The control group for some hospital-based studies comprised infertile women undergoing surgery for non-endometriosis-related reasons which may not be representative of the background population of women. Furthermore, endometriosis can develop in infertile women as a co-morbidity factor, confounding interpretation of studies which use infertile patients without endometriosis as controls (Pauwels et al., 2001).

4.3. Disease definition

The definition of endometriosis may vary based on location and severity and is still very controversial among clinicians. Minimal or mild cases are especially controversial because they tend to be characterized by the appearance of subtle and non-pigmented lesions. Most studies did not identify lesion location, but some focused only on deep endometriosis, excluding the cases with the peritoneal form (Martinez-Zamora et al., 2015; Ploteau et al., 2017), or compared deep endometriosis with peritoneal lesions (Heilier et al., 2005). The varying histological nature of the different endometriosis sub-types, predisposed through genetic variations, suggests each may have different aetiological mechanisms or related risk factors (Borghese et al., 2015; Nisolle and Donnez, 1997). This remains unclear due to a lack of evidence on the divergent pathogenesis and a strong correlation between the presence of deep endometriosis with the presence of peritoneal and/or ovarian endometriosis (Gordts et al., 2017).

4.4. Outcome ascertainment

Diagnostic method for cases and controls is most often laparoscopic examination with histological confirmation in hospital-based studies with a few exceptions. One population-based cohort relied on existing diagnoses from medical records for outcome ascertainment. The ENDO study used MRI to diagnose incident cases, resulting mainly in OMAs (Buck Louis et al., 2012). In some cases, diagnostic method had a substantial impact on risk estimates for several chemicals, with changing magnitude and direction of estimates depending upon the biospecimen used for quantifying exposures (i.e., serum versus omentum fat), severity of endometriosis, or choice of comparison group (women without endometriosis versus those who have other gynaecologic pathologies potentially linked to OCPs such as fibroids). In one case, diagnostic method affected incidence of endometriosis by two orders of magnitude, i.e., 0.7% for only histology, 7% for only MRI and 41% for visualized disease (Buck Louis et al., 2011).

4.5. Confounding variables

During bias assessment, we identified confounding variables that may be relevant to the causal pathway of organochlorine exposures and endometriosis. We considered age and body mass index BMI as key confounding variables because their acknowledged relevance on OCC pharmacokinetics and potential relationships with endometriosis. Other reported potential variables, including gravidity, parity and breastfeeding, particularly for clinical study populations, were identified and explored (Peterson et al., 2013). Parity and breastfeeding are also known excretion routes for OCCs, but these variables were not considered as confounders because their uncertain role within the overall framework. Actually, the adjustment for parity and breastfeeding has been critically discussed by different authors, arguing that may be in the same causal pathway depicted by OCCs and endometriosis, that could prone to over-adjustment or selection bias (Upson et al., 2013; Ploteau et al., 2017). Parity and breast-feeding are both sequentially determined by fertility, which would result in a collider of endometriosis and OCCs. However, the evidence supporting the relationships between OCCs and fertility has not been systematically established and remains fairly inconclusive to draw assumptions (Gore et al., 2015). In the present meta-analysis, few studies adjusted for breastfeeding and/or parity, which showed small influence on the meta-estimates when excluded in the sensitivity analysis. Hence, over-adjustment or selection bias may represent a minor concern for the present meta-analysis. Nonetheless, there is an acknowledged need to delineate the causal ordering of exposure, fecundity and endometriosis.

4.6. Exposure assessment

The use of reliable and accurate exposure assessment methods to characterize individual internal levels of organochlorine pollutants is essential to avoid measurement error and exposure misclassification. Analytical methods were mainly based on high resolution gas chromatography using published laboratory standard operating procedures inclusive on quality assurance/quality control protocols. Two early

studies used the CALUX assay to measure the bioactivity of dioxin-like chemicals to activate the AhR. Overall, authors provided information or external citations of analytical performance and quality assessment of analytical methods; hence, we conclude that internal organochlorine levels were measured reliably and accurately.

Given the high lipophilicity of OCCs, adipose tissue is considered the 'gold standard' matrix in biomonitoring. Nonetheless, the invasive nature of fat biopsies favors the use of blood or serum as proxies for internal dose in epidemiological studies. The majority of studies in this review used serum or plasma; only three studies used adipose tissue or both (Table 2). Serum biomarkers may fail to detect associations given their lower detectable concentrations, which may contribute to imprecision or bias in miss-specified models for key variates such as serum lipids (O'Brien et al., 2016; Schisterman et al., 2005). The perturbation of lipid metabolism and adipose distribution linked to endometriotic phenotypes is a major issue to take into account in model specification and interpretation of results (Backonja et al., 2017; Cordeiro et al., 2015; Dutta et al., 2016; Goetz et al., 2016; Liu and Zhang, 2017; Melo et al., 2010). No satisfactory statistical model exists to date that fully represents the underlying biological structure of pollutant dynamics (Cano-Sancho et al., 2018). In summary, the accurate characterization of exposure concentrations of OCCs in target tissues, either the eutopic or ectopic endometrium, is a critical research need.

Temporality of exposure is another methodological issue. Among the identified studies, only Eskenazi et al. (2002) reported a retrospective temporal window of 20 years between biospecimen collection and outcome assessment. The remaining studies are largely cross-sectional and subject to possible reverse causation. Furthermore, the use of a single exposure time point constrains the elucidation of exposure trends that contribute to pharmacokinetic variability of biomarkers, and is prone to exposure miss-classification (Wolff et al., 2007). For that reason, declining levels of OCCs over time should be considered in terms of comparability and applicability to current background exposure levels despite OCCs remaining in many developing countries. The influence of extreme exposures (e.g. Seveso or Michigan PBB cohorts) could distort the interpretation of results, but we did not appreciate a relevant effect on the influence analysis.

4.7. Future directions

The findings from this SR support the need for further epidemiological research to better understand the link between environmental exposures and endometriosis. Future epidemiological studies should carefully consider several methodological constraints to enforce the robustness of findings, including the selection and confirmation of control groups, the heterogeneity of endometriosis sub-types, and the choice and interpretation of exposure biomarkers. Multiple biological sampling and longitudinal data collection of covariates would be ideal to capture the pharmacokinetic variability. Accurate characterization of OCC exposure concentrations in target tissues is another critical research need. There is need for a systematic evaluation of the different causal structures when serum biomarkers are used compared to adipose tissue, whose chemical concentrations are more stable to metabolic alterations.

As demonstrated by the included studies, women with and without endometriosis are exposed to complex mixtures of OCCs and other chemicals, emphasizing the need of using advanced statistical methods capturing the complexity. Such methods should efficiently deal with multicollinearity for variable selection and/or regression of variable groups with highly redundant data matrices as obtained with OCCs. Some inspiring examples have been reported in the context of endometriosis: Roy et al. (2012) applied a Bayesian Belief Network to assess chemical mixtures and Zhang et al. (2012) used latent class models for a joint analysis of the prevalence of endometriosis following exposure to PCBs.

In utero development of endometriosis has been explored through epigenetic mechanisms following chemical exposure during sensitive windows of developmental differentiation (Cummings et al., 1999; Louis, 2012). The evaluation of perinatal exposures in humans is a subject for future research and will rely on large prospective cohorts for reliable nested case-control studies.

5. Conclusions

The results of this systematic-review support an association between exposure to OCCs and endometriosis in epidemiological studies with a moderate degree of confidence. Risk estimates were statistically significant with an OR (95% CI) of 1.65 (1.14; 2.39) for dioxins (n = 10), 1.70 (1.20; 2.39) for PCBs (n = 9), and 1.23 (1.13; 1.36) for OCPs (n = 5). These estimates should be considered with caution, however, given considerable heterogeneity and small estimated effect size. The overall level of evidence for the associations was considered moderate, supporting the need for further well-designed epidemiological research to fill lingering data gaps. Carefully designed observational studies are an important next step, given the complexity of endometriosis and lack of known biomarker suitable for population-based research, as will be the use of evolving modeling approaches capable of handling environmental exposures to chemical mixtures. Attention to exposures during sensitive windows will shed further light on the possible developmental origin of endometriosis. Considering the high economic and societal cost associated with endometriosis, further research in this field may largely help policy makers establish preventative strategies to attenuate the impact of chemicals with endocrine disruption potential on the economy and women's health.

Conflict of interest

The authors declare no conflict of interest. No specific grants have been attributed to this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.11.065.

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