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Review article

Associations between exposure to organochlorine chemicals and endometriosis in experimental studies: A systematic review protocol



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ABSTRACT

Background: Endometriosis is a hormone-dependent gynaecological disease characterised by the presence and growth of endometrial tissues outside of the uterus. There is growing experimental evidence that suggests environmental endocrine disrupting chemicals, specifically organochlorine chemicals (OCCs), may play a role in the pathogenesis of endometriosis, but to date, there are no studies attempting to gather and synthesise the published literature systematically.

Objectives: The main objective of this SR is to evaluate the associations between the exposure to OCCs and endometriosis in experimental models (*in vivo* and *in vitro*).

Methods: The SR framework has been developed following the guidelines established in National Toxicology Program/ Office of Health Assessment and Translation (NTP/OHAT) Handbook for Conducting a Literature-Based Health Assessment, which provides a standardised methodology to implement the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health assessments. The review process will be managed and documented through HAWC, an open-source content management system, to guarantee transparency.

Eligibility criteria: Only experimental studies, *in vivo*, *ex vivo* or *in vitro*, exploring associations between controlled exposures to OCCs and endometriosis and related outcomes will be included. Eligible studies will include peer reviewed articles of any publication date which are sources of primary data. Only studies published in English will be considered.

Information sources: We will apply the search strings to the scientific literature databases NCBI PubMed, Web of Science and SCOPUS. Manual searches will be performed through the list of references of included articles.

Data extraction and synthesis or results: Data will be extracted according to a pre-defined set of forms and synthesised in a narrative report. Given sufficient commensurate data, a meta-analysis may also be performed.

Risk of bias: A quality assessment will be performed for *in vivo* and *in vitro* studies using the NTP/OHAT Risk of Bias Rating Tool for Human and Animal Studies.

Level of evidence rating: Following a comprehensive assessment of the quality of evidence for both *in vivo* and *in vitro* studies, a confidence rating will be assigned to the body of literature and subsequently translated into a rating on the level of evidence (high, moderate, low, or inadequate) regarding the research question.

Systematic review registration: PROSPERO CRD42018102618.

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1. Introduction

1.1. Background and rationale

Endometriosis is a hormone-dependent gynaecological disease characterised by the presence and growth of endometrial tissues outside of the uterus. Estimates of prevalence range from 10 to 45% of people who menstruate although the true burden of this disease is likely higher due to the unknown prevalence among those who are asymptomatic (Buck Louis et al., 2011; Rawson, 1991). The precise aetiology is also unknown, and, while several hypotheses have been suggested, it is most likely to be multifactorial, involving genetic and environmental factors (Sourial et al., 2014; Van der Linden, 1996).

There is presently a growing body of literature analysing the association between endometriosis and the exposure to synthetic organochlorine chemicals (OCCs), a group of organic compounds with chlorinated aromatic molecules which are recognised to have an adverse impact on human health, such as polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), biphenyls (PCBs), and pesticides (OCPs) (Anger and Foster, 2008; Arisawa et al., 2005; Bruner-Tran et al., 1999; Guo et al., 2009). OCCs are characterised to be highly lipophilic, persistent and bioaccumulative in trophic chains. Because of this, despite the installation of laws banning or regulating these substances in the 1970s and 1980s, OCCs are still found in human blood and fatty tissues worldwide (Pumarega et al., 2016; UNEP, 2017).

Some epidemiological studies have reported positive associations between PCDD/Fs, PCBs and other OCCs and endometriosis (Buck Louis et al., 2012; Martinez-Zamora et al., 2015; Ploteau et al., 2017; Porpora et al., 2009), but the overall body of evidence remains inconclusive, often due to acknowledged methodological limitations (Smarr et al., 2016). Human epidemiological evidence, however, provides only an incomplete picture of the total existing evidence linking such pollutants and endometriosis, missing the potential causal and mechanistic relationships. Controlled experimental studies *in vivo* and *in vitro* can help fill the gap left by epidemiological studies. Endometriosis occurs spontaneously in only humans and several other non-human primates, including rhesus and cynomolgus monkeys and baboons, which are considered referent animal models due to their similarities to humans in reproductive anatomy and physiology (D'Hooghe et al., 2009; Nishimoto-Kakiuchi et al., 2018). In fact, the question was raised regarding the role of environmental chemical exposures on endometriosis following a study that demonstrated an increase in incidence and severity of endometriosis in an experimental population of rhesus monkeys exposed to dioxin (Rier et al., 1993).

Non-human primate and murine models can act as human analogues to elucidate the processes involved between environmental exposures and the onset or progression of endometriosis, and *in vitro* testing allows for the exploration of potential molecular mechanisms of action and more complex cellular interactions. Due to low frequency of spontaneous endometriosis in non-human primates, endometriosis is sometimes surgically induced by transplantation in experiments to provide insight into the pathophysiology of disease progression. This approach has been also shown to be successful in rodents, either by transplantation of endometrial tissue from the same or syngeneic animal (autologous models), or by transplantation of human endometrial tissue (humanised models) in immunocompromised mice (Bruner-Tran et al., 2018; Grümmer, 2006).

For *in vitro* models of endometriosis, there exist several immortalised human endometriotic cell lines (e.g. epithelial 12Z; stromal 22B), but it is often preferable to obtain primary cultures of endometrial stromal or epithelial cells isolated from human biopsies (Arosh et al., 2015; Banu et al., 2009). Cell co-cultures and 3D models have shown the existence and complexity of cross-talk between epithelial and stromal cells, endocrine and paracrine responses, and the extracellular matrix (Arnold et al., 2001; Wild et al., 1994). Overall, *in vitro* studies allow for more in depth analysis of the mechanisms of action and

signalling cascades involved following exposure to certain environmental pollutants.

To date, the underlying pathophysiology of endometriosis remains tenuous, as does the mechanistic understanding linking specifically OCCs and endometriosis. Several theories (*i.e.* induction, transplantation) have been proposed to explain the plethora of processes underlying such heterogeneous disease (further discussed by Signorile and Baldi, 2010; Sourial et al., 2014). At the cellular and molecular level, it has been acknowledged that progesterone resistance, estrogen dependence, oxidative stress and pro-inflammatory conditions, and/or immunosuppression with genetic epigenetic predisposition are hallmarks favouring the migration, adhesion and progression of endometriotic tissues (Bulun et al., 2002). Endocrine disrupting chemicals such as OCCs are likely to interact with nuclear receptors and impact molecular pathways of direct relevance for endometriosis. For instance, dioxin and dioxin-like PCBs have been shown to interact with the estrogen pathway through the estrogen receptor or by binding aryl hydrocarbon receptor (AhR), leading to downstream effects on gene and protein regulation involved in cell adhesion, matrix remodelling, proliferation and apoptosis of endometrial cells (Bruner-Tran et al., 2010). The action of OCCs on the AhR pathway independent of estrogen-mediated actions may also alter endometrial cell stress responses, metabolism and cell migration (Willing et al., 2011). Furthermore, the potent 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) may alter the progesterone action by downregulation of progesterone receptors, a pattern of progesterone resistance leading to the dysregulation of matrix metalloproteinases (MMPs), promoting the growth and invasion of endometriotic tissue (Bruner et al., 1997; Bruner-Tran et al., 2010). Other physiological processes tightly linked to endometriosis have been associated with OCCs, including immunosuppression, inflammation or oxidative stress, however the directed acyclic relationships and causal ordering of these underlying molecular events remains still unclear (Birnbaum and Cummings, 2002).

Systematic reviews (SR) are a powerful tool that allow for an unbiased synthesis of all existing evidence in a specific field, which may assist in the development and justification of regulatory and healthcare decisions through evidence summaries and quality assessments (Higgins and Green, 2011; Hooijmans et al., 2018; Rooney et al., 2014). During the last decade, a substantial effort has been made to develop and adapt SR workflows to environmental health domains, including tailored protocol guidelines and risk of bias tools, such as the Navigations Guide or the National Toxicology Program/ Office of Health Assessment and Translation (NTP/OHAT) Handbook (Higgins and Green, 2011; Hooijmans et al., 2018; Rooney et al., 2014). As a result, we have seen a substantial increase of SR-based publications focusing on environmental chemicals, especially for epidemiological studies with a few emerging reviews on experimental studies. The lack of validated tools developed to assess *in vitro* studies constrains the use of mechanistic data to supporting decisions within chemical health risk settings (Al Saadi et al., 2016; Rooney et al., 2016; Samuel et al., 2016). To date, only narrative reviews have been conducted to synthesise the available evidence from experimental studies on the associations between environmental chemicals and endometriosis (Birnbaum and Cummings, 2002; Bruner-Tran et al., 2010; Bruner-Tran and Osteen, 2010; Guo et al., 2009). Recently, we have conducted a systematic-review focusing on the associations between OCCs and endometriosis in human epidemiological studies using a rigorous and comprehensive GRADE-based protocol following the NTP/OHAT guidelines (Cano-Sancho et al., 2018). There is thus a need to conduct a SR covering the experimental body of evidence (*in vivo* and *in vitro*) to complement our existing knowledge from epidemiological studies and to provide a complete systematic summary of the overall body evidence on the associations between OCCs and endometriosis.

1.2. Objectives

The main objective of this SR is to evaluate the associations between the exposure to organochlorine chemicals (OCCs) and endometriosis in experimental models (*in vivo* and *in vitro*).

We are considering the following sub-objectives:

- to create a comprehensive narrative synthesis of the current body of knowledge from experimental studies (*in vivo* and *in vitro*) evaluating the association between the exposure to OCCs and the pathogenesis of endometriosis; and
- to appraise the quality of evidence with a confidence rating and establish a level of evidence for the presence or absence of endometriosis with respect to exposure to OCCs in experimental data.

2. Methods

This SR framework has been developed to follow the guidelines established in NTP/OHAT Handbook for Conducting a Literature-Based Health Assessment, which provides a standardised methodology to implement the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health assessments (OHAT, 2015a; Rooney et al., 2014). The NTP/OHAT framework adapted to the specific research question will thus guide the structure of this systematic review. The workflow for this SR is displayed in Fig. 1, with the corresponding supporting platforms. Selection, data extraction, data synthesis and risk of bias assessment will be performed and managed using Health Assessment Workspace Collaborative (HAWC), an open-source, modular web-based content management system with a user interface (<https://hawcproject.org/>), developed by Andy Shapiro et al. in 2014 in collaboration with EPA National Center for Environmental Assessment (EPA NCEA) and National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP) (Shapiro, 2015). HAWC provides transparency throughout the entire assessment process, from literature search and review, data extraction and evidence synthesis, endpoint analysis, risk of bias assessment, data visualisation, and even meta-analysis, should that be performed. This protocol has been developed in accordance with the reporting guidelines established by the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) 2015 and PRISMA for Abstracts (PRISMA-A) (Moher et al., 2015), and registered in the

International Prospective Register of Systematic Reviews on July 17th 2018 (PROSPERO) (registration number CRD42018102618). The results will be structured and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.1. Eligibility criteria

In order to be eligible for inclusion, studies will need to comply with the elements of the PECO (Population, Exposure, Comparators and Outcomes) statement below, summarised in Table 1.

- **Population:** The population of interest of this review will focus on experimental models, both *in vivo* and *in vitro*.
 - *In vivo* models will include non-human primates (e.g. baboons, rhesus monkeys, cynomolgus monkeys), rodents (e.g. rats and mice regardless of strain), and any other experimental animal model in which endometriosis may be surgically induced.
 - For *in vitro* studies, we will include endometrial and endometriotic primary cells (stromal and epithelial) isolated from human biopsies and immortalised endometriotic cell lines (e.g. epithelial cell line 12Z; stromal cell line 22B). Co-cultures, three-dimensional models and explants of endometrial tissues will also be included. Endometrial cancer cell lines (e.g. Ishikawa) will be excluded.
- **Exposure:** The exposure of interest will be organochlorine chemicals, a group of organic compounds with chlorinated aromatic molecules which are recognised to have an adverse impact on human health. This group of chemicals includes dioxins, furans, PCBs, pesticides, and other industrial chemicals. This review will exclude pharmaceuticals and therapeutic drugs, hormone treatments, and phytoestrogens or flavones/flavonoids.
- **Comparators:** Reference groups will comprise any animal or cell-treatment group not exposed to OCCs or treated only with the vehicle control. Studies without a reference group will be excluded.
- **Outcomes:**
 - *In vivo* models
 - Primary outcomes of interest will be 1) the onset or aggravation of endometriosis in animal models where spontaneous endometriosis can occur and 2) the proliferation or growth of surgically induced endometriotic lesions in all other models. Endometriosis is the presence of endometrial tissue outside the

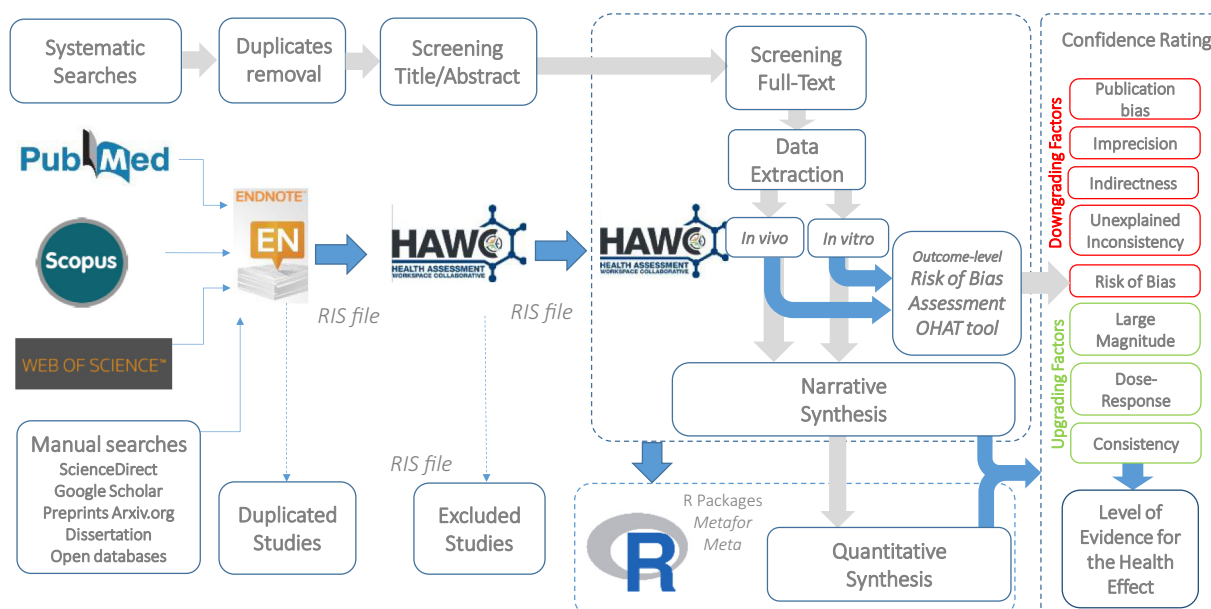


Fig. 1. Workflow diagram for the systematic review framework. Reasons for exclusion must be recorded at "Screening Full-Text" step.

Table 1
PECO statement.

PECO	Inclusion criteria	Exclusion criteria
Population	<i>In vivo</i> • Experimental animal models <i>In vitro</i> • Endometrial epithelial and stromal cells, endometrial tissues, and related co-cultures	• Humans • Cells from organs and tissues other than endometrium • Cancer cells • Chemicals that are not organochlorine chemicals
Exposure	<i>In vivo</i> • Organochlorine chemicals • All dose levels, routes of administration, duration and frequency <i>In vitro</i> • Above applicable to <i>in vitro</i>	• Above applicable to <i>in vitro</i> • Lacks control group • Above applicable to <i>in vitro</i>
Comparators	<i>In vivo</i> • Has positive, negative, and/or vehicle control group <i>In vitro</i> • Above applicable to <i>in vitro</i>	• Above applicable to <i>in vitro</i> • Outcomes irrelevant to endometriosis
Outcomes	<i>In vivo</i> • Onset or aggravation of endometriosis • Proliferation or growth of induced endometriotic lesions • Presence-of “endometriotic-like” phenotypes with human reference standard <i>In vitro</i> • Proliferation, migration, and/or invasion of endometrial cells • Other biomarkers of primary outcomes such as gene/protein/receptor/interleukin expression associated with endometriosis	• Above applicable to <i>in vitro</i>

uterus and fits to code N80 of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

- Secondary outcomes. For all animal models, the presence or aggravation of “endometriosis-like” phenotypes will be considered as a secondary outcome. Studies must define “endometriosis-like” phenotypes in comparison with an equivalent human standard to maintain relevance to the research question (e.g. endometriosis-like glands or tube formation). Only studies that use a human endometriosis reference standard for endometriosis-like phenotypes *in vivo* will be considered.
- o *In vitro* outcomes will be defined to be as inclusive as possible while maintaining relevance to endometriosis and will be considered secondary to outcomes from *in vivo* studies due to their potentially heterogeneous nature, as exact mechanisms of action between OCC exposure and endometriosis are unknown and these mechanistic pathways are not specific to endometriosis.
- Primary outcomes for *in vitro* models will include proliferation, migration, and/or invasion of endometrial and endometriotic cells.
- Secondary outcomes will include the expression and levels of intermediary molecular markers and signalling pathways relating directly with endometriosis, such as estrogen or progesterone receptor activity and expression, endometriosis-related protein or enzyme activity (like aromatase and matrix metalloproteinase expression), endometriosis-related inflammation, and expression or activation of endometriosis-related genes. The mechanistic cell-based experiments should elucidate a direct link between intermediates and apical outcomes through study design and/or cell models. Supplemental Table 2 provides the list of inclusive endometriosis-related genes which were identified through a comprehensive PubMed text-mining approach and validated to be statistically relevant to endometriosis (Liu and Zhao, 2016).
- **Publication types:** Articles that do not contain original data, such as reviews, editorials, or commentaries, or conference abstracts, studies published in languages other than English, and non-experimental studies (e.g. human epidemiologic or other observational studies) will also be excluded. All publication years will be considered.

2.1.1. Exclusion criteria prioritisation

The studies will be excluded if those are:

- 1) Duplicates OR
- 2) Not primary data OR
- 3) Irrelevant population (e.g. not experimental animal model or not

endometrial cells) OR

- 4) Irrelevant exposure (e.g. not organochlorine chemical) OR
- 5) Irrelevant outcome (e.g. not endometriosis-related, as previously defined) OR
- 6) Not in English

2.2. Search strategy

The literature search will be performed simultaneously in three scientific databases (i.e. PubMed, Web of Science, SCOPUS). All retrieved references will be imported into reference management software ENDNOTE® wherein duplicate documents will be manually eliminated from the pool of studies. The remaining studies will then be imported into HAWC for eligibility screening. Additional articles may be added through manual searches through the list of references of included articles.

2.2.1. Databases

The searches will be conducted in the following scientific databases:

- NCBI PubMed - <http://www.ncbi.nlm.nih.gov/pubmed>
- ISI Web of Knowledge [v.5.29] - <https://apps.webofknowledge.com>
- SCOPUS - <https://www.scopus.com>

2.2.2. Search strings

The search string combines the EXPOSURE and OUTCOME elements from the PECO statement, nested through the Boolean operators “AND/OR”. Search terms are intended to identify all relevant published evidence on endometriosis and endometriosis-related effects following exposure to organochlorine chemicals and were identified by (1) reviewing PubMed Medical Subject Heading (MeSH) terms and literature tags used by previously identified endometriosis-related epidemiologic studies for relevant and appropriate terms, (2) adapting and expanding on existing lists of pollutants (UNEP, 2017; Wassenaar et al., 2017), and (3) extracting several potential endometriosis-related mechanistic outcomes (Liu and Zhao, 2016). More details about the development of the search string is available in Section 1.1. Literature Search of the Supplementary Material. The search string will be adapted and calibrated to run in Web of Knowledge and SCOPUS as well. No restrictions will be made in either database to limit publication dates, and no other filters will be applied. A test set of relevant studies will be used to calibrate the overall search strategy. The calibration and piloting of this search string can be found in the Supplementary Material.

2.3. Study selection

Two reviewers (KM and GCS) will independently perform the study

Table 2
Body of evidence structure based on major experimental outcomes of endometriosis to guide grouping endpoints and experiments.

Level	Endometriosis-related outcomes	Endpoint/assay examples	Body of evidence grouping examples
Primary/apical outcomes	Spontaneous endometriosis	In vivo: onset after chronic/transgenerational exposure in non-human primates	1-Spontaneous endometriosis in animals
	Migration/attachment	In vivo: experiments evaluating the invasiveness of implants in rodents or primates In vitro: migration assays in cell models	2- Invasiveness of endometriotic tissue in animals 3 – Invasiveness of endometriotic tissue in cell cultures
	Survival/proliferation/apoptosis	In vivo: experiments on proliferation/expansion of endometriotic lesions in rodents and/or primates In vitro: proliferation/viability/apoptosis cell assays	4 – Survival/proliferation of lesions in animals
Intermediary /secondary	Progesterone resistance	In vivo: PR-B/A expression	5- Proliferation in cell culture
	Aromatase/steroidogenic pathway	In vitro: CYP19A1 expression	6- Progesterone resistance in animals
	Inflammatory cytokines	In vivo: IL6 levels	7- Disruption of aromatase pathway in cell culture
	Other outcomes: immunosuppression, oxidative stress		8 - Inflammation in animals

selection, and conflicting results will be discussed with a third reviewer (JPA). Study selection will occur in two phases. Phase I will consist of an initial screening of title and abstracts, according to the pre-established inclusion/exclusion criteria (Table 1). Studies whose titles/abstracts do not provide enough information to decide or are otherwise unclear will be automatically moved to the next phase for full text assessment. Retained articles from Phase I will be exported into a Research Information Systems (RIS) file for transparency and uploaded into the HAWC Literature Review module for Phase II.

Phase II will consist of a comprehensive full-text review of all the articles retained from Phase I. The full text of retained records will be gathered in print or electronic pdf and linked within HAWC for ease of accessibility. In the event that full text to a study is not available, the reason that limited the accessibility to the document will be clearly reported in a tracking document. Exclusion at this stage will also be recorded in the tracking document with a brief justification of exclusion rationale.

2.4. Data extraction

The data extraction method will be piloted in duplicate by two reviewers (KM and GCS) to calibrate consistency using comprehensive data forms specifically designed for animal and *in vitro* studies available in HAWC, adapted from the NTP/OHAT Protocol (OHAT, 2015a). Complete data forms are available in Supplemental Table 4. The following items will be extracted from the studies:

- Study identification information (*i.e.* Title, Author, Journal, Date of Publication)
- Funding Source and Conflicts of Interest
- Type of Study (*i.e.* Animal Bioassay, *In vitro*)
- Exposure (*i.e.* Chemical name, class, purity, vehicle, *etc.*)
- Population (*i.e.* Animal species, strain, sex, source, age; Cell line, tissue culture, source, *etc.*)
- Dosing methodology (*i.e.* Route of exposure, duration, frequency, dose groups, vehicle, *etc.*)
- Controls (positive, negative, vehicle)
- Randomisation or blinding procedure(s)
- Endpoint (*e.g.* onset of endometriosis, severity of endometriosis, lesion diameter, nuclear receptor expression levels, changes in gene expression, effect sizes, *etc.*)
- Diagnostic or method to measure endpoint (*e.g.* laparoscopy; assay name, source, *etc.*)
- Statistical methods (*e.g.* significance levels)

Data provided only on plots will be extracted directly from the image using the WebPlotDigitizer (version 4.0 PLOTCON 2017 - Oakland, CA), a semi-automated web-based tool. Whenever relevant information is missing, the authors will be contacted to provide further details.

2.5. Body of evidence structure

The evidence will be organised in outcome-related groups favouring data synthesis and confidence rating at health outcome level. Evidence grouping by outcomes and/or biological endpoints aligns with regulatory decision-making frameworks based on mode of action (MOE) or adverse outcome pathways (AOPs), where intermediary biological perturbations required for toxicity are identified as key events (Villeneuve et al., 2014; Becker et al., 2015). The criteria to determine the inclusion of specific studies or experiments in each outcome group will consider the evidence stream (*i.e.* *in vivo*, *in vitro*), animal model (*e.g.* non-human primates, rodent models), health outcomes/endpoints (*e.g.* spontaneous apparition, proliferation of implants) or exposure regime (*e.g.* high or low exposures, type of OCCs, duration). Literature suggests that OCCs may contribute the endometriosis pathogenesis at different apical levels, here identified as primary outcomes; 1) by increasing the spontaneous apparition of endometriotic lesions, 2) increasing the proliferation/gravidity of already established endometriotic lesions and 3) increasing the capacity of endometrial cells to migrate and attach in ectopic tissues. Secondary outcomes are envisaged to represent intermediary endpoints upstream of primary outcomes which may be grouped around specific signalling or functional pathways. Grouping and sub-grouping of experiments in outcomes will be guided by expert judgement considering the significance of overall conclusions. Some anticipated examples of outcome-based groups of evidence are depicted in Table 2.

Sub-group analysis will be conducted considering the nature and heterogeneity of included experiments, including but not limited to the study design, animal models/species, OCC congener, exposure duration, dose level, and assays.

2.6. Internal quality assessment

The internal quality for both streams of evidence (*i.e.* *in vitro*, *in vivo*) will be evaluated using the Risk of Bias (RoB) Rating Tool developed by OHAT (2015b). The OHAT RoB tool is consistent with the other existing RoB tools (*e.g.* Navigation Guide), with substantial overlapping of RoB domains and/or questions, yet lack of harmonisation has been already

Table 3
Confidence Rating process (OHAT, 2015b).

Initial confidence by key features ^a of study design	Factors decreasing confidence	Factors increasing confidence	Confidence in the body of evidence
High (+ + + +) – 4 features	• Risk of bias	• Large magnitude of effect	High (+ + + +)
Moderate (+ + +) – 3 features	• Unexplained inconsistency	• Dose response	Moderate (+ + +)
Low (+ +) – 2 features	• Indirectness	• Consistency	Low (+ +)
Very low (+) – ≤1 feature	• Imprecision	- Across animal models or species	Very Low (+)
	• Publication bias	- Across dissimilar populations	
		- Across study design types	

^a Features: (1) controlled exposure, (2) exposure prior to outcome, (3) individual outcome data, and (4) use of comparison group.

recognised (Rooney et al., 2016). The OHAT RoB tool consists of a common set of questions catered to each experimental stream of evidence, addressing main bias domains as follows:

Selection bias

1. Was administered dose or exposure level adequately randomised?
2. Was allocation to study groups adequately concealed?

Performance bias

3. Were experimental conditions identical across study groups?
4. Were the research personnel blinded to the study group during the study?

Attrition bias

5. Were outcome data incomplete due to attrition or exclusion from analysis?

Detection bias

6. Can we be confident in the exposure characterisation?
7. Can we be confident in the outcome assessment?

Selective reporting bias

8. Were all measured outcomes reported?

Other

9. Were there any other potential threats to internal validity?

Each question within the tool will receive one of five possible responses: “Definitely Low Risk of Bias”, “Probably Low Risk of Bias”, “Probably High Risk of Bias”, “Definitely High Risk of Bias” or “Not Reported”, with a statement of justification based on the study text. Responses will be determined by two independent assessors (KM and GCS) following the pre-specified criteria detailed in Suppl. Mat. 1 Section 3.2.1.1: Risk of Bias Response Criteria, which are specific to each type of evidence stream. Discrepancies will be compared and discussed to reach a consensus, and, if needed, other members of the review team will be consulted to resolve remaining disagreements. In case of incomplete data or dubious reporting, study authors will be contacted for clarification.

Risk of bias will be evaluated at individual and outcome level, meaning that one individual study subject to different outcome-based experiments will receive multiple RoB evaluations. Summaries of RoB will be presented through heatmaps for each stream of evidence and specific outcome. The 3-Tier approach proposed by the NTP/OHAT Handbook will be used to synthesise RoB evaluations across studies included in the same outcome. The tiered approach establishes a Tier for each study considering the RoB responses of every question, from Tier 1 (Most answers including from the key questions, rated as

“Definitely” or “Probably” low) to Tier 3 (Most answers including from the key questions, rated as “Definitely” or “Probably” high) (See details in Suppl. Mat. Section 3.2.1: Risk of Bias). The “Key Questions” are those domains which have a greater impact on the overall bias. Randomisation bias, outcome detection bias and performance bias related to blinding of assessors comprise the Key Questions for RoB assessment. The application of the tiered approach here does not seek to exclude Tier 3 (High Risk of Bias) studies but to support decisions for sub-group analysis based on RoB.

The entire assessment will be performed and registered within the Risk of Bias Module in the HAWC platform to ensure the transparency.

2.7. Confidence rating for each body of evidence

The health outcomes from each stream of data (*i.e. in vitro, in vivo*) will be considered as independent bodies of evidence. An assessment will be performed for each to determine a confidence rating reflecting the confidence with which the study findings accurately reflect a true effect of given organochlorine chemicals on endometriosis-related outcomes, following the NTP/OHAT Systematic Review framework, based on GRADE guidelines (OHAT, 2015a).

Each body of evidence is given an initial confidence rating, which is subsequently downgraded or upgraded according to factors that decrease or increase confidence in the results. Eventually both confidence ratings will be integrated to deliver a final rating for the overall body of evidence for the exposure of OCCs on endometriosis for both *in vivo* and *in vitro* studies.

Briefly, the initial confidence rating is determined by the presence or absence of four features (*i.e.* controlled exposure, exposure prior to outcome, individual outcome data, and use of comparison group) (Table 3). Both experimental animal studies and *in vitro* studies generally receive an initial “High confidence” rating, as controlled experimental study designs tend to incorporate all four features. This initial rating is then downgraded (*i.e.* Risk of Bias, Unexplained Inconsistency, Indirectness, Imprecision, Publication Bias) or upgraded (*i.e.* Magnitude, Dose Response, Consistency Across Species/Model) upon evaluation of the aforementioned factors (Table 2) (OHAT, 2015a). The confidence rating independently determined for each stream of evidence will then be combined to reflect the entire body of evidence. Full details on the confidence rating process can be found in the Suppl. Mat. 1 Section 3. Rating the Body of Evidence.

2.8. Translation of confidence rating into level of evidence

As the confidence rating in the body of evidence does not reflect the direction of the effect, a final step will be performed to translate the confidence rating into a level of evidence for the health effect according to NTP/OHAT framework.

OHAT proposes the following descriptors to translate the final confidence rating into the level of evidence for the health effect for each stream of evidence considering the confidence in the body of evidence and direction of the health effect (OHAT, 2015a):

- **High level of evidence:** There is high confidence in the body of

evidence for an association between exposure to the substance and the health outcome(s)

- **Moderate level of evidence:** There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- **Low level of evidence:** There is low confidence in the body of evidence for an association between exposure to the substance and the health outcome(s), or no data are available.
- **Evidence of no health effect:** There is high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s).
- **Inadequate evidence:** There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s).

The direction or nature of the effect will be considered in the translation process as following:

If there is evidence of a health effect, confidence in the body of evidence translates directly into one of four category descriptors for level of evidence of the health effect (“High”, “Moderate”, “Low”, or “Inadequate”). Only there is a high confidence in the body of evidence that there is no health effect will the level of evidence be considered that there is evidence of no health effect; otherwise, the level of evidence will be considered inadequate (Table 4). See details in Suppl. Mat. 1 Section 3.5: Translation of Confidence Rating into Level of Evidence.

2.9. Data synthesis

A narrative synthesis will be performed for data from both *in vivo* and *in vitro* studies. Data from each stream of evidence will be synthesised separately, supported by tables and plots summarising the main direction of effects using visualisation tools available in HAWC. Subgroup analyses will be performed as data deems fit. Though exact subgroups depend on the nature of extracted data and thus cannot be precisely anticipated, potential subgroups may include but are not limited to: animal model (e.g. primate, rodent-autologous, rodent-heterologous), chemical exposure (e.g. dioxins and dioxin-like chemicals, non-dioxin-like chemicals), experimental design (e.g. acute, subchronic, chronic, developmental), dosing regime (e.g. dosing levels, frequency, timing, duration, route of administration), variation in study risk of bias level (e.g. high risk of bias, low risk of bias) for specific domains or overall ratings. Subgroups will be analysed for their impact on not only degree of effect but also direction of effect. An emphasis will be placed on the primary and secondary outcomes of *in vivo* studies, using the evidence provided by *in vitro* studies as support.

Meta-analysis will be conducted only on primary outcome measures when at least two studies provide quantitative and commensurate data of the same endpoint and exposure that may be combined. The main objectives of the meta-analysis will be to evaluate the consistency

Table 4
Translation of confidence rating into level of evidence.

Confidence in the body of evidence	Direction of the effect	Level of evidence for the health effect
Health effect		
High	→	High
Moderate	→	Moderate
Low	→	Low
Very low or no evidence	→	Inadequate
No health effect		
High	→	Evidence of no health effect
Moderate	→	Inadequate
Low	→	Inadequate
Very low or no evidence	→	Inadequate

between studies, to estimate of the overall size and direction of associations and to identify sources of heterogeneity. If a quantitative synthesis is deemed appropriate, for dichotomous outcomes (e.g. spontaneous endometriosis onset in non-human primates), we will build contingency tables and calculate odds ratios. For continuous outcomes (e.g. proliferation of endometrial lesions) we will estimate the standardised mean difference (SMD) with 95% confidence intervals (CIs) using Hedge's G effect sizes which corrects for small sample size bias (Vesterinen et al., 2014). Between-study variance will be represented by tau-squared (τ^2). Inconsistency will be assessed with the I^2 statistic, which quantifies the heterogeneity and degree of inconsistency among studies, and will be interpreted according to the Cochrane's criteria. Potential small study bias will be evaluated by funnel plots and Egger's test (Harbord et al., 2006). Publication bias will be corrected with the “trim and fill” method, which trims the asymmetrical studies to estimate the true centre of the funnel plot, then fills the assumed missing studies (mirror image), allowing for the estimation of adjusted overall confidence intervals (Duval and Tweedie, 2000). The influence of each individual study in the meta-analysis will be investigated by omitting one study at the time, and re-calculating the summary estimates (leave-one-out method). The statistical analysis will be performed with R software. More details on study synthesis and calculations for potential bias adjustments can be found in Suppl. Mat. 1 Section 3: Rating the Body of Evidence.

3. Pilot study

3.1. Search string calibration

The search strings were refined and evaluated through an iterative process by applying targeted search terms to the different search engines. Details on the calibration process are available in the Supplementary Material 2. 658 articles were identified from PubMed, 375 from SCOPUS, and 497 in Web of Science.

3.2. Workflow feasibility pilot

A preliminary pilot was performed to test the feasibility of the proposed tools and protocol, and consisted of a literature search and subsequent study selection and data extraction process for a subset of studies published between 1996 and 1997. The above calibrated search string was applied to PUBMED, SCOPUS and WOS with dates filters limiting the studies between 1 and 1-1996 and 31-12-1997. No other filters were applied. Results of this feasibility pilot aim to provide clarity and transparency for the workflow of this review process (from literature review to data selection, risk of bias assessment, and data synthesis preparation) and are available in Supplementary Material 1 Annex 1.

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Conflict of interest

The authors declare no other conflict of interests.

Authors contributions

JPA and GCS performed problem formation and gathered the review team. KM and GCS coordinated protocol development. KM wrote the draft protocol, and SP, XC, MK, BLB and JPA have made substantial contributions and edits on the protocol draft version. Expertise on systematic review methodology, risk of bias and statistics was provided by JPA, GCS and KM; expertise on endocrinology, gynaecology and

pathophysiology was led by SP and MK; molecular biology and experimental modelling was covered by SC, MK and GCS; technical advice on endocrine disruption, exposure and risk assessment was provided by JPA, BLB and GCS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2018.12.063>.

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