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Supplemental Material

Associations between Exposure to Organochlorine Chemicals and Endometriosis: A Systematic Review of Experimental Studies and Integration of Epidemiological Evidence

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Section 3: Risk of bias

Risk of Bias Response Criteria

References

1. SECTION 1: TABLES

Table S1. Search string for PUBMED.

Block	Search Terms
Exposure	("Aldrin" [MeSH] OR "aldrin" [All Fields] OR "Isodrin" [All Fields] OR "Aldrine" [All Fields]OR"Chlordan" [MeSH] OR "Chlordan" [All Fields] OR "Chlordane" [All Fields] OR "Octachlor" [All Fields] OR "Octachlordane" [All Fields] OR "Dichlorochlordene" [All Fields] OR"Chlordecone"[MeSH] OR "Chlordecone" [All Fields] OR "Kepone" [All Fields] OR"Dieldrin"[MeSH] OR "Dieldrin"[All Fields] OR "Alvit 55"[All Fields] OR "Alvit"[All Fields] OR "Dieldren"[All Fields] OR "Dieldrex"[All Fields] OR "Dieldrine"[All Fields]OR"Endrin"[MeSH] OR "endrin"[All Fields] OR "hexadrin"[All Fields] OR "HEOD" [All Fields]OR "Heptachlor"[MeSH] OR "Heptachlor"[All Fields] OR "Agroceres"[All Fields] OR "Heptox"[All Fields] OR "Heptachlore"[All Fields]OR "Hexachlorobenzene"[MeSH] OR "hexachlorobenzene"[All Fields] OR "Perchlorobenzene"[All Fields] OR "HCB"[All Fields] OR "Hexachlorobenzol"[All Fields] OR "Anticarie"[All Fields] OR ("Hexachlorobutadiene"[Supplementary Concept] OR "hexachlorobutadiene"[All Fields]) OR "hexachlorobutadiene"[Supplementary Concept] OR "hexachlorobutadiene"[All Fields] OR "hexachloro-1,3-butadiene"[All Fields] OR "Hexachlorbutadiene"[All Fields] OR "Perchlorobutadiene"[All Fields] OR "HCBD"[All Fields]OR"Alpha hexachlorocyclohexane"[All Fields] OR "alpha-hexachlorocyclohexane"[Supplementary Concept] OR "alpha-hexachlorocyclohexane"[All Fields] OR "alpha-HCH"[All Fields]OR"Beta hexachlorocyclohexane"[All Fields] OR "beta-hexachlorocyclohexane"[Supplementary Concept] OR "beta-hexachlorocyclohexane"[All Fields] OR "beta-HCH"[All Fields] OR "beta-HCH"[All Fields] OR "beta-Lindane"[All Fields] OR "beta-hexachlorocyclohexane"[All Fields] OR ("Lindane"[MeSH Terms] OR "lindane"[All Fields]) OR "Lindane"[Mesh] OR "Lindane"[All Fields] OR "hexachlorane"[All Fields] OR "gamma-HCH"[All Fields] OR "Benzene hexachloride"[All Fields] OR "gamma-BHC"[All Fields] OR "Hexicide"[All Fields] OR "gamma 666"[All Fields] OR "Jacutin"[All Fields] OR ("Mirex"[MeSH Terms] OR "mirex"[All Fields]) OR "Mirex"[MeSH] OR "Dechlorane"[All Fields] OR "Perchloropentacyclodecane"[All Fields] OR "Paramex"[All Fields] OR "Dodecachloropentacyclodecane"[All Fields] OR "Dodecaclor"[All Fields]OR ("Pentachlorobenzene"[Supplementary Concept] OR "pentachlorobenzene"[All Fields]) OR "Pentachlorobenzene"[All Fields] OR "PeCB"[All Fields] OR "Pentachlorbenzol"[All Fields] OR ("Pentachlorophenol"[MeSH Terms] OR "pentachlorophenol"[All Fields]) OR "Pentachlorophenol"[MeSH] OR "Pentachlorophenol"[All Fields] OR "Permite"[All Fields] OR "Pentachlorophenate"[All Fields] OR "Chlorophen"[All Fields] OR "Lauxtol"[All Fields] OR "Dowicide 7"[All Fields] OR "Fungifen"[All Fields] OR "Liroprem"[All Fields] OR ((Polychlorinated[All Fields] OR Dichlorinated[All Fields] OR Trichlorinated[All Fields] OR Tetrachlorinated[All Fields] OR Pentachlorinated[All Fields] OR Hexachlorinated[All Fields] OR Heptachlorinated[All Fields] OR Octachlorinated[All Fields]) AND ("naphthalenes"[MeSH Terms] OR "naphthalenes"[All Fields] OR "napthalene"[All Fields])) OR chloronaphthalene[All Fields] OR (Short-chain[All Fields] AND chlorinated[All Fields] AND ("paraffin"[MeSH Terms] OR "paraffin"[All Fields] OR "paraffins"[All Fields])) OR (Technical[All Fields] AND ("endosulfan"[MeSH Terms] OR "endosulfan"[All Fields])) OR "115-29-7"[All Fields] OR "endosulfan sulfate"[All Fields]OR"Tetrabromodiphenyl ether"[All Fields] OR "pentabromodiphenyl ether"[Supplementary Concept] OR "pentabromodiphenyl ether"[All Fields] OR

	"halogenated diphenyl ethers"[MeSH Terms] OR (Tetrabromodiphenyl[All Fields] AND ("oxides"[MeSH Terms] OR "oxides"[All Fields] OR "oxide"[All Fields])) OR "2,2',4,5'-Tetrabromodiphenyl ether" OR "pentabromodiphenyl ether"[All Fields] OR "2,2',4,4',5-Pentabromodiphenyl ether" OR "2,2',4,4',6-Pentabromodiphenyl ether" OR "PBDE"[All Fields] OR"Toxaphene"[MeSH Terms] OR "toxaphene"[All Fields] OR "polychlorocamphene"[All Fields] OR"Dichloro-diphenyl-trichloroethane"[All Fields] OR "DDT"[All Fields] OR "DDT"[MeSH] OR "methoxychlor"[All Fields]OR"Hexachlorobutadiene"[All Fields] OR "HCBD"[All Fields] OR "hexachloro-1,3-butadiene"[All Fields] OR "hexachlorobuta-1,3-diene"[All Fields] OR "Hexachlorbutadiene"[All Fields]OR"Pentachlorobenzene"[Supplementary Concept] OR "pentachlorobenzene"[All Fields] OR "1,2,3,4,5-Pentachlorobenzene"[All Fields] OR "PeCB"[All Fields] OR "Pentachlorbenzol"[All Fields] OR (Polychlorinated[All Fields] AND dibenzo[All Fields] AND ("dioxins"[MeSH Terms] OR "dioxins"[All Fields])) OR "Dioxins and Dioxin-like Compounds"[MeSH] OR "Dibenzofurans, Polychlorinated"[MeSH] OR "Dioxins"[MeSH] OR TCDD[All Fields] OR "Polychlorinated Dibenzodioxins"[MeSH] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[All Fields] OR "Chlorinated Dibenzo-p-dioxins"[All Fields] OR "PCDD"[All Fields] OR "TCDD"[All Fields] OR "Tetrachlorodibenzodioxin"[All Fields] OR "Polychlorinated Biphenyls"[MeSh] OR "Polychlorinated Biphenyls"[All Fields] OR “Aroclors"[MeSH] OR "Aroclor"[All Fields] OR "Polychlorinated Biphenyl" OR "Dibenzofurans, Polychlorinated"[MeSH] OR "dibenzofurans"[All Fields] OR "polychlorinated dibenzofurans"[All Fields] OR ("polychlorinated"[All Fields] AND "dibenzofurans"[All Fields]) OR "Chlorodibenzofurans"[All Fields] OR pesticide* OR pesticides[Pharmacological Action] OR "pesticides"[MeSH Terms] OR pesticid*[All Fields] OR insecticide* OR insecticides[Pharmacological Action] OR "insecticides"[MeSH Terms] OR insecticid*[All Fields] OR "persistent organic pollutant" OR organochlor*[All Fields] OR polychlorinated[All Fields] OR "Hydrocarbons, Chlorinated"[Mesh] OR "Hydrocarbons, Halogenated"[Mesh])
Outcome	(endomet* OR Endometriosis[MeSH] OR endometriosis [tiab] or endometriosis [All fields] OR endometriotic [tiab] OR endometrial[All fields])

Note: Exposure block was connected to outcome block with boolean operator “AND”. Abbreviations: Medical Subject Headings (MeSH), title and abstract (tiab). Syntax was adapted for each of the other databases.

Table S2. List of all organochlorine chemicals identified as Persistent Organic Pollutants listed in the Stockholm Convention (UNEP 2017)

Nr	Annex	Name	Type	OCC
1	A[a]	Aldrin	Pesticide	Y
2	A	Chlordane	Pesticide	Y
3	A	Chlordecone	Pesticide	Y
4	A	Decabromodiphenyl ether (commercial mixture, c-decaBDE)	Industrial chemical	N
5	A	Difocal	Pesticide	Y
6	A	Dieldrin	Pesticide	Y
7	A	Endrin	Pesticide	Y
8	A	Heptachlor	Pesticide	Y
9	A	Hexabromobiphenyl	Industrial chemical	N
10	A	Hexabromocyclododecane (HBCDD)	Industrial chemical	N
11	A	Hexabromodiphenyl ether and heptabromodiphenyl ether	Industrial chemical	N
12	A	Hexachlorobenzene (HCB)	Pesticide, Industrial chemical	Y
13	A	Hexachlorobutadiene	Industrial chemical	Y
14	A	Alpha hexachlorocyclohexane	Pesticide	Y
15	A	Beta hexachlorocyclohexane	Pesticide	Y
16	A	Lindane	Pesticide	Y
17	A	Mirex	Pesticide	Y
18	A	Pentachlorobenzene	Pesticide, Industrial chemical	Y
19	A	Pentachlorophenol and its salts and esters	Pesticide	Y
20	A	Perfluorooctanoic acid (PFOA), its salts and PFOA-related compounds	Industrial Chemical	N
21	A	Polychlorinated biphenyls (PCB)	Industrial chemical	Y
22	A	Polychlorinated naphthalenes	Industrial chemical	Y
23	A	Short-chain chlorinated paraffins (SCCPs)	Industrial chemical	Y
24	A	Technical endosulfan and its related isomers	Pesticide	Y
25	A	Tetrabromodiphenyl ether and pentabromodiphenyl ether	Industrial chemical	N
26	A	Toxaphene	Pesticide	Y
27	B[b]	DDT	Pesticide	Y
28	B	Perfluorooctane sulfonic acid, its salts and perfluorooctane sulfonyl fluoride	Pesticide, Industrial chemical	N
29	C[c]	Hexachlorobenzene (HCB)	Unintentional Production	Y
30	C	Hexachlorobutadiene (HCBD)	Unintentional Production	Y
31	C	Pentachlorobenzene	Unintentional Production	Y
32	C	Polychlorinated biphenyls (PCB)	Unintentional Production	Y
33	C	Polychlorinated dibenzo-p-dioxins (PCDD)	Unintentional Production	Y
34	C	Polychlorinated dibenzofurans (PCDF)	Unintentional Production	Y
35	C	Polychlorinated naphthalenes	Unintentional Production	Y

[a]Annex A – "Parties must take measures to eliminate the production and use of [these] chemicals"
[b]Annex B – "Parties must take measures to restrict the production and use of [these] chemicals"
[c]Annex C – "Parties must take measures to reduce the unintentional releases of [these] chemicals…with the goal of continuing minimization and, where feasible, ultimate elimination"

Table S3. Data extraction items.

Study Identification Information		
Study Identification	COI Reported	Author Contact Information
Study URL	COI Details	Author Contacted
Short Citation	Funding Source	Study Summary
Full Citation	Study Type (Animal Bioassay, In Vitro)	
In Vivo		
Animal Group Information		
Experiment Identification	Chemical Source	Diet
Experiment Name	Purity Available/Qualifier	Litter Effects
Experiment Type	Purity	Guidance Compliance
Chemical Name/CAS	Vehicle	Experiment Description
Animal Group Species	Animal Group Strain	Animal Source
Life Stage Exposed	Life Stage Assessed	Observation Duration
Dosing Regime Information		
Dosing Regime Identification	Duration of Exposure	Positive Control
Dosed Animal Group	Duration of Exposure Description	Negative Control
Route of Exposure	Number of Dose Groups	Dosing Regime Description
Endpoint Information		
Endpoint Identification	Confidence Interval	Additional Endpoint Fields
Endpoint Name	Data Reported	Dose Units
System	Data Extracted	Dose Group
Organ	Values Estimated	Sample Size (N)
Effect	Expected Adversity Direction	Incidence
Effect Subtype	Monotonicity	Response
Observation Time	Statistical Test	Variance
Observation Time Units	Trend Value	Lower CI
Observation Time Description	Trend Result	Upper CI
Data Location in Text	Diagnostic for Determination	Significance
Response Units	Power Notes	Significance Level
Data Type (Continuous, Dichotomous)	Results Notes	NOEL/LOEL/FEL
Variance Type (SE, SD)	Endpoint Notes	
In Vitro		
Chemical Identification	Dose Units	NOEL/LOEL
Chemical Name	Metabolic Activation	Monotonicity
CAS	Transfection	Overall Pattern
Chemical Purity	Endpoint Identification	Trend Test Result
Experiment Identification	Endpoint Name	Minimum Dose
Cell Origin Species	Endpoint Description	Maximum Dose
Cell Origin Strain	Assay Type	Number of Doses
Cell Origin Sex	Response Units	Change from Control
Cell Type	Observation Time	Significance ($P < 0.05$)
Cell Tissue	Observation Time Units	Cytotoxicity

Note: Abbreviations in order of appearance: Conflict of Interest (COI), Chemical Abstracts Service (CAS), Confidence Interval (CI), No Observed Effect Level (NOEL), Lowest Observed Effect Level (LOEL), Frank Effect Level (FEL), Standard Error (SE), Standard Deviation (SD)

Table S4. Summary of confidence rating procedure (OHAT, 2015).

Initial Confidence by Key Features* of Study Design	Factors Decreasing Confidence	Factors Increasing Confidence	Confidence in the Body of Evidence
High (++++) – 4 features	• Risk of Bias • Unexplained Inconsistency • Indirectness • Imprecision • Publication Bias	• Large Magnitude of Effect • Dose Response • Consistency −across animal models or species −across dissimilar populations −across study design types	High (++++)
Moderate (+++) – 3 features			Moderate (+++)
Low (++) – 2 features			Low (++)
Very Low (+) – ≤1 feature			Very Low (+)

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

Note: Adapted from Figure 6 in the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, by NTP/OHAT, 9 Jan 2015. Retrieved from. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

Table S5. Determination of initial confidence rating based on confidence features of study design.

Study Design	Controlled Exposure	Exposure Prior to Outcome	Individual Outcome Data	Comparison Group Used	Initial Confidence Rating
Experimental Animal Study	likely	likely	likely	likely	**HIGH**
In vitro	likely	likely	likely	likely	**HIGH**

Note: Adapted from Table 8 in the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, by NTP/OHAT, 9 Jan 2015. Retrieved from. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

Table S6. 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

Note: Adapted from Figure 7 in the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, by NTP/OHAT, 9 Jan 2015. Retrieved from. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

- **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).

Table S7. Inventory of chemicals studied in i*n vivo* and *in* vitro studies and the number of experiments studying each chemical.

Chemical	Abbreviation	*In vivo*	*In vitro*
2,3,7,8-Tetrachlorodibenzo-p-dioxin	TCDD	11	16
1,3,6,8-tetrachlorodibenzo-p-dioxin	1,3,6,8-TCDD	1	0
2,3,4,7,8-pentachlorodibenzofuran	4-PeCDF	1	0
3,3',4,4'-tetrachlorobiphenyl	PCB 77	0	1
2,2',4,6,6'-Pentachlorobiphenyl	PCB 104	0	1
3,3',4,4',5-pentachlorobiphenyl	PCB 126	2	3
2,2',4,4',5,5'-Hexachlorobiphenyl	PCB 153	2	2
2,2-dichlorodiphenyl-1,1,1-trichloroethane	p,p’-DDT	0	1
2,2-bis(p-chlorophenyl)ethylene	p,p'-DDE	0	1
2,2-Bis(o,p-chlorophenyl)-1,1,1-trichloroethane	o,p'-DDT	0	2
Hexachlorobenzene	HCB	1	1
4-Chlorodiphenylether	4-CDE	2	0
Atrazine	ATR	0	1
Methoxychlor	MXC	1	0

Table S8. Inventory of cell types of *in vitro* studies and the number of experiments using each cell type.

Cell Type		Count	Total
Endometrial Stromal Cells (ESCs)			16
	unspecified	6	
	eutopic	6	
	ectopic	2	
	immortalised	2	
ESC co-cultures			10
	U937-ESC-HMPC Co-culture	4	
	U937-ESC Co-culture	2	
	ESC-HMPC Co-culture	1	
	ESC-EEC Co-culture	2	
	ESC-monocyte Co-culture	1	
Endometrial Epithelial Cells (EECs)			1
	immortalised	1	
Endometrial Endothelial Cells (EEnCs)			2
	unspecified	2	
Tissues			3
	Endometrial Explant	2	
	Uterine Fibroblasts	1	
Other			1
	Granulosa Cells	1	

Note: Study experiments may contain more than one type of cell.

2. SECTION 2: FIGURES

2.1 METHODS: DATA EXTRACTION PROCESS EXAMPLES

Foster et al. 1997

Actions

Data type(s)	Animal bioassay
Full citation	Foster WG et al. Morphologic characteristics of endometriosis in the mouse model: application to toxicology. Canadian Journal of Physiology and Pharmacology 1997; 75 (10-11):1188-1196.
Abstract	Surgically induced endometriosis in the mouse has been described as a model to investigate the effect of environmental pollutants on the growth of endometriotic implants. The objectives of this study were to evaluate a modified surgical procedure to induce endometriosis and validate the model by comparing the effects of estrogen, 4-chlorodiphenyl ether (4-CDE) as a possible estrogenic contaminant, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a contaminant with predominantly anti-estrogenic activities, on the growth of endometrial implants. Uterine strips (1.0 x 4.0 mm(2)) were autotransplanted to multiple sites in the abdomen of sexually mature female B6C3F1 mice (n = 33), which were randomly assigned to the following groups: intact control (n = 4); ovariectomized (OVX, n = 9); OVX and treated with 4-CDE (n = 6); OVX and treated with 17 beta-estradiol (E-2, n = 9); and OVX and treated with E-2 plus TCDD (n = 5). Endometrial implants survived warm ischemia regardless of implant site and appeared as small clear spherical or ovoid fluid-filled cysts. The diameter of the endometrial cysts in the OVX animals was significantly ($p < 0.0001$) smaller compared with the intact animals and OVX animals replaced with E-2 or 4-CDE. In contrast, TCDD treatment inhibited the growth of endometrial cysts in the presence of estrogen. We conclude that autotransplantation of uterine slices to multiple abdominal sites results in formation of endometriotic cysts that are responsive to estrogen, and that environmental contaminants possess the potential to affect the survival and growth of endometrial cysts. Therefore, we concluded that the mouse endometriosis model described in this paper has applications to investigate the possible role of environmental pollutants in the development of endometriosis.
Reference hyperlink	• DOI
Literature review tags	Animal Study Murine Mouse
COI reported	Not reported
Funding source	Not reported
Author contacted?	✔

Figure S1. Example of general study data form in HAWC .

Available animal bioassay experiments

Name	Type	Comments
4-CDE 30-day mouse endometriosis	Short-term (1-30 days)	Animals were housed in polycarbonate cages in rooms maintained at 22 ± 2°C and between 30 and 50% relative humidity. Lights were on from 07:00 to 19:00. Free access to food (Purina mouse chow) and water was maintained throughout the study.
TCDD 30-day mouse endometriosis	Short-term (1-30 days)	Animals were housed in polycarbonate cages in rooms maintained at 22 ± 2°C and between 30 and 50% relative humidity. Lights were on from 07:00 to 19:00. Free access to food (Purina mouse chow) and water was maintained throughout the study.

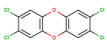
Figure S2. Example of animal bioassay (*in vivo*) experiment(s) form in HAWC.

TCDD 30-day mouse endometriosis

Actions

Name	TCDD 30-day mouse endometriosis
Type	Short-term (1-30 days)
Multiple generations	No
Chemical	TCDD
CAS	1746-01-6
DTXSID	DTXSID2021315: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CASRN 1746-01-6)
Chemical source	AccuStandard
Chemical purity	>99%
Guideline compliance	Canadian Council on Animal Care guidelines
Description and animal husbandry	Animals were housed in polycarbonate cages in rooms maintained at 22 ± 2°C and between 30 and 50% relative humidity. Lights were on from 07:00 to 19:00. Free access to food (Purina mouse chow) and water was maintained throughout the study.

Substance information



Common name	2,3,7,8-Tetrachlorodibenzo-p-dioxin
DTXSID	DTXSID2021315
CASRN	1746-01-6
SMILES	ClC1=CC2=C(OC3=C(O2)C=C(Cl)C(Cl)=C3)C=C1Cl
Molecular weight	321.96

Chemical information provided by USEPA Chemicals Dashboard

Available animal groups

Name	Species	Strain	Sex	Siblings
Female B6C3F1 Mice	Mouse	B6C3F1	Female	None

Figure S3. Example of animal bioassay (*in vivo*) experiment data form in HAWC.

Female B6C3F1 Mice

Actions

Name	Female B6C3F1 Mice
Species	Mouse
Strain	B6C3F1
Sex	Female
Source	commercial breeder
Lifestage exposed	adult
Lifestage assessed	adult
Diet	Purina mouse chow and water (free access)

Dosing regime

Route of exposure	Subcutaneous injection
Exposure duration	daily injection, for 30 days
Duration observation	30 days
Number of dose-groups	2
Positive control	No
Negative control	Vehicle-treated
Doses	**µg/kg-day** 0 0.1
Description	**Treatment**: OVX and treated with E2 plus TCDD at a dose of 100 ng/kg/day (n = 5). **Negative control**: OVX and treated with 17b-estradiol via silastic capsule implanted subcutaneously

Available endpoints

			Groups µg/kg-day	
↕ Endpoint	**Organ**	**Obs. time**	**0**	**0.1**
Sample Size	-	-	8	5
Endometriotic Site Diameter	Endometrium	-	3.52 ± 0.339	1.87 ± 0.045 (-47%)[a]

[a] Significantly different from control ($p < 0.05$)

Figure S4. Example of animal bioassay (*in vivo*) group data form in HAWC.

Endometriotic Site Diameter

Actions

Endpoint Details

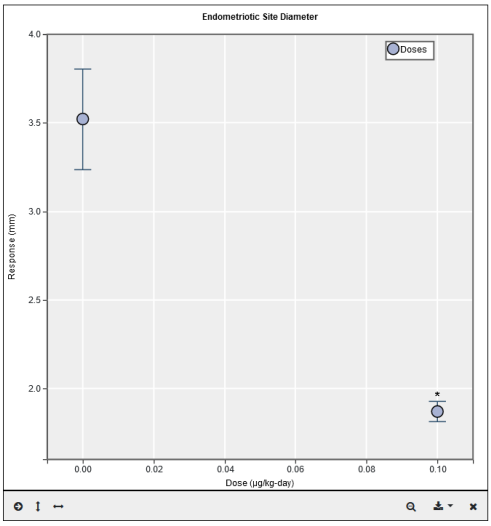
Endpoint name	Endometriotic Site Diameter
System	Reproductive
Organ	Endometrium
Effect	Size of endometriotic implant
Effect subtype	Lesion Diameter
Diagnostic description	necropsy
Data reported?	✔
Data extracted?	✔
Values estimated?	✔
Location in literature	Figure 3
Monotonicity	N/A, single dose level study
Statistical test description	1-way ANOVA
Trend result	not reported
Results notes	E2; 3,52 (E2 UL; 3,64) TCDD; 1,87 (TCDD UL; 1,89) E2 is control with estradiol "TCDD treatment significantly suppressed the stimulating effects of E2 on the growth of endometrial lesions"

Dataset

Dose (µg/kg-day)	Number of Animals	Response (mm)	Standard Error
0	8	3.52	0.12
0.1[a]	5	1.87	0.02

[a] Significantly different from control ($p < 0.05$)

Plot



Methodology

Compared to OVX no treatment, TCDD treated mice had larger lesions.

But compared to OVX+Estradiol treatment, TCDD duppressed estrogenic activities

Figure S5. Example of dose-response endpoint visualisation in HAWC

2.2 METHODS: HAZARD IDENTIFICATION

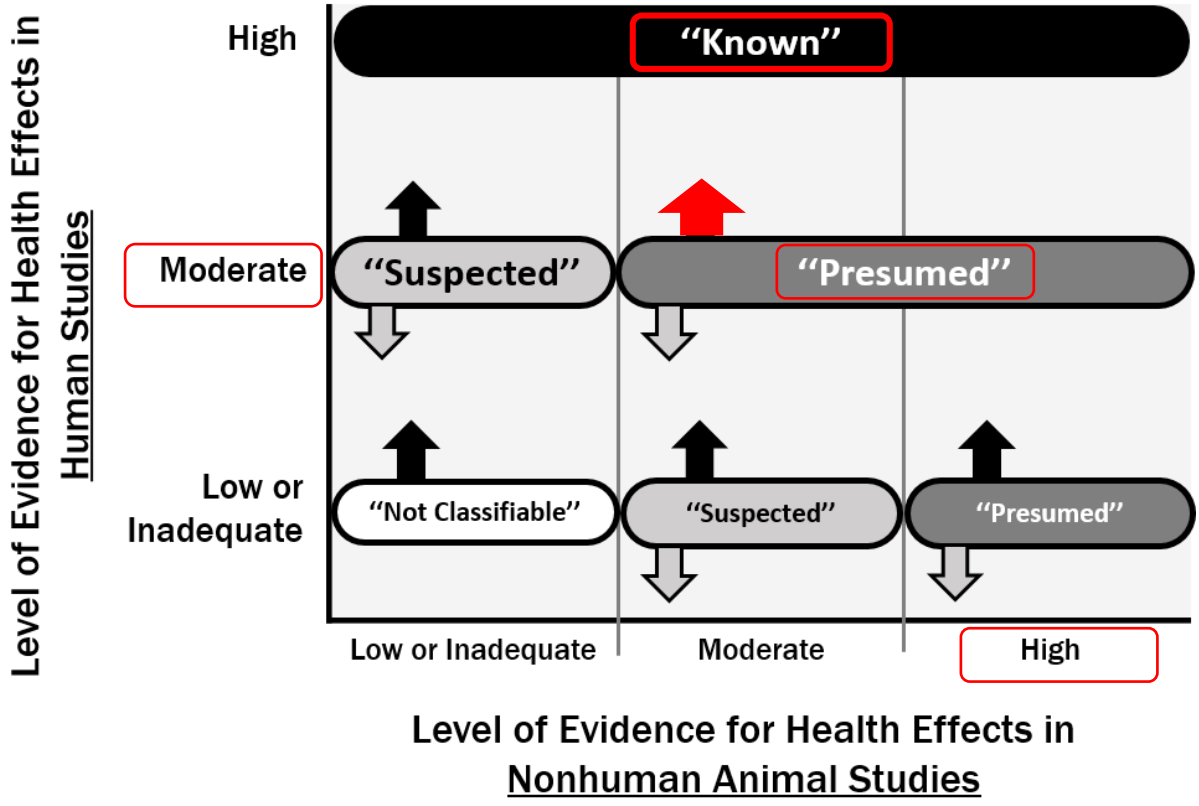


Figure S6. Hazard Identification Scheme.

Note: Reprinted from Figure 8 in the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, by NTP/OHAT, 9 Jan 2015. Retrieved from. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

2.3 RESULTS: RISK OF BIAS

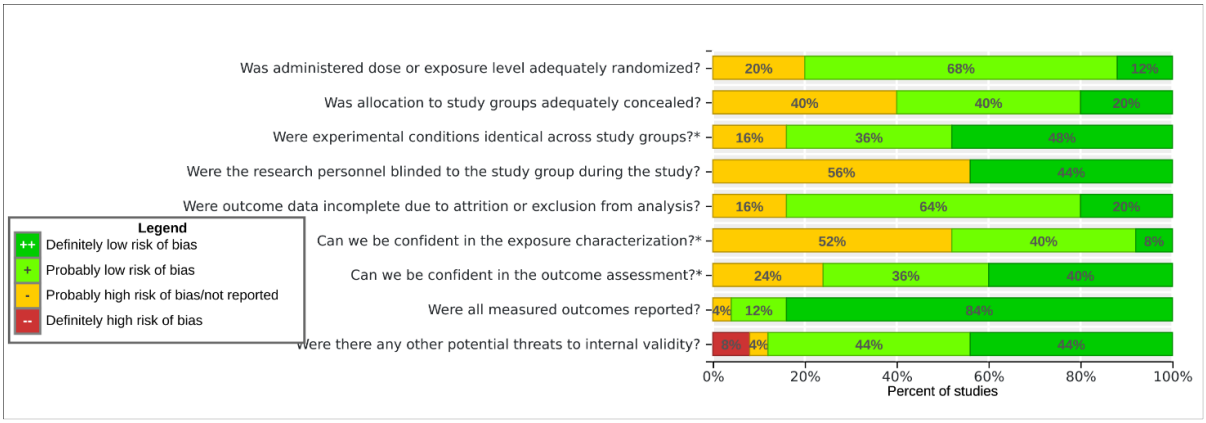


Figure S7. Risk of Bias Assessment of individual studies on all primary endpoints. Ratings are illustrated by percentage (out of 25 total studies; n = 16 for *in vivo* studies, n = 9 for *in vitro* studies). Interactive figure with additional information and justifications in HAWC **Figure S7**.

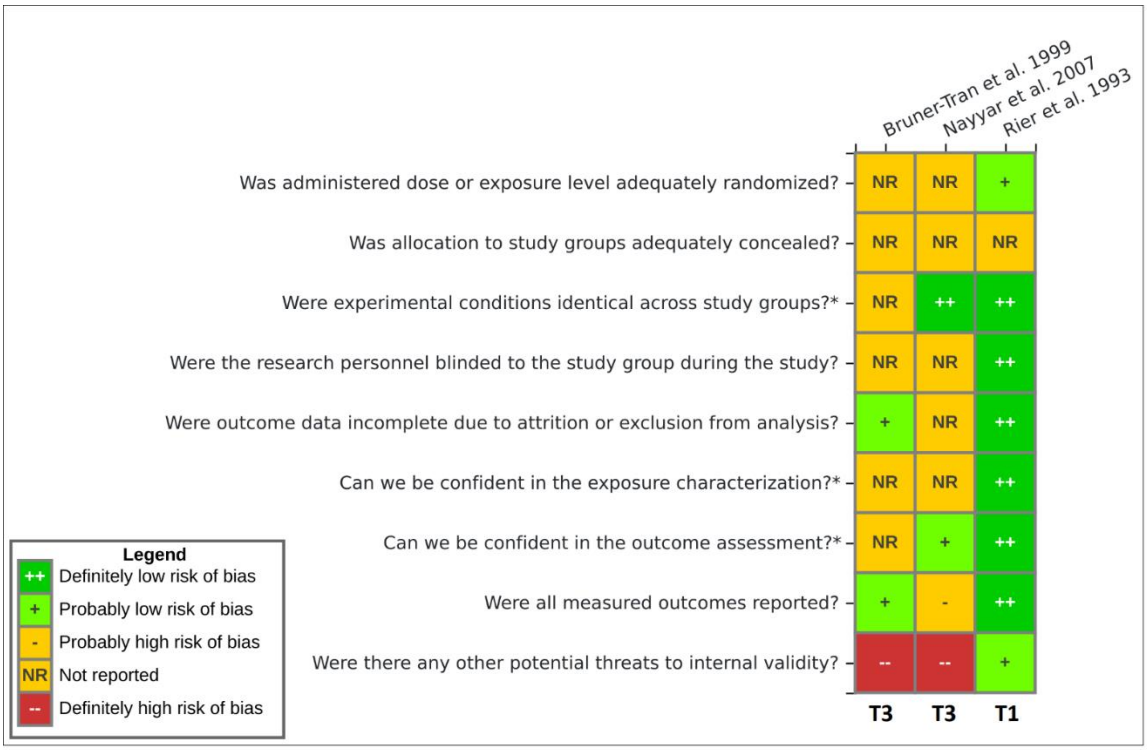


Figure S8. Risk of bias (RoB) heatmap for TCDD on *in vivo* onset. Key elements are marked by *. Tiers 1-3 are tiered rankings as determined by responses to the RoB questions. Tier 1 (T1) study responses are mostly "definitely low" and "probably low". Tier 3 (T3) responses are mostly "not reported" or "probably high" or "definitely high". Interactive figure with additional information and justifications in HAWC **Figure S8**.

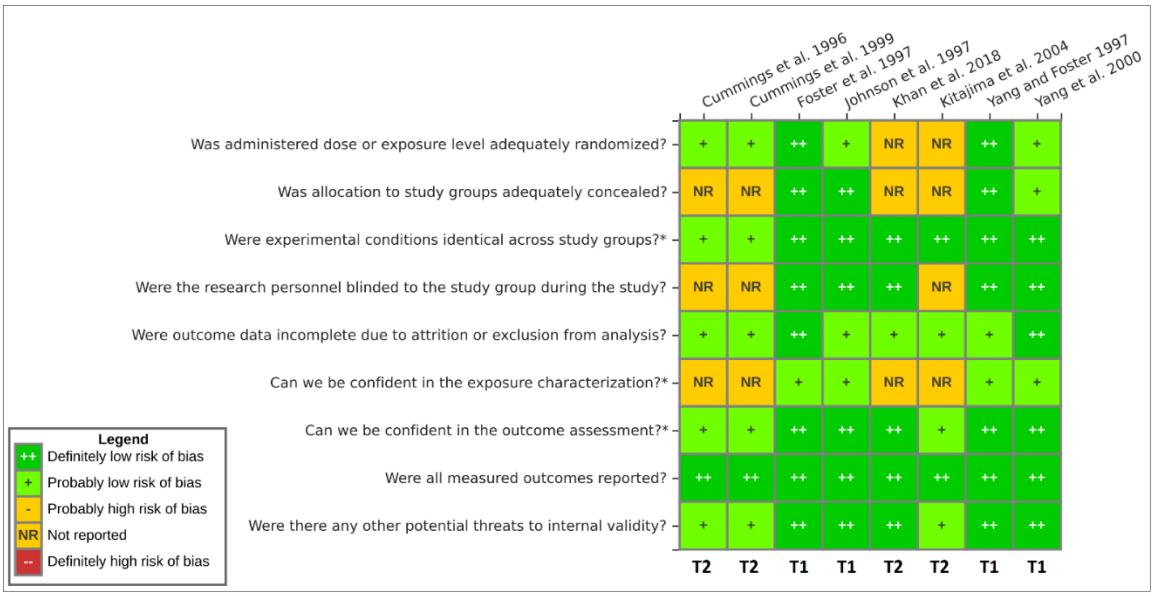


Figure S9. Risk of bias (Rob) heatmap for TCDD on *in vivo* lesion growth. Key elements are marked by *. Tiers 1-2 are tiered rankings as determined by responses to the RoB questions. Tier 1 (T1) study responses are mostly "definitely low" and "probably low". Tier 2 (T2) responses are mostly "probably low" with some "not reported". Interactive figure with additional information and justifications in HAWC **Figure S9**.

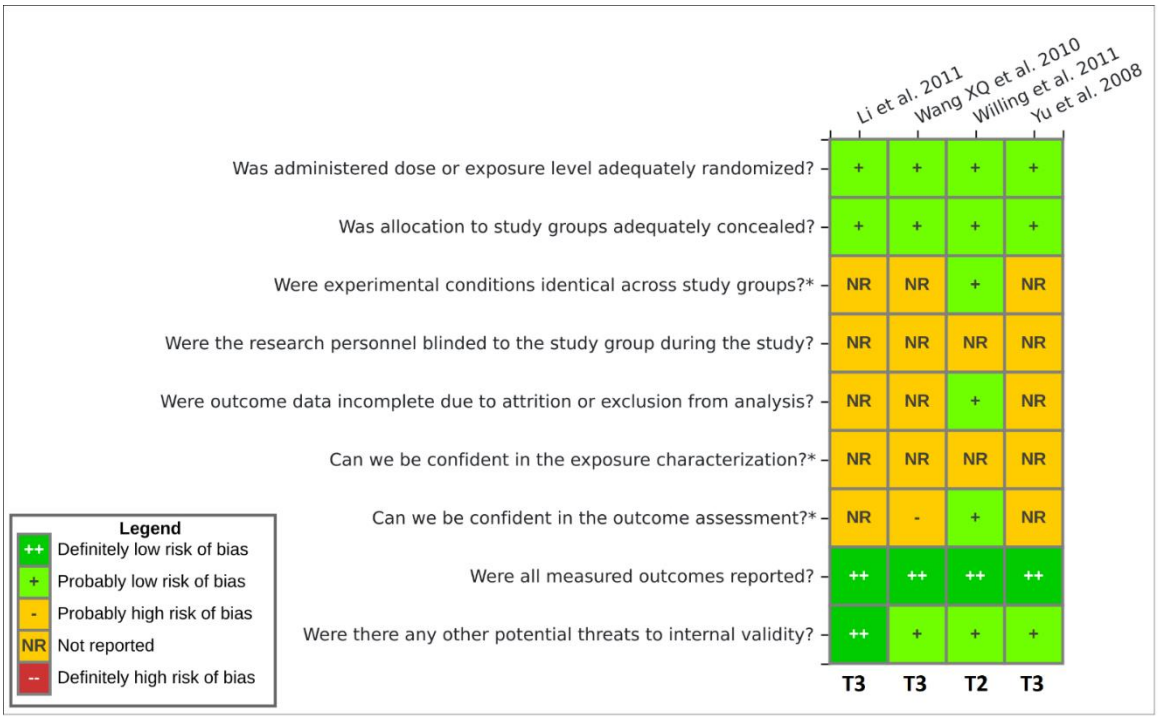


Figure S10. Risk of bias (RoB) heatmap for TCDD on *in vitro* migration/invasion. Key elements are marked by *. Tiers 2-3 are tiered rankings as determined by responses to the RoB questions. Tier 2 (T2) responses are mostly "probably low" with some "not reported". Tier 3 (T3) responses are mostly "not reported" or "probably high" or "definitely high". Interactive figure with additional information and justifications in HAWC **Figure S10**.

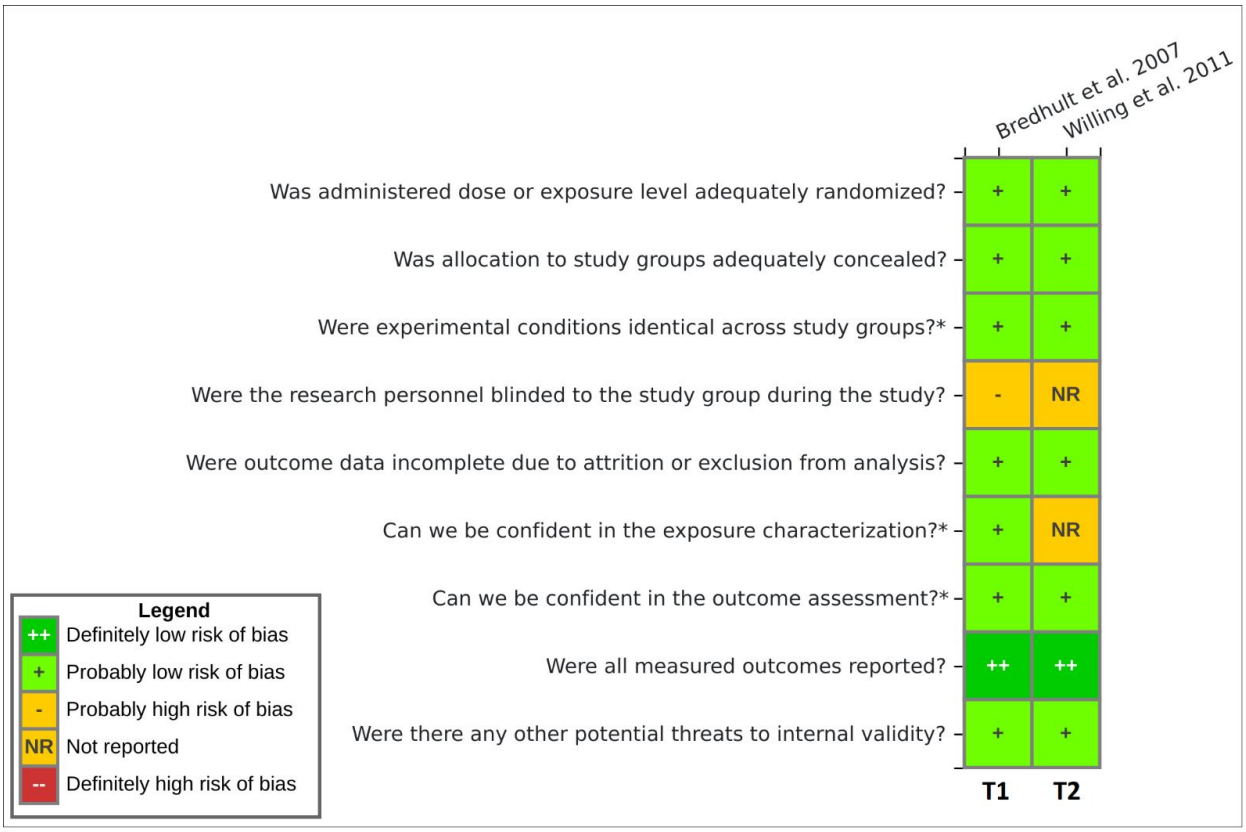


Figure S11. Risk of bias (RoB) heatmap for TCDD on *in vitro* viability/proliferation. Key elements are marked by *. Tiers 1-2 are tiered rankings as determined by responses to the RoB questions. Tier 1 (T1) study responses are mostly “definitely low” and “probably low”. Tier 2 (T2) responses are mostly “probably low” with some “not reported”. Interactive figure with additional information and justifications in HAWC **Figure S11**.

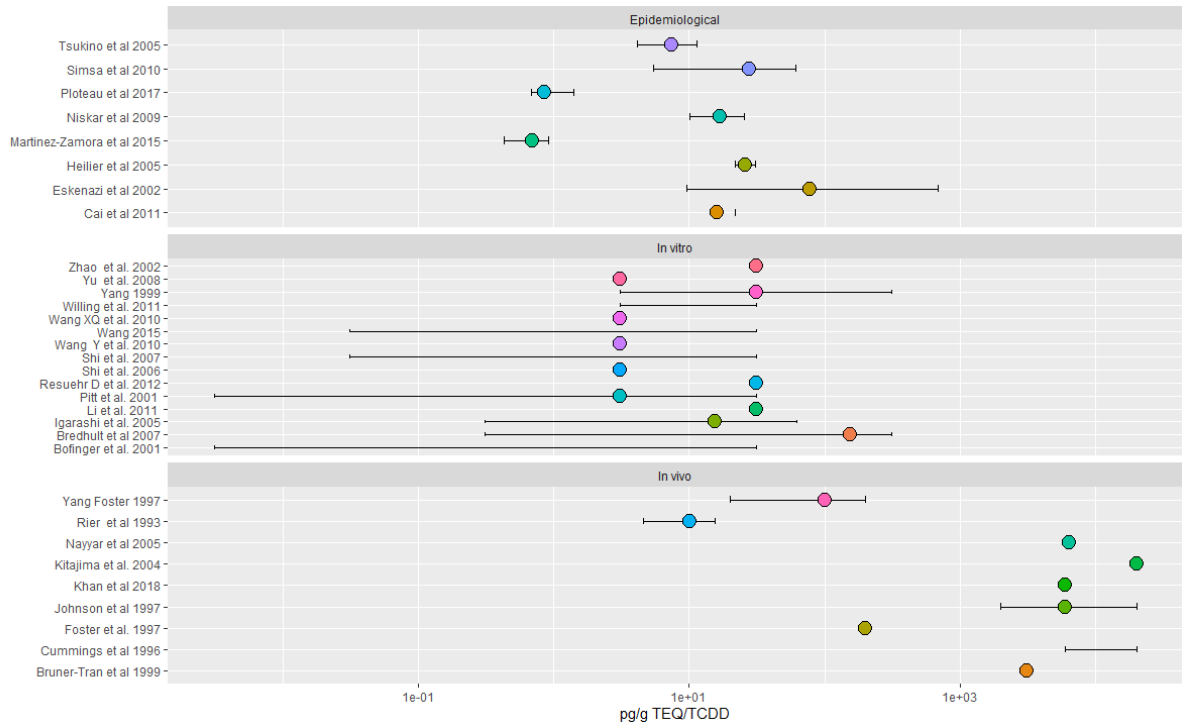


Figure S12. Tested doses of TCDD (pg/g TEQ/TCDD) in *in vitro* and *in vivo* studies plotted to compare with measured internal doses from human epidemiological studies.

Note: Epidemiological studies included here were reviewed in Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis, by Cano-Sancho et al., 2019, *Environment International*, Vol 123, p. 209-223, https://doi.org/10.1016/j.envint.2018.11.065.

3. SECTION 3: RISK OF BIAS

RISK OF BIAS RESPONSE CRITERIA

The following criteria was used to determine Risk of Bias rating for individual studies, using the NTP/OHAT Risk of Bias Tool (OHAT, 2015b) and the OHAT Evaluation of PFOA or PFOS Exposure Protocol, for *in vitro* studies (NTP 2016):

Q1. Was administered dose or exposure level adequately randomized?

Randomization of exposure or sequence generation (along with allocation concealment in question #2) helps to assure that treatment is not given selectively based on potential differences in experimental animals. Randomization requires that each subject had an equal chance of being assigned to any study group including controls (e.g., use of random number table or computer generated randomization). This applies to a concurrent negative control group (i.e., a group for which exposure is to vehicle or media alone or un-treated) which must be included in the study to address randomization as well as any positive control group that may be part of the study.

- *Definitely Low risk of bias*: There is direct evidence that animals were allocated to any study group including controls using a method with a random component, AND there is direct evidence that the study used a concurrent control group as an indication that randomization covered all study groups.
    - For *in vitro* studies: OR all cells in culture come from a homogenous cell suspension recently collected from cell culture vessels following appropriate cell culture techniques
- *Probably Low risk of bias*: There is indirect evidence that animals/cells were allocated to any study group including controls using a method with a random component (i.e., authors state that allocation was random, without description of the method used), AND there is direct or indirect evidence that the study used a concurrent control group as an indication that randomization covered all study groups, OR it is deemed that allocation without a clearly random component during the study would not appreciably bias results.
- *Probably High risk of bias*: There is indirect evidence that animals/cells were allocated to study groups using a method with a non-random component, OR there is indirect evidence that there was a lack of a concurrent control group

- *Definitely High risk of bias*: There is direct evidence that animals/cells were allocated to study groups using a non-random method including judgment of the investigator, the results of a laboratory test or a series of tests.
- *Not Reported*: There is insufficient information provided about how subjects were allocated to study groups.

Q2. Was allocation to study groups adequately concealed?

Allocation concealment prior to assigning the exposure level or treatment group (along with randomization in question #1) helps to assure that treatment is not given selectively based on potential differences in experimental animals or cell groups. Allocation concealment requires that research personnel allocating animals or cells to treatment groups (including the control group) could not foresee which administered dose or exposure level is going to be assigned at the start of a study. A lack of allocation concealment can bias results away from the null towards larger effect sizes.

- *Definitely Low risk of bias*: There is direct evidence that at the time of assigning study groups the research personnel did not know what group animals/cells were allocated to, and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable.
    - For *in vitro* studies: This may also be the case for *in vitro* studies with very low potential differences between cells that comprise the different groups, e.g., cells pipetted from a homogeneous cell suspension (single or mixed cell types) recently collected from cell culture vessels by accepted methods.
- *Probably Low risk of bias*: There is indirect evidence that at the time of assigning study groups the research personnel did not know what group animals/cells were allocated to and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable, OR it is deemed that lack of adequate allocation concealment would not appreciably bias results.
- *Probably High risk of bias*: There is indirect evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals/cells were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable.
- *Definitely High risk of bias*: There is direct evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals/cells were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable.

- *Not Reported*: There is insufficient information provided about allocation to study groups.

Q3. Were experimental conditions identical across study groups?

Housing conditions and husbandry practices should be identical across control and experimental groups because these variables may impact the outcome of interest (Duke, Zammit, & Lawson, 2001; Gerdin et al., 2012). Identical conditions include use of the same vehicle in control and experimental animals.

- *Definitely Low risk of bias*: There is direct evidence that same vehicle was used in control and experimental animals, AND there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).
    - For *in vitro* studies: Direct evidence that culture conditions included identical concentrations of any solvents (e.g., DMSO) used in getting the treatment compound into solution, AND the same media was used for control and experimental cells particularly for biological materials such as serum which must be from the same lot, AND appropriate adjustments were made such as normalization to blank/media controls, cell numbers in culture, use of positive and negative control responses in acceptance criteria, or others, AND non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).
- *Probably Low risk of bias*: There is indirect evidence that the same vehicle was used in control and experimental animals/cells, OR it is deemed that the vehicle used would not appreciably bias results AND as described above, identical non-treatment-related experimental conditions are assumed if authors did not report differences in housing or husbandry.
- *Probably High risk of bias*: There is indirect evidence that the vehicle differed between control and experimental animals/cells, OR there is indirect evidence that non-treatment-related experimental conditions were not comparable between study groups.
- *Definitely High risk of bias*: There is direct evidence from the study report that control animals/cells were untreated, or treated with a different vehicle than experimental animals/cells, OR there is direct evidence that non-treatment-related experimental conditions were not comparable between study groups.
- *Not Reported*: Authors did not report the vehicle used

Q4. Were the research personnel blinded to the study group during the study?

Blinding requires that research personnel do not know which administered dose or exposure level the animal subject is being given (i.e., study group). In animal studies, blinding of study group during the course of the study is often not possible for animal welfare considerations and the need to determine if treated animals are affected relative to controls in a treatment or dose-dependent manner (examples include clinical observations and histopathologic assessment of non-neoplastic lesions). Knowledge and tracking of higher exposed animals may also be part of animal welfare practices designed to avoid suffering associated with overtly toxic treatment doses. Under some conditions it is unlikely that blinding of research personnel during the course of a study can be fully achieved. However, animal studies are in general more tightly controlled than human studies and additional measures may be taken to reduce the risk of bias, such as the generation and use of standard operating procedures, training, and randomized husbandry or handling practices (e.g., placement in the animal room, necropsy order, etc.).

- *Definitely Low risk of bias*: There is direct evidence that the research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.
    - For *in vitro* studies: OR the use of robotic testing systems during the study that are deemed to eliminate the opportunity for performance bias to influence results.
- *Probably Low risk of bias*: There is indirect evidence that the research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study, OR it is deemed that lack of adequate blinding during the study would not appreciably bias results.
- *Probably High risk of bias*: There is indirect evidence that the research personnel were not adequately blinded to study group.
- *Definitely High risk of bias*: There is direct evidence that the research personnel were not adequately blinded to study group.
- *Not Reported*: There is insufficient information provided about blinding to study group during the study.

Q5. Were outcome data incomplete due to attrition or exclusion from analysis?

Attrition or exclusion because of illness, death, or other reasons can introduce bias when missing outcome data are related to both exposure and outcome. Attrition bias can potentially change the collective (group) characteristics of the relevant groups and their observed outcomes in ways that affect study results by confounding and spurious associations (Viswanathan M et al., 2012). Concern over bias from incomplete outcome data is mainly theoretical and most studies that have looked at

whether aspects of missing data are associated with magnitude of effect estimates have not found clear evidence of bias (reviewed in Higgins and Green 2011). In In vitro studies, loss of cells due to test chemical toxicity may seriously alter the interpretation of results from specific assays, thus viability assays at same tested doses and incubation condition should be included to rule out unwanted interactions (OECD 2018).

- *Definitely Low risk of bias*: There is direct evidence that loss of animals (or cells, for *in vitro* studies) was adequately addressed and reasons were documented when animals (or wells/plates, for *in vitro* studies) were removed from a study. Acceptable handling of attrition includes: very little missing outcome data; reasons for missing animals/cells unlikely to be related to outcome (or for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; missing outcomes is not enough to impact the effect estimate, OR missing data have been imputed using appropriate methods (insuring that characteristics of missing individuals are not significantly different from ones retained in the analysis).
- *Probably Low risk of bias*: There is indirect evidence that loss of animals/cells was adequately addressed and reasons were documented when animals/cells were removed from a study, OR it is deemed that the proportion lost would not appreciably bias results. This would include reports of no statistical differences in characteristics of animals/cells removed from the study from those remaining in the study.
- *Probably High risk of bias*: There is indirect evidence that loss of animals/cells was unacceptably large and not adequately addressed.
- *Definitely High risk of bias*: There is direct evidence that loss of animals/cells was unacceptably large and not adequately addressed. Unacceptable handling of attrition or exclusion includes: reason for loss is likely to be related to true outcome, with either imbalance in numbers or reasons for loss across study groups.
- *Not Reported*: There is insufficient information provided about loss of animals/cells.

Q6. Can we be confident in the exposure characterization?

This considers the accuracy of the exposure characterization, including both purity and stability for controlled exposure studies. The risk of bias associated with exposure to impurities depends on the identity of the impurities and the sensitivity of the outcome of interest which could result in potential effects of those impurities on the outcome of interest.

- *Definitely Low risk of bias*: There is direct evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was independently characterized and purity confirmed generally as ≥99% for single substance or non-mixture evaluations, AND that exposure was consistently administered (i.e., with the same method and time-frame) across treatment groups.
- *Probably Low risk of bias*: There is indirect evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was independently characterized and purity confirmed generally as ≥99% (i.e., the supplier of the chemical provides documentation of the purity of the chemical), OR direct evidence that purity was independently confirmed as ≥98% it is deemed that impurities of up to 2% would not appreciably bias results, AND there is indirect evidence that exposure was consistently administered (i.e., with the same method and time-frame) across treatment groups.
- *Probably High risk of bias*: There is indirect evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was assessed using poorly validated methods.
- *Definitely High risk of bias*: There is direct evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was assessed using poorly validated methods.
- *Not Reported*: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.

Q7. Can we be confident in the outcome assessment?

"Detection bias can be minimized by using valid and reliable methods to assess the outcome applied consistently across groups (i.e., under the same method and time-frame). Objectivity of the outcome assessment and the need for blinding are two sides of the same issue. Blinding requires that outcome assessors do not know the study group or exposure level of the animal when the outcome was assessed. The objectivity of procedures used for measuring and reporting an outcome will impact the degree to which outcome assessors could bias the reported results."

In most animal species, endometriosis cannot spontaneously occur, so endometriotic lesions must be induced by surgical implantation of autologous endometriotic tissues into the animals' uterus (Vernon and Wilson 1985) for rats and (Cummings and Metcalf 1995a) for mice. Lesions are counted and measured at least twice (upon induction and after treatment) to determine lesion survival and changes in size. Despite it being previously shown that measurement from a single dimension (i.e. diameter in

mm) is sufficient to determine growth of endometriotic sites (Vernon and Wilson 1985), some studies have measured lesion size in either multiple dimensions (i.e. length and width) or by volume or weight.

For *in vitro* studies, well-established methods will depend on the outcome, but examples of such methods may include: objectively measured cell migration, cytokine concentrations with diagnostic methods using commercial kits, commercial laboratories with experience in the assay, or standard assays such as ELISAs for IgG and with sufficiently low variation and limits of detection to allow discrimination of responses between treatment groups (or direct evidence that the assay could have detected a difference based on responses to a positive control). The OECD Guidance Document on Good In Vitro Method Practices (GIVIMP) may support the identification of standard methods for in vitro tests (OECD 2018).

- *Definitely Low risk of bias*: There is direct evidence that the outcome was assessed using well-established methods (the gold standard), AND assessed at the same length of time after initial exposure in all study groups, AND there is direct evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.
- *Probably Low risk of bias*: There is indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard), AND assessed at the same length of time after initial exposure in all study groups, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures. For some outcomes, particularly histopathology assessment, outcome assessors are not blind to study group as they require comparison to the control to appropriately judge the outcome, but additional measures such as multiple levels of independent review by trained pathologists can minimize this potential bias.
- *Probably High risk of bias*: There is indirect evidence that the outcome assessment method is an insensitive instrument, OR the length of time after initial exposure differed by study group, OR there is indirect evidence that it was possible for outcome assessors to infer the study group prior to reporting outcomes without sufficient quality control measures.
- *Definitely High risk of bias*: There is direct evidence that the outcome assessment method is an insensitive instrument, OR the length of time after initial exposure differed by study group,

OR there is direct evidence for lack of adequate blinding of outcome assessors, including no blinding or incomplete blinding without quality control measures.

- *Not Reported*: There is insufficient information provided about blinding of outcome assessors

Q8. Were all measured outcomes reported?

Selective reporting of results is a recommended element of assessing risk of bias (Guyatt, Oxman, Vist, et al., 2011; Higgins & Green, 2011b; Viswanathan M et al., 2012). Selective reporting is present if pre-specified outcomes are not reported or incompletely reported. It is likely widespread and difficult to assess with confidence for most studies unless the study protocol is available. Selective reporting bias can be assessed by comparing the "methods" and "results" section of the paper, and by considering outcomes measured in the context of knowledge in the field. Abstracts of presentations relating to the study may contain information about outcomes not subsequently mentioned in publications. Selective reporting bias should be suspected if the study does not report outcomes in the results section that would have been expected based on the methods, or if a composite score is present without the individual component outcomes (Guyatt, Oxman, Vist, et al., 2011). It may be useful to pay attention to author affiliations and funding source which can contribute to selective outcome reporting when results are not consistent with expectations or value to the research objectives.

- *Definitely Low risk of bias*: There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance.
- *Probably Low risk of bias*: There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported OR analyses that had not been planned at the outset of the study (i.e., retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the omitted analyses were not appropriate and selective reporting would not appreciably bias results. This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not).
- *Probably High risk of bias*: There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.
- *Definitely High risk of bias*: There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that

are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect).

- *Not Reported*: There is insufficient information provided about selective outcome reporting.

Q9. Were there any other potential threats to internal validity?

This question was used to examine appropriateness of statistical methods, adherence to the study-protocol, and if the study design or analysis account for important confounding and modifying variables (including unintended co-exposures) in experimental studies.

- Statistics: Incorrect unit of measurement or incorrect analysis, i.e. confirmation of homogeneity of variance for ANOVA and other statistical tests that require normally distributed data.
- Deviations from the protocol: Evidence of deviations in the protocol are noted as direct (definitely high risk of bias) or indirect (probably high risk of bias).
- Unintended co-exposures for experimental studies: Evidence of other exposures that are anticipated to bias results are noted as direct (definitely high risk of bias) or indirect (probably high risk of bias) evidence of other exposures anticipated to bias results, if present and not appropriately adjusted for. Non-differential co-exposures that are likely to bias the results toward the null are considered in the context of the study findings.

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