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1 **Associations between human internal chemical exposure to Persistent Organic Pollutants (POPs)**
2 **and *In Vitro* Fertilization (IVF) outcomes: Systematic review and evidence map of human**
3 **epidemiological evidence**

4

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25 **Keywords**

26 Persistent organic pollutants; biomarkers; follicular fluid; In Vitro Fertilization; infertility; systematic

27 review

28 **1. Introduction**

29 The constant advances in chemical and technological industry have provided unquestionable
30 advantages for humans. Nonetheless, as a side effect, a large list of synthetic compounds, whose safety
31 is increasingly being called into question by the scientific community and public health authorities, are
32 released to the environment. Special concern has been growing around synthetic substances
33 structurally analogous to endogenous hormones, capable to induce mimetic or antagonistic biological
34 effects in hormone systems, thus known as endocrine disrupting chemicals [1]. As a matter of concern,
35 modern synthetic substances merge with mixtures of historical pollutants, banned decades ago but still
36 present in the environment and the food chain due to their stable and bioaccumulative nature [2].
37 These historical chemicals known as persistent organic pollutants (POPs), include substances used in
38 agriculture like organochlorine pesticides (OCP) or industrial applications including polychlorinated
39 biphenyls (PCBs), which can be also released unintentionally through thermal processes like the
40 family of dioxins [3]. Other classes of more emerging concern includes polybrominated diphenyl
41 ethers (PBDE) used as flame retardants, and perfluoroalkylated substances (PFAS) with large
42 industrial and consumer applications [4]. They have received international attention because of their
43 hydrophobic or amphiphilic nature, and thus accumulated in fatty tissues of living organisms,
44 including humans [5]. In addition, some of these congeners have been associated with notorious
45 adverse health effects in animals and humans [1], and thus banned or strongly regulated. Despite the
46 regulatory efforts, substantial amounts of POPs can still be detected in fatty tissues and fluids from
47 human worldwide, including blood lipids, breast milk or adipose tissue [6,7].

48 The health impacts of POPs include, among others, developmental defects, metabolic dysregulation
49 and cancers [1], but there is also an increasing concern on their effects on human reproductive health
50 [8,9]. Due to the ability of some POPs to interfere with the hypothalomo-hypophyseal-gonadal axis,
51 the highly hormone-sensitive female reproductive system becomes especially vulnerable to endocrine
52 disrupting substances. For that reason, a list of POPs have been proposed to contribute to
53 gynaecological diseases including uterine fibroids [10], endometriosis [11,12], polycystic ovary

54 syndrome [13] longer time-to-pregnancy [14] or infertility [15,16]. Infertility is a pathology defined by
55 the World Health Organization (WHO) as the absence of pregnancy after 12 months or more with
56 regular unprotected sexual intercourse [17]. Affecting 8-12% of reproductive aged women worldwide,
57 it has become a public health priority in many countries [18]. As a consequence, a growing number of
58 couples requires Assisted Reproductive Technologies (ART) including *in vitro* fertilization (IVF),
59 whose low success rates has been related to a number of female factors including the body burden of
60 environmental pollutants [19]. Studies on the associations between POPs and IVF outcomes provide
61 highly valuable information on the specific population attending ART, often with more severe forms
62 of infertility, however it may not be generalizable to general population presenting infertility.

63 To date, the impact of POPs on couple fecundability has been recently reviewed [13,20] and more
64 specifically, the impact of POPs on IVF has been narratively discussed elsewhere with special focus
65 on follicular fluid [21]. However, no formal systematic review on the specific between associations
66 POPs and IVF outcomes has been conducted. In this context, the aim of the present study was to
67 evaluate the published evidence on the association between human internal chemical exposure levels
68 of POPs and IVF outcomes in infertile women in order to identify knowledge gaps and guiding future
69 studies.

70 **2. Materials and methods**

71 We applied a systematic review approach following the National Toxicology Program Office of
72 Health Assessment and Translation's (NTP/OHAT) Handbook for Conducting a Literature-Based
73 Health Assessment guidelines, which provides a standardized methodology to implement the Grading
74 of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental
75 health assessment [22,23]. A systematic review (SR) protocol was developed a priori, calibrated and
76 registered at PROSPERO (Register number CRD42020159267). Search and selection were performed
77 in duplicate by two reviewers (TL and GCS). Assessment of risk of bias was also performed in
78 duplicate by two independent members (TL and CGS) and discrepancies were discussed after
79 proofreading the articles with a third reviewer TF. The results were structured and presented in

80 accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
81 and Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines for Meta-analyses
82 and Systematic reviews of Observational Studies [24]. The entire systematic review process was
83 calibrated beforehand in order to refine the different steps. Specifically, a test set of articles were used
84 to pilot and refine the search strategy iteratively developed to ensure the eligible retrievals with minor
85 burden of non-eligible items.

86 **2.1 Study question**

87 The research question was: “Is exposure to persistent organic pollutants associated with in vitro
88 fertility outcomes in women?” (See supplemental Material Section 1.2)

89 **2.2 Search**

90 The initial search was performed on the 8th of November 2019 using the electronic literature databases
91 MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed>) and WEB of SCIENCE (WoS,
92 <https://apps.webofknowledge.com>), using a comprehensive search string with the main PECO
93 (Population; Exposure; Comparators and Outcomes) elements (See Supplemental Material Section 1.3
94 and Figure S1). No filters were implemented during the search, including all publication years. A
95 follow-up search was conducted on the 20th of September 2020 for updated results based on the
96 identical previously used search string.

97

98 **2.3 Eligibility criteria and selection**

99 Eligibility criteria for the key PECO elements were defined and summarized in the PECO statement
100 (See Supplemental Material Section 1.3.1). Were excluded conference and review papers, articles not
101 written in English, studies without quantitative exposures and studies overlapping information with
102 another publication.

103 **Participants/ population:** Only women undergoing in vitro fertilization treatment were studied
104 without restrictions on country, race and religion.

105 **Exposure(s):** Exposure to one or multiple POPs listed in the Stockholm Convention (including
106 derivatives or isoforms) [25], based on internal concentrations and surrogate biomarkers.
107 Environmental measures or indirect measures were not considered. The exposure must be measured
108 individually using direct validated based on biomonitoring methods, irrespectively of the biological
109 matrix used (i.e. serum, FF).

110 **Comparator(s).** Reference groups of population exposed at lower levels of POPs than the rest of
111 population groups were considered.

112 **Outcome(s):** Primary outcome: pregnancy rate (PR). Secondary outcome 1: number of oocytes
113 retrieved (NOR). Secondary outcome 2: fertilization rate (FR). Secondary outcome 3: embryo quality
114 (EQ). Secondary outcome 4: live birth rate (LBR).

115 Only peer-reviewed reports containing original data were included. Conference and review papers
116 were excluded from the analysis. Studies with overlapping information with another publication were
117 also excluded (the most complete publication originating from the same cohort was the only one
118 considered). Study selection was carried out using a two-stage sequential process, with step-1 based on
119 title/abstract agreement to the eligibility criteria and step-2 based on full-text examination. All
120 references were screened and assessed by two independent reviewers (TL and GCS). Three additional
121 reviewers (SP, TF and JPA) checked the final reference list and made the final decision in case of
122 disagreement (See Supplemental Material Section 1.3).

123 **2.4 Data extraction**

124 Data from included records were extracted using a predefined form (Supplemental Material Section
125 1.3.4) and included: year, study design, recruitment strategy, inclusion/exclusion criteria, dates of
126 study and sampling time frame, geography, number of participants, age, race/ethnicity, type of POP
127 and compartments (serum, follicular fluid), exposure assessment with methodological details and
128 units, exposure levels, type of infertility, number of oocyte retrieved, embryo quality, clinical outcome
129 measure (pregnancy rate, live birth rate), adjustment with patients' characteristics, statistical approach
130 and main conclusion.

131 **2.5 Risk of bias assessment**

132 The ‘NTP/OHAT Risk of Bias Rating Tool for Human and Animal Studies’ was used to classify each
133 individual study in a tier (1 to 3) of risk of bias (See Supplemental Material Section 1.3.5). The
134 NTP/OHAT’s risk of bias tiered approach considered some key questions or risk of bias domains of
135 higher relevance to establish the classification criteria for each individual study. The risk of bias
136 domains and related questions were: **A) Confounding Bias:** (Key question 1) Did the study design or
137 analysis account for important confounding and modifying variables? **B) Attrition/Exclusion Bias:**
138 Were outcome data incomplete due to attrition or exclusion from analysis? **C) Detection Bias:** Can we
139 be confident in the exposure characterization? (Key question 2) Can we be confident in the outcome
140 assessment (Key question 3)? **D) Selective Reporting Bias:** Were all measured outcomes reported? **E)**
141 **Other sources of bias:** Were there other threats to internal validity? The risk of bias evaluation was
142 entirely conducted and managed in Health Assessment Workplace Collaborative (HAWC) to ensure
143 transparency, publicly available at <https://hawcproject.org/assessment/1021/>.

144 **2.6 Data synthesis**

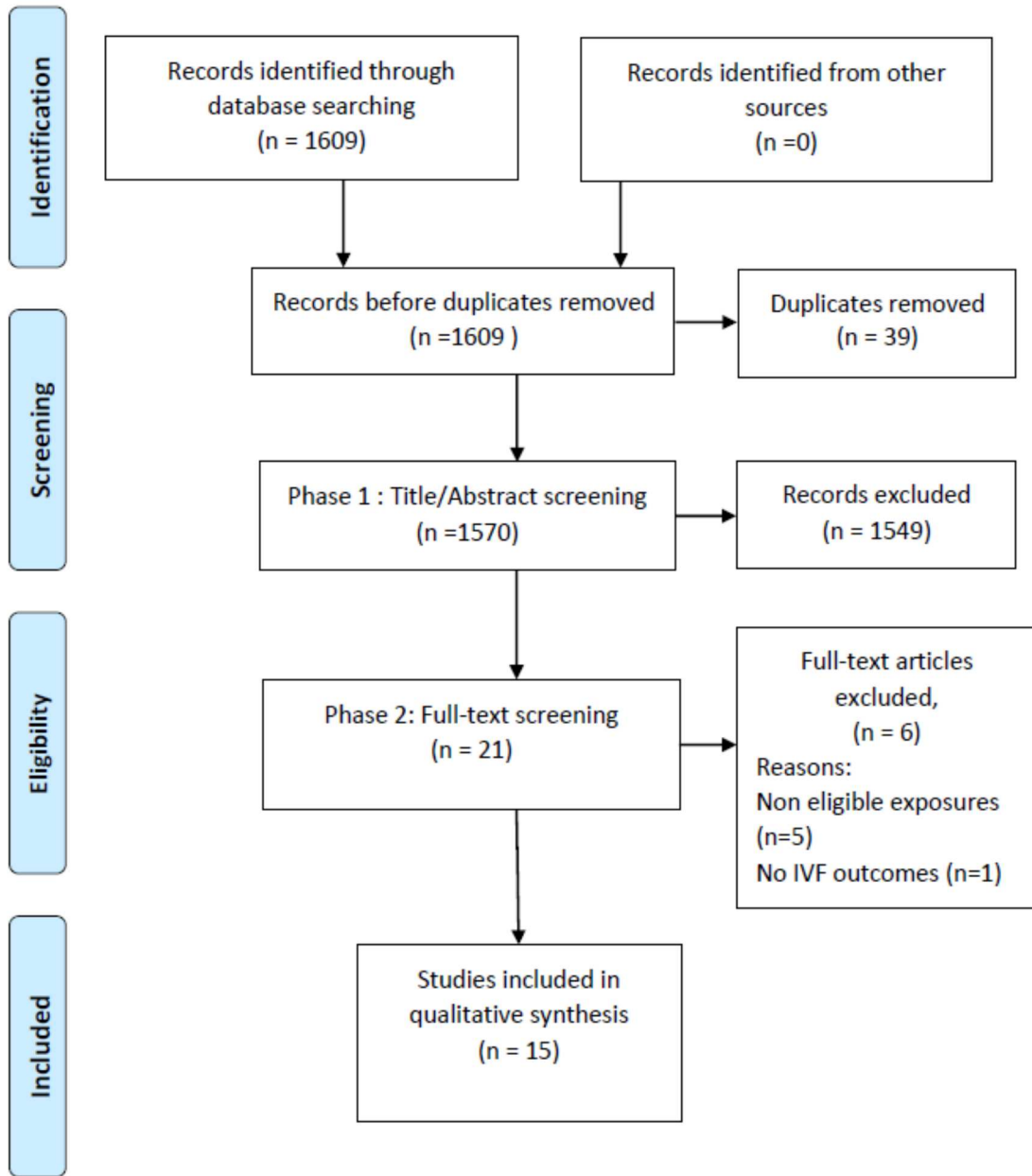
145 For facilitated interpretation and summarized result purposes, chemicals were grouped to four main
146 families of POPs (PFAs, PCBs, OCPs and PBDEs) and five main IVF outcomes (Number of oocyte
147 retrieved, Fertilization rate, Embryo quality, Pregnancy rate and live birth rate). A quantitative
148 synthesis with meta-analysis was unfeasible due to the low number of studies reporting quantitative
149 effect estimates in common metrics for the exposure-outcome pairs. Thus, we conducted qualitative
150 synthesis presented in summary tables with the main overall direction of results for each exposure-
151 outcome pair. In order to harmonize the outcome language, we considered “Pregnancy rate” a
152 consolidated outcome combining the results from outcomes reported as “Pregnancy rate”, “Clinical
153 pregnancy rate” and “Failed implantation”. Indeed, “Pregnancy rates” and “Failed implantation rates”
154 refer to similar event in reverse metrics, we therefore inversed the direction of the “Failed
155 implantation” effect to ease the visualization of overall effects. The overview of gathered evidence
156 across exposures and outcomes was displayed in an evidence map, an emerging feature that facilitates
157 the visualization of heterogeneous evidence and the identification of research gaps [26].

158 **3. Results**

159 **3.1 Source and selection of key studies**

160 The process applied for sourcing and selection key studies is summarized in the PRISMA flow
161 diagram given in Figure. 1. The initial search resulted in 1609 items, reduced to 1570 after duplicated
162 removal of pooled retrievals from Pubmed and WoS. Among the 21 studies retained for the full-text
163 screening, 15 studies were finally eligible for data extraction and synthesis. Manual searches did not
164 contribute additional manuscripts to be included.

165 **Figure 1.** PRISMA flow diagram representing the identification, screening and selection process
 166 performed in the current systematic review
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173 **3.2 Study characteristics**

174 The characteristics of included studies are summarized in Table 1. The records included in the main
175 body of evidence comprised 12 prospective cohort studies and 3 case control studies. Taking into
176 account that 5 records focused on the same 2 populations, this systematic review covered a total of
177 2033 individuals. Study populations were generally modest in size, with 11 studies including <100
178 samples (range 16-99) [27-37], while others ranged from 215 [38] to 765 participants [39-41]. Six out
179 of the 15 studies were conducted in the United States [30,34,35,38-40], while others were conducted
180 in various countries. Concerning the exposures, OCPs (n=8 studies) and PCBs (n=7 studies) were the
181 most evaluated POPs among the selected studies, followed by PFAs (n=4) and PBDEs (n=2). The
182 number and type of particular exposure markers varied across studies for all POP families, for
183 instance, the number of monitored PCB congeners varied from 2 [27] to 57 [40], but most of studies
184 ranged between 2 and 8 PCBs. The most commonly analyzed markers among the OCPs substance
185 class were dichlorodiphenyltrichloroethane (DDT) and the metabolite
186 dichlorodiphenyldichloroethylene (DDE), followed by Lindane, Dieldrin, Mirex, Endosulfan,
187 hexachlorobenzene (HCB), hexachloroethane (HCE), 1,2,4-trichlorobenzene (TCB) and beta-
188 hexachlorocyclohexane (β -HCH). In case of PBDEs, both selected studies included at least the most
189 abundant exposure markers commonly reported for this substance class (i.e. BDE47, 99, 100, 153,
190 154) [42], whereas Ingle et al. 2020 also analyzed the hydroxylated forms [38].

191 Most studies reported the simultaneous determination of exposure biomarkers in FF and
192 serum. Serum was collected at different phases of IVF stimulation: prior, during stimulation [35,39] or
193 on the day of oocyte retrieval [27,28,32,33]. Concerning the IVF outcomes, 9 studies evaluated the
194 association between POP and the number of oocytes retrieved [27-29,31,32,34-36,38], 11 studies
195 analyzed fertilization rate [27-29,31-35,37,38,41], 6 evaluated embryo quality [27,28,31-34], 12
196 analyzed pregnancy rate or failed implantation [27-32,34,36,38-41], and 5 analyzed live birth rate
197 [32,34,35,38,40].

Table 1. Summary characteristics of included studies.

Reference	Dates	Population		n	Outcomes	Confounders	Exposure assessment		Statistics	
		Country	Age ^a				Chemicals ^b	Matrix (Units)		Analytical Method
Al Hussaini et al 2018[36]	2010- 2013	Egypt	31.5 ± 6.2 (20-38)	94	N° oocytes Pregnancy rate	NR	PCB 28,52,138,180 OCP: Lindane, DDT	FF (µg/L)	GC/MS SIM	Linear regression
Al-Saleh et al 2009 [41]	2002-2003	Saudi Arabia	31.8 ± 5.1 (19-50)	619	Fertilization rate Pregnancy rate	Age, residence the former province, location of former, school, fish consumption	3 OCPs (DDE)	Serum FF (µg/L)	GC-MS-ESI	Logistic Regression (OR)
Bloom et al 2017 [34]	2007- 2008	California US	35.6 (28-42)	32	N° oocytes Fertilization rate Quality embryo Pregnancy rate Live birth rate	BMI, smoking, race, age	43 PCB (grouped in oestrogenic and antioestrogenic), OCP: DDT, DDE	FF (ng/ml)	GC/MS-SIM	MLR (β/RR) Negative binomial Poisson regression GEE
Governini et al 2011 [29]	NR	Italy	33.6 ±2.6	16	N° oocytes Fertilization rate Pregnancy rate	None	PFAs	FF	HPLC-MS ESI	t-test, Chi square Correlation analysis
Ingle et al 2020 [38]	2005-2016	Massachusetts US	Median:35	215 (330 cycles)	N° oocytes Fertilization rate Pregnancy rate Live birth rate	Lipids, age, BMI, race, year of collection, IVF protocol, FSH (previous treatment, education, E2 level, infertility diagnosis, ICSI, endometrial thickness)	PBDE 47,99,100,153 and 154 4 OH-BDE metabolites	Serum (ng/g)	GC-MS LC-MS/MS	Multivariate mixed models Poisson/logbin GEE
Jirsová et al 2010 [33]	2003-2004	Czech Republic	30.9 ± 3.7 (25.3-41.3)	99	N° oocytes Fertilization rate Embryo quality Pregnancy rate	NR	36 PCB (PCB 44,81,101,105,118,123,158) 3 OCP (DDT, DDE)	FF (ng/g of lipid)	GC-MS	Wilcoxon/Kruskal 1 Wallis tests MLogR /Poisson (OR)
Johnson et al 2012 [30]	1994- 2003	Boston, US (3sites)	38 ±3.8 (27-44)	65	Failed implantation	Age, BMI (ethnicity, smoking status, serum levels of PBCs)	PBDE (28, 47, 99, 100, 153, 154, 183, 209)	Serum (ng/g) FF	GC-MS NCI	MLogR (OR)
Kim et al 2020 [37]	2006-2011	Australia	35 ± 4 (23-42)	97	Fertilization rate	Age	32 PFAs (8 detected)	FF	HLPC-MS/MS ESI	ANOVA
Mahalingaiah et al 2012 [39]	1994- 2003	Boston, US (3sites)	35.9±4.21	720 (774 cycles)	Failed implantation	TSL, site, study phase, ethnicity, previous live birth, age, BMI, smoking, gonadotropins, protocol, ICSI, N° embryos, diagnosis	HCB, p-p'DDE, Total DDT (p,p'-DDT, o,p'DDT, p-p'DDE and o,p'DDE)	Serum (ng/g of serum and ng/g of lipid)	GC-MS ESI	MLR/MLogR Random effects Q4-2 vs Q1 (OR)
McCoy et al 2017 [35]	2013- 2014	South Carolina, US	33.7 ± 4.5	26-31	N° oocytes Fertilization rate Live birth rate	Age (BMI)	15 PFAs (6 detected: PFHxA, PFOA, PFNA, PFDA, PFUnA, PFOS)	FF Plasma (ng/g)	LC-MS/MS ESI-	Partial correlation analysis (age-corrected)
Meeker et al 2011 [40]	1994- 2003	Boston, US (3sites)	35.9 ±4.2	720 (774 cycles)	Failed implantation Live birth rate	TSL, site, study phase, ethnicity, previous live birth, age, BMI, smoking, gonadotropins, protocol, ICSI, N° embryos	57 PCB (PCB 11, 138 and 153; on 3 bioactivity-based groups; and on sum of PCB)	Serum (ng/g serum and lipid)	GC-ECD	MLR/MLogR Random effects Q4-2 vs Q1 (OR)

Petro et al 2012 [32]	2008–2009	Belgium	34.5 ± 4.4 (25.2-42.8)	20	N° oocytes Fertilization rate Embryo quality Pregnancy rate Live birth rate	Age, estradiol, BMI, male subfertility, ICSI	26 PCB (PCB 118 138 153 170 180) 7 PBDE (Not detected >50%) OCPs (HCB, β-HCH, DDE)	FF (pg/ml) Serum (pg/ml and ng/g lipid)	GC-MS ECNI	PCA-MLR (OR)
Petro et al 2014 [31]	2008–2009	Belgium	34.6 ± 4.4 (25.2-42.8)	20	Fertilization rate Embryo quality	Age, estradiol, BMI, male subfertility, ICSI	14 PFAs (PFOA, PFOS, PFNA, PFHxS)	FF Serum (ng/ml)	UPLC ESM–MS/MS	PCA- MLR (β/OR)
Weiss et al 2006 [27]	NR	Germany	NR	21 Germany	N° oocytes Fertilization rate Embryo quality Pregnancy rate	None	5 PCB (PCB 138, 153) 8 OCPs (DDT, DDE, Dieldrin)	FF Serum (µg/kg)	GC	ANOVA t-test
Younglai et al 2002 [28]	NR	Canada	28-38	21	N° oocytes Fertilization rate Embryo quality Pregnancy rate	None	35 PCB (PCB 49, 99, 138, 153, 180) 36 OCPs (Endosulfan, DDE, HCE, TCB, Mirex)	Serum FF (pg/ml)	GC-MS	t-test Linear/Logistic Regression (OR)

199 ^a Mean ± standard deviation (range)

200 ^b Analyzed chemicals (detected chemicals included in statistical analysis)

201 Abbreviations: β, beta ; BMI, body mass index; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; ESI, Electro-Spray Ionization ; ECNI,
202 electron-capture negative ionization ; ESM, electrospray interface operating in negative ion mode ; FF, follicular fluid ; GC Gas Chromatography ; GC-ECD, Gas
203 Chromatography with dual micro-Electron Capture Detection ; GEE, generalized estimating equation; HCB, hexachlorobenzene; HCE, hexachloroethane ; HCH,
204 hexachlorocyclohexane; HPLC, High Performance Liquid Chromatography ; IVF, In Vitro fertilization ; LC-MS/MS, Liquid Chromatography tandem Mass Spectrometry ;
205 Logbin, logbinomial; MS Mass Spectrometry ; MLR/MLogR, multivariate linear/logistic regression ; N°, number ; NCI negative chemical ionization; NR, Not reported ; OR
206 Odds Ratio ; PCA Principal Component Analysis ; PCB Polychlorinated Biphenyls ; PFA Perfluoroalkyl Acids ; PFDA, perfluorodecanoic acid; PFHpA, perfluoroheptanoic
207 acid; PFHpS, perfluoroheptanesulfonic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane
208 sulfonic acid; PFUnDA, perfluoroundecanoic acid; Q Quartile ; SPE Solid Phase Extraction system ; SIM Selective Ion Monitoring Mode ; TCB, 1,2,4-trichlorobenzene;
209 TSL, total serum lipids; UPLC Ultra Performance Liquid Chromatography

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212 **3.3 Association between PFAs exposure and IVF outcomes**

213 The evidence on the associations between exposure to PFAs and IVF outcomes is summarized in
214 Table 2, either for sums of congeners or selected ones like perfluorooctanoic acid (PFOA),
215 perfluorooctane sulfonic acid (PFOS) or perfluorononanoic acid (PFNA). The four studies reported
216 PFAs concentration levels in FF while only 2 reported PFAs in serum [33,35]. No significant
217 association was found between PFAs and number of oocyte retrieved [29,35]. Concerning fertilization
218 rate, results were inconsistent across the different studies, with reported negative [29], positive [33], or
219 no association [35,37]. The one available study on embryo quality reported a positive association
220 between embryo quality and follicular level of PFAs [33]. No associations among PFAs and
221 pregnancy rate nor live birth rate were reported [29,35].

222 **Table 2.** Summary of main associations between internal concentrations of PFAS and IVF outcomes.
 223

Reference (n)	Detected congeners	Level FF				Levels Serum/Plasma				Main effects on IVF outcomes				
		Units	DF (%)	Mean	SD (range)	Unit s	DF (%)	Mean	SD (range)	NOR	FR	EQ	PR	LBR
Governini et al 2011 [29] (n=16)	∑PFAs	ng/m L	NR	6.65	3.54					⊖	↓↓↓	NA	⊖	NA
Kim et al 2020 [37] (n=97)	PFOS	ng/ml	98	4.8	3.1									
	PFHxS		98	1.7	2.7									
	PFHpS		96	0.1	0.1									
	PFOA		98	2.4	1.7					NA	⊖	NA	NA	NA
	PFNA		97	0.5	0.3									
	PFDA		98	0.2	<LOD									
	PFHpA		90	0.01	0.008									
	PFUnDA		97	0.1	0.007									
Mc Coy et al 2017 [35] (n=36)	∑PFAs	ng/g	100	10.1	0.8	ng/g	100	12.6	1.1	⊖	⊖	NA	NA	⊖*
Petro et al 2014 [33] (n=20)	PFOA	ng/m	92	1.8	(0.3-3.3)									
	PFOS	L	97	7.5	(0.1-									
	PFNA		76	0.4	30.4)					NA	↑ (PC1	↑ (PC1	NA	NA
	PFHxS		76	0.3	(0.2-2.1)))		
					(0.1-1.4)									

224 Main effect annotation: ⊖ No statistical associations ; *Data not shown ; ↓↓↓ statistically significant decrease (p<0.001) ; ↑ statistically significant increase
 225 (p<0.05). Abbreviations: DF, detection frequency; EQ Embryo quality; FR Fertilization Rate; FF Follicular Fluid; LBR, live birth rate; NA, not assessed;
 226 NOR number of oocytes retrieved; NR, not reported; P plasma; PC1, principal component 1; PFAs, perfluoroalkyl substances; PFDA, perfluorodecanoic acid;
 227 PFHpA, perfluoroheptanoic acid; PFHpS, perfluoroheptanesulfonic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA,
 228 perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFUnDA, perfluoroundecanoic acid PR pregnancy rate; SD standard deviation

229 **3.4 Associations between PCBs exposure and IVF outcomes**

230 The association between PCBs exposure and IVF outcomes is summarized in Table 3. Three studies
231 analyzed PCB in FF [31,33,36], 1 in serum [40] and 3 studies in paired serum and FF samples
232 [27,28,32]. Most studies evaluated the associations with number of oocytes retrieved showing mainly
233 no statistical associations and only two studies found statistically significant associations in opposite
234 directions for different exposure markers. Bloom et al. [34] noted that higher PCB151 was associated
235 with fewer oocyte retrieved [RR -0.54 (-0.93; -0.13) $p < 0.05$] but not for the rest of congeners.
236 Conversely, Al-Hussaini et al. [36] found that PCB28 was positively associated (adjusted $\rho = 0.07$, $p =$
237 0.0001). Similarly, for the five studies that evaluated fertilization rate, three of them found null results
238 (detailed data not shown in the original publications) and two studies significant yet divergent results.
239 Whereas Bloom et al. [34] found positive association between PCB105 and oocyte fertilization, Petro
240 et al. [32] associated it negatively ($p < 0.0001$) with the first principal component scores representing
241 the overall contamination of FF (including PCBs and OCPs). This discrepancy must be analyzed with
242 care because the analysis of the impact of one pollutant is different from the analysis of a mixture of
243 pollutants Two out of four studies that analysed the associations between embryo quality and PCBs,
244 reported significant inverse associations [32,34] and the other two reported no association [28,31]. The
245 7 included studies evaluated impact of PCBs on pregnancy rate or failed implantation rate. Meeker et
246 al. [40] found that serum PCB 153 and sum of PCBs were significantly correlated with failed
247 implantation. In accordance, Bloom et al reported that higher FF PCB 28 and 66 and sum of PCB
248 (total and oestrogenic) were associated with lower embryo implantation. But PCB146 were associated
249 with higher implantation rate, but the authors remarked a very low detection frequency for this
250 compound (6.2%). In turn, Younglai et al. [28] reported a positive correlation between PCB 49 level in
251 FF and pregnancy rate; while Petro et al., Weiss et al., and Al-Hussaini et al., reported no associations
252 (data not shown) [27,32,36]. Jirsova et al., did not find statistically significant associations, however
253 the authors highlighted that associations with PCB47 were marginally significant (OR=0.73, $p < 0.1$)
254 [31]. Only 3 studies evaluated impact of PCBs on live birth rate reporting no correlation in one study

255 [32] and negative correlation in the 2 others [34,40] for part of the PCBs analysed (PCB 153, 66, 74,
256 101 and sum of PCB).

257 **Table 3.** Summary of main associations between internal concentrations of PCBs and IVF outcomes.

Reference (n)	Detected congeners	Levels FF				Levels Serum/Plasma				Main effects on IVF outcomes					
		Units	DF (%)	Mean	SD (range)	Units	DF (%)	Mean	SD (range)	NOR	FR	EQ	PR	LBR	
Al Hussaini et al. 2018 [36] (n=94)	PCB 28	ng/mL ²	NR	0.05	0.09					↑↑↑ (PCB28)	NA	NA	⊙* (CPR)	NA	
	PCB52			0.4	0.05										
	PCB 138			0.15	0.02										
	PCB 180			0.10	0.02										
Bloom et al. 2017 [34] (n=32)	∑PCBs	ng/mL ²	1-100	∑PCBs	0.45					↓ (PCB151)	↑ (PCB105)	↓↓↓ (PCB87, 149, ∑PCBs)	↓ (PCB28, 66, ∑PCBs, ∑ae-PCBs)	↓ (PCB66, 74, ∑e-PCBs)	
	∑e-PCBs			1.22	0.22										
	∑ae-PCBs*			∑e-PCBs	0.06					⊙ (∑PCBs)	⊙ (∑PCBs)	∑ae-PCBs	↑ (PCB146)	⊙ (∑PCBs)	
Jirsova et al. 2010 [31] (n=99)	PCB 44	ng/g of lipid	NR	1.8	2.5					⊙*	⊙*	⊙*	⊙*	NA	
	PCB 47			13.1	34										
	PCB 101			8.1	9.1										
	PCB 158			10.2	10.9										
Meeker et al. 2011 [40] (n=827)	PCB 153					ng/g of serum	NR	0.23 / 45.4	NR						
	∑PCB					- ng/g of lipid		1.32 / 257		NA	NA	NA	↓ (I-FIR)	↓	
Petro et al. 2012 [32] (n=20)	PCB118	ng/mL	68	0.06	0.01	ng/mL	100	0.04 / 8.1	0.03 / 0.9	⊙	↓↓↓ (PC1)	↓ (PC1)	⊙ (CPR)	⊙	
	PCB 138		98	0.05	0.03	-	100	0.12 / 23.5	0.06 / 9.2						
	PCB 153		98	0.07	0.04	ng/g of lipid	100	0.20 / 39.2	0.11 / 17.6						
	PCB 170		85	0.02	0.01		100	0.04 / 8.7	0.02 / 4.4						
	PCB 180		93	0.05	0.03		100	0.11 / 21.9	0.06 / 10.9						
	∑PCBs			0.21	0.14			0.56 / 110	0.29 / 48.9						
Weiss et al. 2006 [27] (n=21)	∑PCB138+153	ng/g ²	>90	0.26	0.02	ng/g	NR	0.25	0.05	⊙*	⊙*	NA	⊙*	NA	
Younglai et al. 2002 [28]	PCB 49	ng/mL ²	>50	0.62	0.07	ng/mL	<50	NR	NR	⊙*	⊙*	⊙*	↑ ⊙*	NA	
	PCB 99		<50	NR	NR		>50	0.77	0.02						

(n=21)	PCB 138	<50	NR	NR	>50	0.24	0.03	⊙*
	PCB 153	>50	0.073	0.07	>50	0.24	0.03	⊙*
	PCB 180	>50	0.062	0.05	>50	0.14	0.02	⊙*

258 ^a Statistical models build between the first principal component, including the mixture of PCBs and the outcomes using multivariate regression models Main effect
259 annotation: ⊙ No statistical associations *Data not shown; ↑ Statistically significant increase (p<0.05) ↑↑↑ (p<0.001) ↓ Statistically significant decrease (p<0.05) ↓↓↓
260 Statistically significant decrease (p<0.001). [‡]No adjustment on lipid
261 Abbreviations: ae-PCB antiestrogenic PCBs; CPR clinical pregnancy rate; DF, detection frequency; e-PCB estrogenic PCBs; ER embryo quality; FR Fertilization Rate; FF
262 Follicular Fluid; I-FIR inverse of failed implantation rate; LBR live birth rate; NA Not assessed; NOR number of oocytes retrieved; PR pregnancy rate; S serum; SD standard
263 deviation.
264 * ∑PCBs (PCB 28,44,49, 52,66,74,87,99,101,105,110,118,138,146,149,151,153,170, 180,183,187); ∑e-PCBs (PCB 44,52,49, 99,101,110,15) ∑ae-PCBs (PCB 105,118)

265 **3.5 Associations between OCPs and IVF outcomes**

266

267 Main findings from the 8 studies evaluating the association between OCPs exposure and IVF
268 outcomes are summarized in Table 4. All 6 studies evaluating the impact of OCPs on oocyte
269 number retrieved no statistically significant association. Six studies evaluated the association
270 between OCPs and fertilization rate. Among them, 2 found a statistically significant decrease
271 [28,32]. Concerning embryo quality, only one study out of 6 reported a negative association
272 with the overall exposure estimate [32]. The levels of DDT or the main metabolite DDE were
273 not found to be associated with pregnancy rate in any of the 8 studies considered. A
274 statistically significant negative association was found for HCB and pregnancy rate [39], and
275 for lindane and lower implantation rate [36]. Only 2 studies evaluated the impact of DDT (or
276 DDE) on live birth rate leading to discordant conclusions. Bloom et al., reported a positive
277 association between DDE and live birth rate using the exposure contrast in quartiles, yet this
278 association was not confirmed with continuous log-transformed DDE [34]. Petro et al, reported
279 no association [32].

280 **Table 4.** Summary of main associations between internal concentrations of OCPs and IVF outcomes.

Reference (n)	Detected congeners	Levels FF				Levels Serum/Plasma				Main effects on IVF outcomes				
		Units	DF (%)	Mean	SD (range)	Units	DF (%)	Mean	SD (range)	NOR	FR	EQ	PR	LBR
Al Hussaini et al. 2018 [36] (n=94)	Lindane DDT	ng/mL	NR	0.41 0.02	0.17 0.04					⊖	NA	NA	↓↓↓ (IR) ⊖* (CPR)	NA
Al-Saleh et al. 2009 [41] (n=619)	DDE	ng/mL	50.6	0.41	1.35	ng/mL	77.7	1.65	1.63	NA	⊖	NA	⊖	NA
Bloom et al. 2017 [34] (n=32)	DDT DDE	ng/mL	21 100	0.01 0.68	0.03 0.92					⊖	⊖	⊖	⊖	†(DDE)
Jirsova et al. 2010 [31] (n=99)	DDE DDT	ng/g fat	NR	3303.3/7 5.9	4205.2/75.9					⊖*	⊖*	⊖*	⊖*	NA
Mahalingaiah et al. 2012 [39] (n=774)	HCB DDE ΣDDT					ng/g	100	0.088 1.09 1.22		NA	NA	NA	↓↓↓ (HCB)	NA
Petro et al. 2012 [32] (n=20)	HCB DDE β-HCH	ng/mL	93 98 78	0.03 0.39 0.03	0.02 0.35 0.04	ng/mL	100 100 95	0.06 0.62 0.04	0.03 0.41 0.02	⊖	↓↓↓ (PC1)	↓ (PC1)	⊖ (CPR)	⊖
Weiss et al. 2006 [27] (n=21)	DDT+DDE Dieldrin	ng/g	NR	0.58 0.03	0.10 0.01	ng/g	NR	0.91 0.02	0.13 0.01	⊖*	⊖	⊖	⊖	NA
Younglai et al. 2002 [28] (n=21)	DDE Endosulfan Mirex HCE TCB	ng/g, ng/mL	>50 <50 >50 <50 <50	2.7 NR 3.6 0.2 0.2	1.5 NR 0.6 0.03 0.02	ng/g, ng/mL	>50 <50 <50 <50 <50	7.9 0.8 NR NR NR	5.6 0.2 NR NR NR	⊖*	↓ (DDE)	⊖*	⊖*	NA

281
282 Abbreviations: CPR clinical pregnancy rate; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DF, detection frequency; ER embryo quality;
283 FR Fertilization Rate; FF Follicular Fluid; HCB, hexachlorobenzene; HCE, hexachloroethane ; HCH, hexachlorocyclohexane; IR implantation rate; LBR live birth rate; NA

284 Not assessed; NOR number of oocytes retrieved; TCB, 1,2,4-trichlorobenzene; PC1, principal component 1; PR pregnancy rate; S serum; SD standard deviation. Main effect
285 annotation: ⊙ No statistical associations *Data not shown; ↑ Statistically significant increase (p<0.05) ↑↑↑ (p<0.001) ↓ Statistically significant decrease (p<0.05) ↓↓↓
286 Statistically significant decrease (p<0.001)

287 **3.6 Associations between PBDE exposure and IVF outcomes**

288 The association between PBDE exposure and IVF outcomes is summarized in Table 5. Only 2 studies
289 reported the association between PBDEs and IVF outcomes [30,38]. A similar study attempted to
290 quantify PBDEs by finally excluded them from statistical analysis because the detection frequency
291 was below 50% [32]. Johnson et al., analysed BDE28, 47, 99, 100, 153, 154 and 183 in serum and FF,
292 finding detection frequencies over 50% for BDE47, 99, 100 and 154 in serum and BDE47 in FF [30].
293 The authors reported significantly higher failed implantation risk with high levels of BDE 53 in FF
294 [Age and body mass index (BMI) adjusted OR 95%CI: 10 (1.9-51); $p=0.0006$]. They did not analyse
295 the number of oocytes retrieved, fertilization rate, embryo quality, neither live birth rate. Ingle et al.,
296 reported an unexpected positive association between implantation, clinical pregnancy and live birth
297 rates and BDE 153 (Relative Risk [RR] = 1.16; 95% CI: 1.16, 1.36, RR = 1.25; 95% CI: 1.16, 1.35,
298 RR = 1.26; 95% CI: 1.13, 1.41, respectively) and 5-OH-BDE47 (RR = 1.56, 95% CI: 1.14, 2.14,
299 RR = 1.56; 95% CI: 1.12, 2.18, and RR = 1.84, 95% CI: 1.26, 2.68, respectively) [38]. Nonetheless, no
300 associations were observed for PBDEs and OH-BDEs with IVF outcomes prior to implantation.

301 **Table 5.** Summary of main associations between internal concentrations of PBDEs and IVF outcomes.

Reference (n)	Detected congeners	Levels FF				Levels Serum/Plasma				Main effects on IVF outcomes				
		Units	DF (%)	Mean	SD (range)	Units	DF (%)	Mean	SD (range)	NOR	FR	EQ	PR	LBR
Johnson et al. 2012 (n=62) [30]	BDE 28	ng/g-	39	0.001	ND-0.001	ng/g-	43	0.3	ND-0.9					
	BDE47	ng/mL	70	0.026	ND-0.012	ng/mL	90	7.1	2.3-9.7					
	BDE 100		38	0.006	ND-0.002		83	1.4	0.3-2.0				↓↓ (1/FIR)	
	BDE 99		47	0.014	ND-0.003		70	2.1	ND-3.3	NA	NA	NA	(BDE53)	NA
	BDE 154		44	0.003	ND-0.002		86	2.1	0.8-2.9					
	BDE 153		44	0.007	ND-0.002		44	1.9	ND-1.2					
	∑BDEs		39	0.058	0.002-0.03		44	15.8	5.5-20.8					
Ingle et al. 2020 [38] (n=215)	BDE 47					ng/g	83	28.1	13.4-57.8					
	BDE 99						59	5.5	2.5-10.6					
	BDE 100						71	5.1	2.3-10.8					
	BDE 153						94	26.3	13.0-47.7	⊙	⊙	NA	↑(BDE53, ∑ OH-BDE)	↑ (BDE 153, ∑ OH BDE)
	BDE 154						43	7.3	4.8-12.2				(IR and CPR)	
	∑BDEs							86.3	44.2-157.8					
	∑OH-BDE							0.33	0.16-0.74					

302

303

304 Main effect annotation: ⊙ No statistical associations *Data not shown; ↑ Statistically significant increase (not reported p-value) ↓ Statistically significant
 305 decrease (p<0.01). Abbreviations: CPR clinical pregnancy rate; DF, detection frequency; ER embryo quality; FR Fertilization Rate; FF Follicular Fluid; IR
 306 implantation rate; LBR live birth rate; NA Not assessed; ND, not detected; NOR number of oocytes retrieved; p, percentile; PR pregnancy rate; S serum; SD
 307 standard deviation.

3.7 Correlation between blood and follicular levels of POPs

Most PFAs detected in FF appeared to be highly correlated to those levels in plasma ($\rho=0.81-0.99$) or serum ($\rho=0.51-0.65$) and remained stable over the course of ovarian stimulation [33,35]. A positive correlation was reported between follicular and serum levels of PCB [28,32] and OCPs [27,28,32,41]. Johnson et al. reported moderate correlations between serum and FF concentrations of BDE 28,47, 100 and 154 (Kendall's tau correlation = 0.29-0.38, $p < 0.005$) but BDE 99 and 153 were not correlated between the 2 matrices (Kendall's tau correlation < 0.2 , $p > 0.05$) [30].

3.8 Risk of bias assessment and evidence gap mapping

Summary of risk of bias evaluations for each individual study can be found in Figure 2. Specific evaluations for each chemical family can be found in the Supplemental Figures S2-S4 and HAWC (<https://hawcproject.org/summary/assessment/1021/visuals/>). Globally, the most concerning domains affected by the evaluation were the confounding bias and the low statistical power for a substantial number of studies. Considering the consistent evaluations across outcomes in the same study we judged minor differences to support stratified risk of bias assessment for each individual IVF outcome. In the case of PFAs, the overall body of evidence was classified as "Very serious" risk of bias considering that 2 studies were classified in Tier 2 and 2 in Tier 3 according the NTP/OHAT guidelines. Small sample size ($n < 100$), lack of adjustment for confounding variables and underreporting of outcome methodology and results were the major threats of confidence. The body of evidence on PCBs compiled with 7 studies was judged to be at "Serious" risk of bias. Lack of adjustment for confounding variables, low sample size for 4 out of 7 studies ($n < 35$) and underreporting of the analytical methodology for exposure biomarker assessment were the main issues. The group of 8 studies on OCPs, mainly focusing on DDT or its metabolite DDE, were also classified at "Serious" risk of bias. The 2 studies on PBDEs were classified in Tier 1 and 2, penalized by the underreporting of exposure assessment methods.

The overall evidence is displayed in Figure 3 for each IVF and chemical family. The aim of the evidence map is to visualize the size and certainty of published evidence in a broad area and identify understudied areas with special research needs. Each bubble represents a single study with size

335 proportional to the population included and colour related to the respective risk of bias Tier
336 classification according the NTP/OHAT approach (e.g. Tier 1 “unlikely”; Tier 2 “serious” and Tier 3
337 “very serious”).

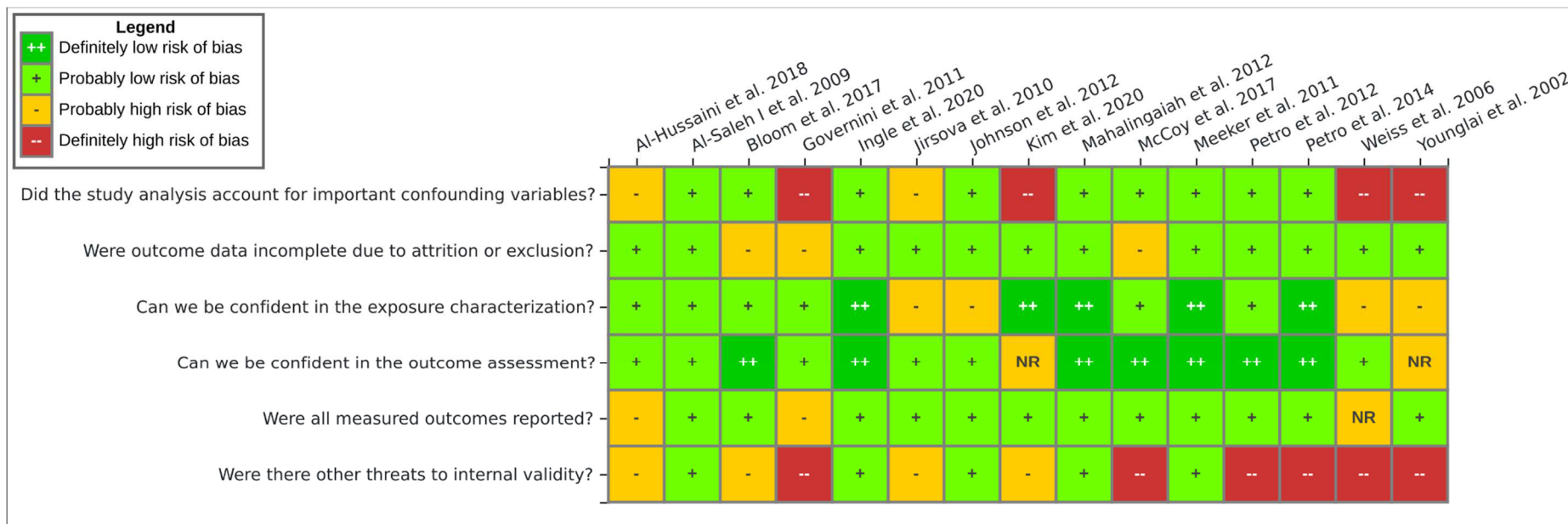
338 **3.9 Confidence ratings and level of evidence**

339 The confidence rating has been conducted using the NTP/OHAT approach, one of the few available
340 guidelines to conduct Systematic Reviews and Evidence Integration tailored for environmental health
341 and based on the GRADE Working Group guidelines [23]. According the NTP/OHAT approach, the
342 initial rating is established on the basis of study design features providing confidence that exposures
343 are causally associated with the outcome. On this regard, the guidelines establish that for human
344 observational studies the initial confidence must be considered at “moderate” due to the lack of
345 experimental control of exposures. The rest of features are ensured by a proper prospective design
346 including that “exposures precede the outcome”, “individual outcome data” or presence of a
347 “comparison group” [24].

348 Among the different factors considered to upgrade (i.e. magnitude, consistence, dose-response,
349 residual confounding) or downgrade the confidence (i.e. risk of bias, unexplained inconsistency,
350 indirectness, impression or publication bias), only risk of bias was identified to be compelling to
351 justify a confidence downgrading of the overall body of body of literature based on “Serious” and
352 “Very serious” classification of studies on PCBs, OCPs and PFAs (Section 3.8). Thus we judged to
353 downgrade the confidence to “low”. The step of translating the confidence into a level of evidence
354 seeks to integrate the confidence with the nature of the effect (“health effect” or “no health effect”).
355 On this regard, we conservatively judged the direction of the effect towards the presence of adverse
356 health effects, despite the lack of consistency across studies. Thus, considering the NTP/OHAT
357 framework, we established the level of evidence being “low”.

358

359 **Figure 2.** Risk of bias heatmap summarizing the evaluations for each key question adapted from the NTP/OHAT tool. Instructions can be found in the
 360 Supplementary Materials Appendix 1. Further details on specific evaluations and justifications in HAWC.

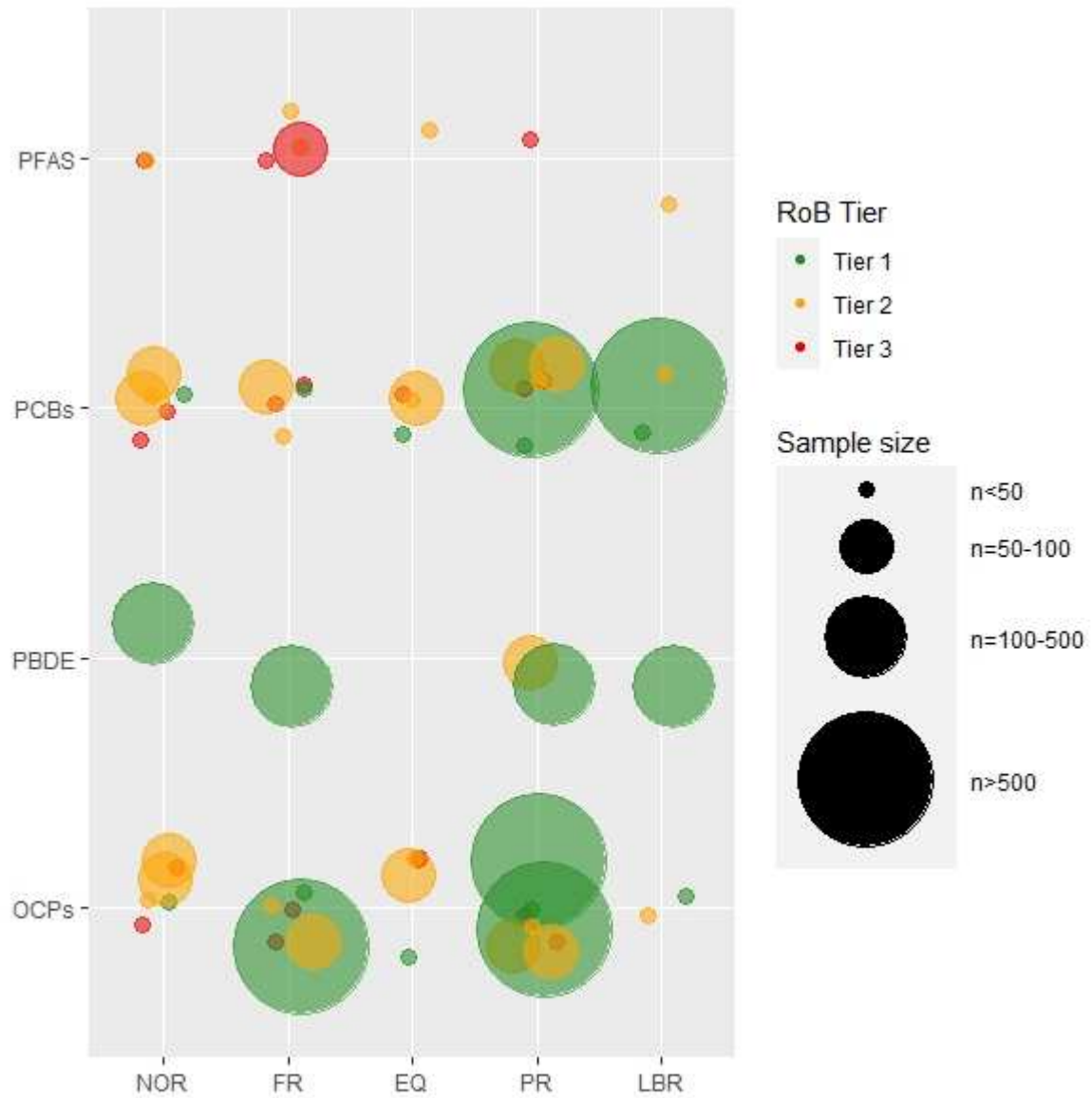


361

362

363 **Figure 3.** Evidence gap map summarizing the size and risk bias tier classification for included studies
 364 assessing the relationships between the main POP families and *In vitro* fertility outcomes. Each
 365 bubble represents a single study with size proportional to the population included in the analysis and
 366 colour related to the respective risk of bias Tier classification according the NTP/OHAT approach.
 367 Tier 1 refers to those studies classified as “unlikely”, Tier 2 as “serious” and Tier 3 “very serious” risk
 368 of bias.

369



370 Abbreviations: EQ, embryo quality; FR, fertilization rate; LBR, live birth rate; NOR, number of
 371 oocytes retrieved; OCPs, organochlorine pesticides; PBDE, polybrominated diphenyl ethers; PCBs,
 372 polychlorinated biphenyls; PFAS, perfluoroalkyl substances; PR, pregnancy rate; RoB, risk of bias.
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378 **4. Discussion**

379 To the best of our knowledge this is the first systematic review on the association between internal
380 exposure levels of POPs in women and IVF outcomes. This review shows that most studies have been
381 performed in small cohorts and focalized on PCBs and OCPs, whereas major research gaps remain for
382 PFAs and PBDEs. Providing an accurate and quantitative synthesis of results was unfeasible due to
383 the heterogeneity of metrics and exposure-outcomes dyads analyzed across the studies. Thus, we
384 focused the synthesis on the identification of research gaps and main direction and magnitude of
385 effects across POPs exposure-IVF outcomes pairs. In this respect and considering the broad topic, we
386 introduced the evidence map as a novel tool to ease the visualization of a broad body of evidence and
387 identification of main research needs. The overall results of studies included in this review were
388 mainly inclusive, but there is evidence that some POPs could impair the chance of successful IVF
389 treatments in infertile women, especially for the PCBs family which exhibited the most consistent
390 deleterious effects. Most studies were classified in Tier 2 or 3, as “Serious” or “Very serious” risk of
391 bias according the NTP-OHAT risk of bias tool due to lack of adjustment for confounding variables,
392 low sample size and/or underreporting of outcome/exposure methods.

393 **4.1. Study design and inter-individual variables**

394 The global inconsistency of results across studies are likely to be due in part to temporal and
395 geographic differences in POPs exposure and infertility treatment practices, as well as differences in
396 congeners measured and study designs. A major methodological issue lies on the small sample size of
397 most included studies (n<50 women). Thus, considering the modest effect size of POPs, it may be
398 likely that many of studies may be underpowered to identify such associations [43]. Geographical
399 differences of studies conducted in 9 different countries may be associated with a high variability on
400 dietary habits and other lifestyles factors affecting IVF outcomes. Indeed, racial and ethnic disparities
401 in exposure to endocrine disrupting chemicals [44] and in the chances of live birth after IVF have
402 been reported [45,46]. Whereas the mean or median age of female was quite consistent across studies
403 (32-35 years), the upper age bounds varied substantially (between 40 and 50 years old) which may

404 also substantially influence the results if not accounted for in the analysis. Indeed, female age has a
405 major impact on the IVF outcomes [47].

406 **4.2. Exposures**

407 The chemicals considered in the present review are mainly hydrophobic, but in a different extent. For
408 instance, the octanol-water partition coefficient ($\log K_{ow}$), a commonly used measure the tendency of
409 chemicals to bioconcentrate in the lipid compartments, vary across congeners from high (e.g. DDE ~
410 6.5) to moderate or weak lipophilicity (e.g. PFOS ~4.5). In this respect, the lipid and protein content
411 of biological matrices intended for chemical analysis may influence the analytical performance of
412 lipophilic and amphiphilic chemicals, respectively, especially for low abundant congeners.
413 Interestingly, many of included studies reported the paired determinations of biomarkers in FF and
414 serum, mostly finding high correlations between both matrices for PCBs, OCPs and PFAs ($\rho > 0.5$) but
415 weaker or even no correlation for PBDES ($\rho < 0.4$). This could be explained by different
416 physicochemical and metabolic properties of congeners. It should be noted that fasting status was not
417 standardized for blood samples. Moreover, blood samples could have been collected at different time
418 points of ovarian stimulation (i.e. prior, throughout stimulation or on the day of oocyte retrieval), and
419 thus the circulating levels of lipophilic POPs (PCBs, OCPs and PBDEs), being affected by lipid
420 mobilization seconding the hormonal status. For instance, endogenous estrogens may modulate the
421 action of lipoprotein lipases and the profiles of free fatty acids and lipoproteins in blood [48] and thus
422 modifying the release lipophilic compounds from lipid droplets [49]. On this regard, Mc Coy et al.
423 reported that levels of PFAS, with both lipophilic and hydrophilic properties, were mostly stable in
424 serum during the stimulation, except for PFOA [35]. The authors actually hypothesized that this
425 change might reflect physiological and hormonal changes, consequently impacting the clearance of
426 PFAs. Whereas we acknowledge that FF may be a convenient and representative matrix of the target
427 site (i.e. ovarian environment), we may anticipate that its lower lipid concentration as compared to
428 serum (e.g. ~ 10 folds) and lipid dynamics during ovarian stimulation might contribute to
429 measurement error and variability [50]. In this regard, the lipid normalization of POPs biomarkers has

430 been widely embraced in biomonitoring. Nonetheless, there is still an active debate about the best
431 modeling practices for POPs biomarkers in epidemiology, especially when circulating lipids may be
432 altered by the exposures or the outcomes [46]. Most included studies used the default approach, and
433 few studies compared results between lipid-normalized and raw biomarkers [32,39,41]. The partition
434 of lipophilic POPs and lipids between blood and FF has not been characterized, precluding related
435 conclusions about the impact of lipid-normalization on statistical models.

436 Another major issue associated to observational research on POPs hampering the comparison across
437 studies is the distribution of chemicals within study population, including the variable average
438 concentration levels, ranges of distributions (e.g. high vs low exposures) or the baseline
439 concentrations in the lower bound of distributions that would determine the exposure contrast. For
440 instance, the mean level and standard deviations of PCB180 in FF ranged between 0.04 ± 0.02 ng/mL
441 [34] and 0.1 ± 0.02 ng/mL [36].

442 **4.3. IVF outcomes**

443 Numerous clinical factors could also contribute to the divergent associations reported between IVF
444 outcomes and POPs. First, populations were heterogeneous and not always described in details. For
445 instance, the infertility etiologies and duration of infertility may impact the consistency of the
446 findings. Although the impact of the type of infertility (primary versus secondary infertility) on IVF
447 outcomes is controversial [51], some etiologies such as adenomyosis, ovulatory dysfunction [52,53]
448 or some individual factors such as age, obesity or long duration of infertility [47,51,54] have been
449 shown to have a clear detrimental impact on IVF outcomes. Furthermore, some studies reported
450 increased levels of POPs in certain comorbidities, such as endometriosis [12], polycystic ovarian
451 syndrome (PCOS) [13] or other ovulatory disorders [20] that could result on infertility through
452 different signalling pathways. From a mechanistic point of view, some studies suggested that POPs
453 acted on reproductive outcomes via disruption or modification of endocrine pathways. Indeed,
454 antisteroidogenic or steroidogenic properties of PCBs, as well as interaction with progesterone
455 receptor pathway have been well documented [55]. The antiestrogenic effect of PBDE, impacting the

456 uterine expression of estrogen and progesterone receptor [30], and the ability of PFAs to bind to
457 peroxisome proliferator-activated receptors have also been described [33]. POPs like dioxins can have
458 pro-inflammatory effects on the endometrium [56], potentially impairing uterine receptivity [57].
459 Concerning progesterone pathway, assisted reproduction generally implies the administration of
460 exogenous progesterone. However, this might not overcome the potential deleterious role of a
461 progesterone disruptor, albeit it might be probably less harmful than in spontaneous cycles. In any
462 case, the evaluation of putative associations between exposure (i.e. endocrine disruptors) and
463 pathophysiological effects should be cautious in the context of a clinical intervention which can bias
464 the analysis. Furthermore, animal studies reported an impact of estrogen levels on the clearance of
465 POPs, such as PFOA [35], that may prone to reverse causation in cross-sectional study designs or
466 modifying the estimates in FF following the stimulation. Second, most studies did not provide
467 information on male partner / factors, although sperm parameters play a critical role in the chances of
468 birth following ART [58]. In the same vein, protocols for controlled ovarian hyperstimulation are
469 rarely described in the available studies, even though this parameter does not seem to be significantly
470 associated with IVF outcomes [59]. Third, the main heterogeneity across literature lies within the
471 various endpoints used to report IVF outcomes. This is illustrated by the dissimilar assessment of
472 more advanced events, for instance by the use of “failed implantation rate” in some studies [29,39,41],
473 while others used more conventional “pregnancy rates”. We considered both as similar events with
474 inverse metrics in this study in order to ease the synthesis. Additionally, whereas early and
475 intermediate IVF outcomes (prior to implantation) provide interesting information on oocyte and
476 embryo quality, most studies failed to assess LBR which is considered the most relevant outcome for
477 infertile couples and medical staff [60]. Indeed, statistical differences found in terms of embryo
478 quality and/or early pregnancy events might be of little or even null clinical relevance if no impact on
479 LBR is found at the end. Thus, future studies should consider including LBR as main outcome in
480 order to provide an overall evaluation of the reproductive process and help improve relevant
481 information and counselling for patients and care providers.

482 It should be noted that findings of this review on the impact of POPs on female reproductive function
483 might not be easily generalizable to fertile women and/or to infertile women not undergoing IVF.
484 Indeed, although one study reported an association between exposure to POPs and increased time to
485 achieve pregnancy [61], further analysis in properly designed prospective cohort studies is required to
486 assess clinical relevance. More specifically, the heterogeneity in IVF population and practices across
487 regions calls for caution when drawing conclusions from such a review and advocates for external
488 validation studies.

489 **4.4. Statistical methods**

490 We have noticed a variety of criteria regarding the inclusion of chemicals in statistical analysis based
491 on detection rates and methods to manage non-detected samples. For instance, some studies included
492 biomarkers detected in at least one sample [34] whereas other studies included biomarkers detected in
493 all samples [39]. Low detection rates may introduce exposure misclassification and generate artefacts
494 in regression models, that could help to explain the counterintuitive positive association between PCB
495 146 (detection frequency of 6.2%) and implantation rate (RR = 4.09; 95% CI 2.09, 8.02) reported by
496 Bloom et al. [34]. Most studies used standard univariate or multivariate regression approaches (either
497 linear, negative binomial, logistic binomial or Poisson models) to study the associations between
498 POPs and IVF outcomes, either considering continuous, counts or binary outcomes. We have noticed
499 that a substantial number of studies have not considered relevant confounding variables in the
500 statistical analysis. For instance, female BMI and age are well-established factors that can affect both
501 the exposure levels of POPs and the IVF outcomes [47,54]. Conversely some few studies considered a
502 comprehensive list of additional confounders, including study phase, ethnicity, previous live birth,
503 smoking, gonadotropins or estradiol levels [30,32,39]. In turn, the lack of proper consideration of
504 negative or positive confounding, interactions or effect modification due to diet or co-occurrence of
505 protective micronutrients (e.g. vitamin D or ω -3 polyunsaturated fatty acids) [62,63], may result in
506 attenuation bias or nullifying the associations [64]. Other common statistical pitfalls in IVF studies
507 have been highlighted elsewhere [60]. For instance, little attention has been generally paid to

508 adjustment for women cycles in order to account for ‘unit of analysis’ errors or the misuse and
509 misinterpretation of odds ratios with binary outcomes [60]. Another source of bias that has not
510 commonly reported in the selected studies involve the exclusion of cycles where embryos were not
511 viable in the analysis of implantation. As Messerlian and Gaskins argued [60], the exclusion of these
512 cycles (about 10-20% of cycles before embryo transfer) will likely lead to bias if the exposure of
513 interest is associated with early ART failure (e.g. no oocytes fertilized or poor embryo). On this
514 regard, some studies have applied generalized estimating equations to accommodate clustering of
515 oocytes and embryo outcomes within women [34,38] or woman-specific random-effect terms to
516 account for the correlation among outcomes from different cycles [39, 40]

517 Most studies considered the biomarkers as independent exposure variables, however the multi-
518 detection methods have shown that most POPs are embedded in complex mixtures of highly
519 correlated chemicals with similar physicochemical properties. Statistical analysis of highly correlated
520 mixtures were not conducted in most included studies, however in some cases the sum of congeners
521 was considered to elaborate a combined variable. Additionally, 2 studies within the same population
522 considered a two-step approach to, first, identify the Principal Component-based variables
523 representing the different chemical mixtures, and second, to estimate the associations of these
524 composed variables in the standard regression models [32,32]. Whereas this principal component
525 analysis approach is a step-forward beyond the analysis of single pollutants, caution should be taken
526 in terms of interpretation of resulting associations because the factor loadings are estimated without
527 taking into account the underlying association with the outcome [65]. The methodological
528 development and computational apparel for multipollutant modeling is quickly evolving to answer
529 multiple questions related to chemical mixtures in epidemiological research, so future studies should
530 consider some of the available models to gain insight on the mixture effects [66,67]. Last but not
531 least, it is noteworthy to consider the potential presence of non-monotonic dose-responses in
532 endocrine-related health outcomes, thus the application of statistical approaches able to identify non-
533 linear effects should be considered as a complementary approach to standard methods [68]. Among

534 included studies few studies have considered for instance the chemical exposures as quartiles, in
535 addition of continuous variables, that may be helpful to elucidate non-monotonic trends [39,40].

536 **5. Conclusion**

537 To the best of our knowledge this is the first attempt to systematically gather and evaluate the
538 evidence about the associations between POPs and IVF outcomes to deliver formal conclusions.
539 Applying a robust evidence-based approach, the present systematic review shows that all main
540 families of POPs are still pervasive in follicular fluid and serum of women attending modern IVF
541 treatments. Complex mixtures of legacy POPs are likely to occur together with more emerging
542 chemicals such as PFAs or PBDEs. The formal synthesis of effects across studies was not feasible due
543 to the heterogeneous designs and metrics favouring a quantitative analysis. Globally, we found
544 inconsistent findings across studies for specific exposure-outcome dyads, suggesting that adverse
545 effects of POPs on IVF outcomes cannot be ruled out. Specifically, our results suggest that POPs,
546 notably some PCBs and OCPs, may impair embryo quality and pregnancy rates, even though the
547 biological mechanisms remain to be deciphered. Most published studies have ‘serious’ or ‘very
548 serious’ risk of bias according the NTP/OHAT framework, mainly due to lack of adjustment for
549 confounding variables or small sample size, that may help to explain the divergent results. Globally,
550 we judged the level of evidence being “low”. We emphasized some gaps and directions for future
551 studies including: 1) the use of individual exposure biomarkers with a large proportion of detected
552 observations for statistical analysis; 2) blood and FF may provide complementary information on POP
553 exposure, but caution should be paid due to the little knowledge available about the respective
554 partition coefficients, the impacts of hormonal stimulation or the biomarker lipid normalization ; 3)
555 LBR should be considered the main outcome recapitulating the entire fertilization process, and thus
556 more biologically relevant than other intermediary outcomes whose statistical findings should be
557 considered with caution; 4) statistical models should accommodate the different women stimulation
558 cycles and non-transferred embryos in the analysis, as well as relevant confounding variables

559 including age and BMI. Given the high economical and societal costs associated with infertility and
560 IVF, further well-designed research is urged to fill the highlighted gaps.

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564 **Conflict of interest**

565 The authors disclose no competing conflict of interest.

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