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Review article

Lack of association between endocrine disrupting chemicals and male fertility: A systematic review and meta-analysis

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ABSTRACT

The incidence of infertility currently affects about 15% of the world's population. Male factors are estimated to be responsible for up to 40–50% of these cases. While the cause of these reproductive disorders is still unclear, the exposure to a family of ubiquitous compounds in our daily life, named endocrine disrupting chemicals (EDCs) could be involved. This paper was aimed at performing a systematic review and meta-analysis of population studies exploring whether human male exposure to EDCs affects male fertility. Clinical and observational studies assessing the exposure to EDCs along with sperm quality, the most common reproductive disorders, sperm DNA damage, sperm oxidative stress, fertilization rate, implantation rate, clinical pregnancy rate, live birth rate, and miscarriage rate were included. The quality assessment tool from the NHLBI-NIH was used to assure that studies met standardized quality criteria. Sensitivity analysis and heterogeneity among studies was assessed. Overall, the 32 selected articles, including 7825 individuals in the systematic review, explored 12 families of EDCs. The results revealed a high heterogeneity among studies in relation to the association between exposure to EDCs and the endpoints analyzed. Meta-analyses were performed with data from 7 articles including 479 individuals, 4 articles assessing the association between BPA in urine and sperm quality, and 3 articles evaluating PCB153 in serum and sperm quality. In the meta-analysis, we identified an unpredicted significant positive association between PCB153 exposure and sperm concentration. However, it would not be clinically relevant. No positive or inverse associations were found neither for BPA, nor for PCB153 and the rest of sperm parameters analyzed.

The high disparity between studies made difficult to draw conclusions on the potential harmful effects of EDCs on male fertility. Consequently, to delineate the potential relationship that EDCs can have on male fertility, an important condition stressing the health system, further investigations are required.

1. Introduction

Exposure to natural or synthetic chemicals is directly related to environmental conditions, dietary and other lifestyle factors. Some of these chemicals are named Endocrine Disrupting Chemicals (EDCs) because of their capability to interfere with the endocrine system. The scientific community established the term EDCs in 1991 (Kwiatkowski et al., 2016). EDCs are entailed by ubiquitous groups of substances, including polychlorinated and polybrominated biphenyls, plasticizers, toxic metals, dioxins and furans, phytoestrogens, fungicides and

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pharmaceuticals, among others (Stukenborg et al., 2021). Albeit some regulations for certain EDCs exist in developed countries, there is a clear lack of legislation in emerging countries (Kassotis et al., 2020).

EDCs are also recognized as neuroendocrine disruptors because of their capacity to act as modulators of the metabolism or synthesis of neurotransmitters or neurohormones, which subsequently can affect production, secretion, distribution, metabolism, excretion, and binding actions of naturally hormones (Zoeller et al., 2012). Furthermore, the adverse effects of EDCs are related to the development of potential and chronic diseases and can be passed on to the next generation, causing detrimental biological responses in organisms (Diamanti-Kandarakis et al., 2009). Human clinical observations, epidemiological studies and animal models' studies agree pointing out exposure to EDCs as a significant concern for public health, especially due to their association with the development of potential and chronic diseases (Diamanti-Kandarakis et al., 2009). Among the substantial number of chronic diseases, infertility has progressively become the one attracting a major medical and social concern (Welsh et al., 2008).

Currently, infertility affects about 15% of the world's population, being male factors responsible for 40–50% of these cases (Vander Borght and Wyns, 2018; Welsh et al., 2008). Male reproductive health is declining over the last years, raising serious concerns for human reproduction (Levine et al., 2017). Although male infertility is known to be a worldwide health problem, its incidence is higher in specific geographical areas of the world, particularly in most technologically advanced and developed countries (Swan et al., 1997). Epidemiological studies show an increase in fertility disorders, with higher incidence of lower sperm quality parameters and a higher occurrence of cryptorchidism and hypospadias (Lymperi and Giwercman, 2018; Stukenborg et al., 2021). Recent studies on poor sperm quality reveal the importance of taking action to identify and tackle the possible factors behind this decline (Barratt et al., 2018; Lokeshwar et al., 2021; Zufferey et al., 2020), highlighting the urgent need of improving the understanding of the causes of male fertility. Although there are different possible causes for this decline, some have postulated the most likely to be related with the lifestyle and exposure to environmental factors (Skakkebæk et al., 2022). In western countries, the production and exposure to EDCs has been increasing in recent decades. In fact, many EDCs are widely found in food and drinking water, personal care products, cleaning products, textiles, etc. Therefore, exposure to EDCs can occur in daily activities via dietary sources, via inhalation and/or dermal contact, and this exposure may affect reproductive health (European Parliament, 2019; Stukenborg et al., 2021). However, while studies in rodents have shown clear relationships between EDCs and decreased sperm counts (Tiwari and Vanage, 2013) or increased risk of hypospadias and/or cryptorchidism (Welsh et al., 2008), it is still not clear to what extent these associations occur in humans (Kilcoyne and Mitchell, 2019; Lymperi and Giwercman, 2018).

Exposure to EDCs and their potential role on male fertility is a topic of an important concern. In fact, in recent years the scientific community has been assessing the adverse effects of several emerging compounds (i.e., pesticides, plasticizers, personal care products, epoxy resins, etc.) on a wide range of male fertility indicators (i.e., sperm quality parameters, reproductive disorders, DNA damage, oxidative stress, time to pregnancy, etc.) (Knapke et al., 2022). However, less effort has been dedicated to systematically reviewing all these studies to better assess whether exposure to these chemicals might be harmful. In fact, the article by Knapke et al. (2022) is -to date- the only systematic review on this topic, which found sound evidence on the association between pesticide exposure and reduced sperm motility, concentration, and DNA integrity. Based on the above, the current systematic and meta-analysis aimed to summarize and explore the association between exposure to EDCs and human male fertility indicators: sperm quality, the most common seminogram disorders (azoospermia, oligozoospermia, asthenozoospermia, asthenozoospermia, teratozoospermia), sperm DNA damage and oxidative stress, fertilization rate, clinical pregnancy rate, implantation rate, live birth rate and miscarriage rate.

2. Methods

2.1. Registration of the systematic review and meta-analysis

This systematic review and meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009). The protocol were registered within the international prospective register of systematic reviews (Pan et al., 2015: www.crd.york.ac.uk/prospero). Code number: CRD42022250964.

2.2. Databases and defined criteria

Systematic search of the literature was performed using Cochrane (https://www.cochranelibrary.com/advanced-search) and the MEDLINE-PubMed (https://www.ncbi.nlm.nih.gov/pubmed) databases, including articles published until February 10, 2022. The literature search followed the inclusion and exclusion criteria described and available in the PECOS (Population, Exposure, Comparison, Outcome, Study) table (Supplementary Material, Table S1). For both databases, the search strategy was to combine unintentional men exposure (high versus low or/and case versus control) to EDCs defined criteria (Supplementary Material, Appendix S1).

2.3. Study eligibility

Studies that followed the criteria shown in the PECOS table (Table S1) were eligible for the present systematic review and meta-analysis: (i) men whose both infertility and unintentional EDCs exposure was assessed; (ii) comparisons performed between men with low and high unintentional EDCs exposure or between unintentional EDCs exposure (case) and non- EDCs exposure (control); (iii) primary outcomes entailed parameters of sperm quality (concentration, vitality, motility, morphology), semen quality (pH and volume) and seminogram alterations (azoospermia, oligozoospermia, asthenozoospermia, asthenozoospermia, teratozoospermia); (iv) secondary outcomes were fertilization rate, sperm DNA damage, sperm oxidative stress, clinical pregnancy rate, implantation rate, and live birth rate.

Studies on *in-vitro*/cell cultures, *in-silico,* and animal models were excluded from our review. In turn, reviews, systematic reviews, and meta-analyses on the topic, as well as case reports, viewpoint articles, summaries for patients, editorials, commentary articles and letters were not included either. Finally, we did not include those studies whose full-text article was not available, or when it was not available in English.

2.4. Screening and quality analysis

The selection of the articles for the systematic review and subsequent meta-analysis was carried out in different stages, as detailed in the flow chart (Fig. 1). First, the searches performed in Cochrane and PubMed were recorded. These searches stored the following information: DOI, title, abstract, authors and type of article. Duplicated studies in both databases were excluded. Secondly, titles and abstracts were screened by two experts in endocrine disruptors and environmental chemicals exposure (M.M. and MÁ.M.), excluding papers that did not fit the eligibility criteria previously mentioned (primary or secondary outcomes). Subsequently, full texts of eligible articles were downloaded and further screened by the same authors to check their eligibility according to the PECOS design (Table S1). Afterwards, when a discrepancy about the potential inclusion of an article raised between MÁ.M. and M.M., two epidemiologist and fertility experts (A.S–H. and N.B.) reached a consensus. Additionally, the quality analysis was performed for each study following the NHLBI-NIH guidelines. Quality assessment tools (www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)

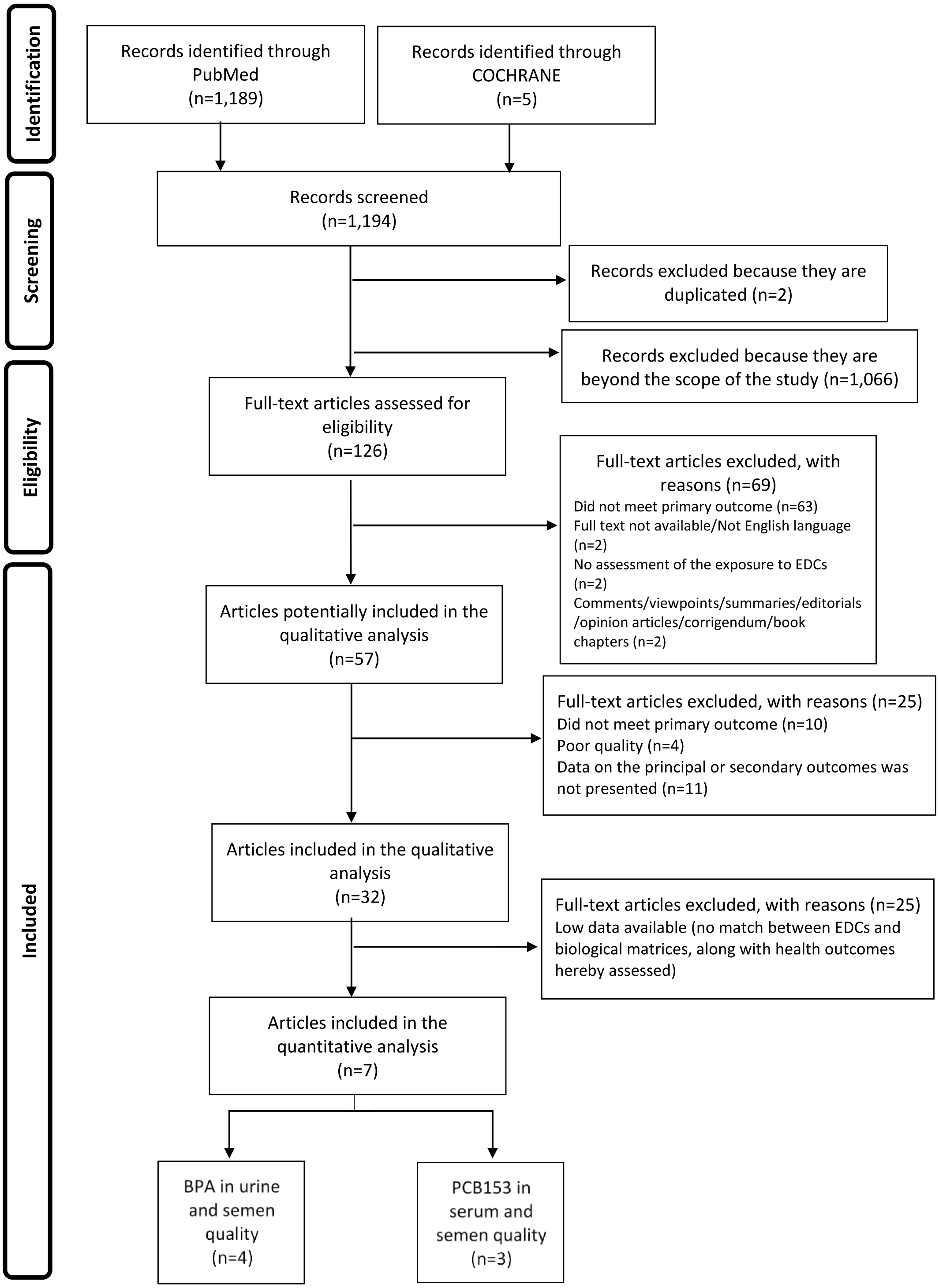

Fig. 1. Flowchart of the literature search and selection process.

were used to evaluate and score the published articles (Ribas-Maynou et al., 2021).

2.5. Systematic review: data extraction

The following data were extracted for each article included in the qualitative analysis: journal, author/s, publication date, title of the article, study design, EDC evaluated, health outcome assessed, sample size, aim, and main conclusion. Afterwards, we classified the articles included in the systematic review according to the study design (case-control study or observational study) and their findings: positive, negative, or without association between EDCs exposure and health outcome, including sperm quality (pH, concentration, volume, vitality, motility, morphology), seminogram disorders (azoospermia, oligozoospermia, asthenozoospermia, asthenozoospermia, teratozoospermia), sperm DNA damage, sperm oxidative stress, fertilization rate, clinical pregnancy rate, implantation rate, live birth rate, and miscarriage rate. The papers considered in this systematic review were published between 2008 and 2021.

2.6. Meta-analysis: data extraction and statistics

For the meta-analysis we selected those studies previously included in the qualitative analysis. A data table (low/high exposure to an EDC and fertility parameter) was created. Subsequently, data on exposure to EDCs and the different outcomes (sperm quality, sperm DNA damage, sperm oxidative stress, fertilization rate, clinical pregnancy rate implantation rate, live birth rate, and miscarriage rate) were extracted for the quantitative analysis.

Meta-analyses were conducted using Doing Meta-Analysis in R package and Meta-Essentials v.1.4 in accordance with the Cochrane guideline (Higgins and Green, 2011). To calculate the effect size (ES) and 95% CI, the mean and standard deviation (SD) were obtained for every study included. If other data were presented in selected studies, those were computed with other data distribution values (e.g., median and interquartile rank, etc.). Main values were obtained by two authors (MÁ.M. and M.M.) and checked by a third author (A.S–H.). Random effect models were used to obtain summary effect sizes due to the heterogeneity of the studies analyzed. Statistical significance level was set at $p < 0.05$ (two-tailed). Heterogeneity between studies was evaluated using the chi-square test and the I^2 index (the significance level was set at $p < 0.1$). Sensitivity analyses were performed for analysis of >3 studies by systematic exclusion of one study at a time and recalculating summary effect sizes.

3. Results

3.1. Identification and selection of articles

A total of 1194 records were identified. Two articles were excluded because of duplication between databases, while 1066 articles were excluded because they were beyond the scope of the study. Hence, 126 full-text articles were downloaded, being the full-text evaluated according to the inclusion/exclusion criteria previously defined (section 2.3. Study eligibility). A total of 69 articles were excluded because they did not meet the primary outcome ($n = 63$), or the exposure to EDCs was not assessed ($n = 2$), or the full text was not available ($n = 2$), or they were comments viewpoints, opinion articles, corrigendum, or book chapters ($n = 2$), leading to 57 articles potentially included in the qualitative analysis. During the quality control, more articles were excluded because they did not meet the primary outcome ($n = 10$), due to poor quality score ($n = 4$) and because data on the principal or secondary outcomes were not presented ($n = 11$). The quality score of each article is shown in Supplementary Material (Table S2a and Table S2b). Overall, the mean quality scores of observational prospective and cross-sectional studies, and case-control studies were 7.62/14 (range: 5–11) and 8.16/12 (range: 7–10), respectively.

3.2. Systematic review. Studies included

A total of 32 studies on EDCs exposure and sperm quality, DNA damage or DNA fragmentation, pregnancy rate, or fecundability, were included in the current qualitative review (Supplementary Material, Table S3). The most common EDs in the 32 articles were the following:

Seven studies assessed dioxins and furans, and polychlorinated biphenyls PCBs in serum and sperm quality, being 1 of them (14%) (Paul et al., 2017) – depending on the PCB congener – positive or inverse associations with sperm quality parameters. Three studies (43%) (Mocarelli et al., 2008; Paoli et al., 2015; Rignell-Hydbom et al., 2004) showed an inverse association with sperm quality, while three studies (43%) (Abdelouahab et al., 2011; Petersen et al., 2015, 2018) did not find any significant association with sperm quality.

Seven studies were involved in bisphenol A (BPA) in urine and sperm quality, DNA damage, DNA fragmentation or fecundability, one of them (14%) (Omran et al., 2018) showed a positive association with DNA damage, four of them (57%) (Adoamnei et al., 2018a; Goldstone et al., 2015; Meeker et al., 2010; Pollard et al., 2019) showed an inverse association with sperm parameters, DNA fragmentation and sperm DNA damage, and two studies (29%) (Buck Louis et al., 2018; Kim et al., 2021) did not find any association with pregnancy outcomes and sperm quality.

Five studies assessed phthalates in urine and sperm quality, DNA fragmentation, pregnancy rate or fecundability, one of them (20%) (Pan et al., 2015) showed positive association with DNA fragmentation and an inverse association with sperm quality. Three studies (60%) (Begum et al., 2021; Smarr et al., 2018; Toshima et al., 2012) showed an inverse association with sperm parameters, DNA fragmentation and pregnancy rate, while one study (20%) (Buck Louis et al., 2018) did not find any association with fecundability.

Four articles were about benzophenones urine and sperm parameters and fecundability. Among these, one study (25%) (Paoli et al., 2015) showed an inverse association with sperm quality parameters, while 3 studies (75%) (Adoamnei et al., 2018b; Buck Louis et al., 2018; Smarr et al., 2018) did not find any association with sperm parameters or fecundability.

Three articles assessed BPA in seminal plasma and sperm quality. Two of these studies (67%) (Vitku et al., 2016; Smarr et al., 2018) showed an inverse association with different sperm parameters, while one study (33%) (Kim et al., 2021) did not find any association with fecundability and sperm quality.

Three articles evaluated per-and polyfluoroalkyl substances (PFASs) in serum and sperm quality. One of these studies (33%) (Joensen et al., 2009) showed an inverse association with sperm parameters, while two studies (67%) (Joensen et al., 2012; Petersen et al., 2018) did not find any association with sperm parameters.

Three articles were involved in triclosan in urine and sperm quality. One study (33%) (Zhu et al., 2016) showed an inverse association with sperm parameters and 2 articles (67%) (Chen et al., 2013; Smarr et al., 2018) did not find any association with sperm parameters.

There are certain EDCs whose occurrence in determined biological matrices *versus* male fertility has been less investigated. Two studies assessed BPA in plasma and sperm quality: Vitku et al. (2016) reported an inverse association, while Kim et al. (2021) did not find any association. In turn, two articles tackled DDT in blood and sperm quality. Both showed an inverse association between DDT and sperm parameters (De Jager et al., 2006; Rignell-Hydbom et al., 2004). Mantzouki et al. (2019) assessed BPA in serum, being inversely associated with azoospermia. Melgarejo et al. (2015) evaluated organophosphate pesticides in urine and it was inversely associated with sperm quality. Adoamnei et al. (2018c) determined parabens in urine, reporting a non-significantly association with sperm parameters. On the other hand, Song et al. (2018) focused their investigation on PFASs in plasma, reporting that it was inversely related with sperm parameters, while Smarr et al. (2017) evaluated paracetamol in urine, being positively related to sperm parameters. In turn, Vitku et al. (2016) reported an inversed association between plasma PCB sperm quality parameters, while Smarr et al. (2018) assessed phthalates in seminal plasma, being inversely associated with sperm parameters. In the study Specht et al. (2015) no associations between phthalates in serum and fecundability were observed, while Xu et al. (2012) evaluated arsenic (As) in plasma and it was inversely associated with sperm quality. Finally, Chen et al. (2013) reported an inverse association between phenols in urine and sperm quality.

There are some disagreements regarding the direction of the association between sperm parameters and DNA damage. However, most studies (Adoamnei et al., 2018a; Begum et al., 2021; De Jager et al., 2006; Goldstone et al., 2015; Joensen et al., 2009; Mantzouki et al., 2019; Meeker et al., 2010; Melgarejo et al., 2015 Mocarelli et al., 2008; Paoli et al., 2015; Pollard et al., 2019; Rignell-Hydbom et al., 2004; Song et al., 2018; Smarr et al., 2018; Toshima et al., 2012; Xu et al., 2012; Zhu et al., 2016) point to an inverse association between exposure to EDCs and sperm quality, by a reduction or abnormalities in different sperm parameters (volume, concentration, sperm counts, pH, motility and morphology), or an increase in DNA damage.

3.3. Meta-analysis. Studies included

Out of the 32 articles included in the qualitative analysis exploring 12 families of EDCs (phthalates, bisphenol A, parabens, pesticides, dioxins and furans, PCBs, benzophenones, metalloids, pharmaceuticals, triclosan, PFASs, and other phenols), 25 articles were excluded because of lack of data (exposure determinations were not available, or biological matrices were not specified). Among the seven articles selected for data analysis, 4 assessed BPA in urine and sperm quality parameters, while 3 articles evaluated PCB153 in serum and sperm quality parameters (Fig. 1).

3.4. Quantitative analysis

A summary of the collective effect estimates from the meta-analysis assessing the association between exposure to BPA and PCB53, and sperm parameters (sperm concentration, count, morphology, total motility and volume) is depicted in Fig. 2. Because of the limited number of studies (<10) funnel plots were not built.

3.4.1. BPA and sperm quality

The results for BPA studies revealed non-significant positive associations for sperm concentration (0.10 sperm cells [spz]/mL; −0.31 to 0.51 spz/mL; $p > 0.05$), sperm count (0.10 spz; −0.54 to 0.74 spz; $p > 0.05$) and semen volume (0.06 mL; −0.48 to 0.61 mL; $p > 0.05$). In contrast, non-significant inverse associations were found for sperm morphology percentage (−0.001%; −0.19 to 0.18%; $p > 0.05$) and sperm total motility percentage (−0.13%; −0.61 to 0.36%; $p > 0.05$), revealing the higher the concentration of BPA levels, the worse the sperm morphology and sperm total motility. The heterogeneity among studies was deemed substantial for motility ($I^2 = 62\%$, $p < 0.05$), and moderate for sperm concentration ($I^2 = 48\%$, $p > 0.05$) and sperm count ($I^2 = 50\%$, $p > 0.05$). In turn, sperm morphology and semen volume studies were homogeneous ($I^2 = 0\%$, $p > 0.05$) (Fig. 2).

3.4.2. PCB153 and sperm quality

The PCB153 studies showed a significant positive association with sperm concentration (0.17 spz/mL; 0.04 to 0.29 spz/mL; $p < 0.001$). However, reaching statistical significance may not imply clinical significance. Non-significant positive associations with sperm count (0.37 spz; −0.97 to 1.70 spz; $p > 0.05$), sperm morphology percentage (0.29%; −3.00 to 3.58%; $p > 0.05$) and sperm total motility percentage (−0.05%; −0.58 to 0.69%; $p > 0.05$) were observed. On the other hand, sperm volume was the only semen quality parameter with a non-significant inverse association (−0.11 mL; −0.63 mL–0.41 mL; $p > 0.05$). The heterogeneity among studies was substantial for both sperm morphology ($I^2 = 80\%$, $p < 0.05$) and sperm count ($I^2 = 85\%$, $p < 0.01$), moderate for sperm motility ($I^2 = 43\%$, $p > 0.05$), and limited for sperm volume ($I^2 = 27\%$, $p > 0.05$) studies. By contrast, results related to sperm concentration ($I^2 = 0\%$, $p > 0.05$) were homogeneous.

3.5. Sensitivity analyses

Because of the reduced number of articles ($n < 3$) evaluating PCB153 in serum and the same sperm quality parameters, sensitivity analysis was only performed for studies assessing BPA in urine and sperm concentration, along with BPA in urine and total sperm motility (Supplementary Material, Table S4).

The systematic omission of one study at a time showed that the association of BPA in urine and sperm concentration modified the ES

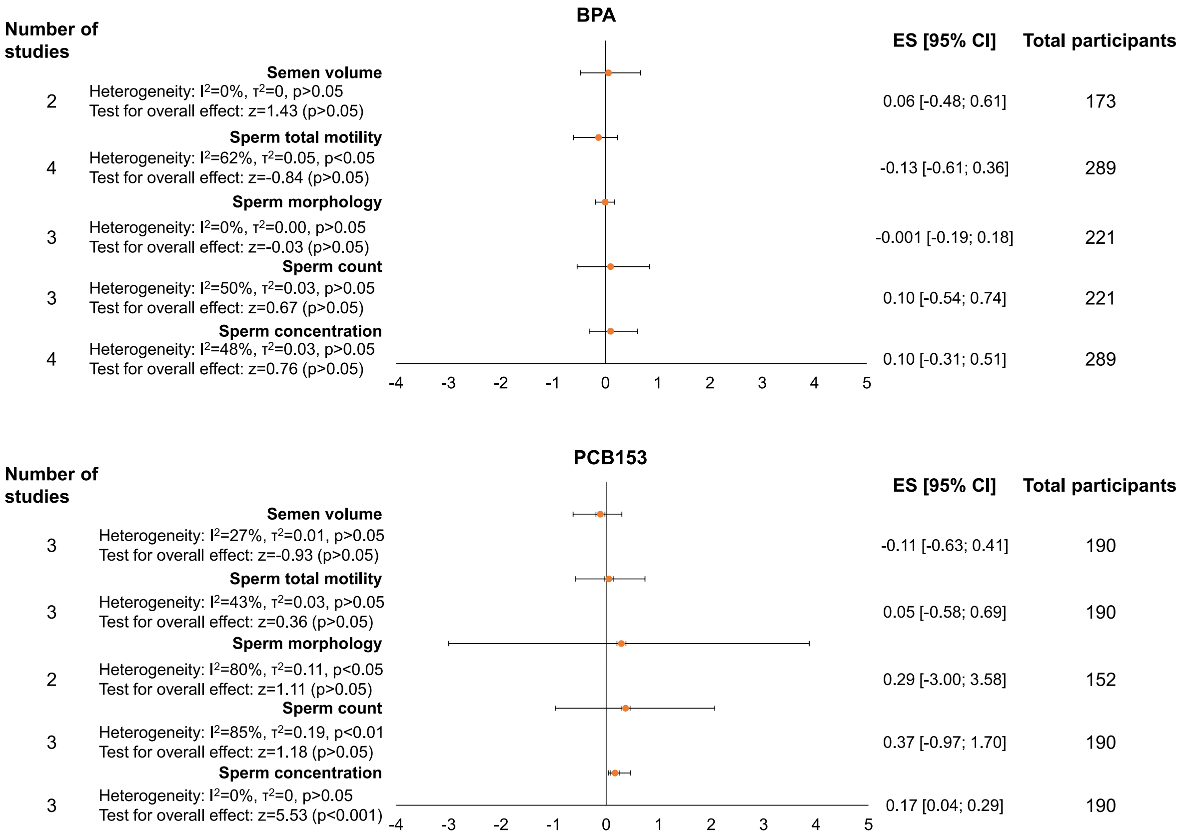

Fig. 2. Forest plot of pooled effect sizes (ES) for studies evaluating the association between the exposure to BPA and PCB153 and sperm quality parameters. *An ES value < 0 indicates a greater risk of an adverse outcome on the assessed fertility parameter compared to the low-exposed group.

$>$10% after deleting data from Adoamnei et al. (2018a) and Goldstone et al. (2015), without changing the non-significant positive association ($p > 0.05$). On the contrary, the exclusion of the study by Meeker et al. (2010) shifted to a non-significant inverse association ($p > 0.05$). Furthermore, Meeker et al. (2010) explained the heterogeneity ($I^2 = 0\%$, $p > 0.05$) among BPA in urine and sperm concentration studies. For BPA in urine and total sperm motility, the exclusion of the articles by Meeker et al. (2010), Goldstone et al. (2015) and Kim et al. (2021) modified the ES $>$10%, but keeping the direction of the trend ($p > 0.05$). In turn, the removal of the paper by Adoamnei et al. (2018a) also changed the ES $>$10%, but lead to the no association between BPA and total sperm motility, explaining the heterogeneity among studies ($I^2 = 0\%$) and changed its statistical significance ($p > 0.05$).

3.6. *Risk of bias*

3.6.1. *Observational cohort and cross-sectional studies*

According to the NIH quality assessment tool for observational cohort and cross-sectional studies, most studies received an overall score of 7 or higher out of a possible score of 14, suggesting good quality and a lower risk of bias. However, 4 studies received a score of 6 and 1 study had a score of 5 suggesting fair quality and moderate risk of bias (Table S2a, Supplementary Material).

3.6.2. *Case-control studies*

According to the NIH quality assessment tool for case-control studies, all of the studies received a score of 7 or higher out of a possible score of 12, suggesting good quality and a lower risk of bias (Table S2b, Supplementary Material).

4. Discussion

The current systematic review and meta-analysis provides expanded and updated data concerning the relationship between exposure to several EDCs and sperm quality parameters, as well as other male fertility indicators, being to the best of our knowledge, the first meta-analysis on this topic. The design of the study and search strategy, along with the qualitative and quantitative analyses, allowed the evaluation of a large set of data from high-quality studies. Data from 7825 individuals and 479 individuals in the systematic review and in the meta-analysis, respectively, were used. To date, the present analysis, including up to 12 families of EDCs along with sperm quality, DNA damage or DNA fragmentation, and pregnancy rate or fecundability, is the most comprehensive.

The systematic review results revealed that out of a total of 32 studies included, 17 of them (53%) showed a negative association between EDCs and male fertility indicators, 3 of them (9.5%) showed a positive association, while 9 of them (28%) showed no association. On the other hand, 3 of them (9.5%) showed inverse or positive associations with male fertility indicators, depending on the metabolite or chemical congener. Although the number of studies included in the current systematic review is notorious, the high disparity between studies (i.e., different EDCs and biological matrices studied, and fertility indicators evaluated) has a significant key role in this lack of a consensus.

Due to the abovementioned disparity among study designs, the meta-analysis was conducted with data from 4 studies on BPA in urine. And 3 studies on PCB153 in serum, along with five sperm quality parameters including sperm concentration, sperm count, sperm morphology, sperm motility, sperm volume. Due to the reduced number of studies and individuals here included, it is important to highlight that our results must be considered with caution. However, we found inverse associations between exposure to BPA and sperm morphology and motility percentages, showing effects sizes of -0.001% and -0.13%, respectively, but without statistical significance. On the contrary, detrimental associations were found with sperm concentration, sperm count and semen volume, with effect sizes of 0.1 spz/mL, 0.1 spz, and 0.06 mL, respectively, either with no statistical significance.

Our sensitivity analysis indicated that Meeker et al. (2010) and Adoamnei et al. (2018a) explained the heterogeneity among BPA in urine and sperm concentration studies, as well as BPA in urine and sperm total motility studies, respectively, although without statistical significance. In addition, excluding the results of Meeker et al. (2010), the trend of the association between BPA in urine and sperm concentration changed to negative, but non-significant. The exclusion of the data of Meeker et al. (2010), Goldstone et al. (2015) and Kim et al. (2021) modified the ES $>$10% of BPA in urine and sperm motility. Nevertheless, it did not change the trend of the association. In turn, Adoamnei et al. (2018a) explained the heterogeneity among studies causing no association between the abovementioned exposure and sperm parameter.

Regarding exposure to PCB153, we found a non-significant inverse association with semen volume, which showed an effect size of -0.11 spz/mL. In turn, non-significant positive associations were revealed for sperm total motility percentage, sperm count, and morphology percentage, with effect sizes of -0.05%, 0.37 spz and 0.29%, respectively. The only significant association was positive and with sperm concentration. However, this result was not clinically relevant (effect size of 0.17 spz/mL). Unfortunately, the sensitivity analysis could not be performed due to the reduced number of studies on PCB153 ($n = 3$) and the lack of coincidence on the measured sperm quality parameters.

4.1. *Strengths and limitations*

The present systematic review allowed to evaluate additional EDCs that could not be incorporated in the meta-analysis, named dioxins and furans, and other PCB congeners than PCB153, phthalates, benzophenones and PFAAs, along with other male fertility indicators beyond sperm quality parameters, like DNA fragmentation, fecundability and pregnancy rate, among others. Our wide search criteria on different forms of the keyword EDCs - instead of directly chemical substances - ensured the inclusion of all the studies aimed at assessing exposure to endocrine-disrupting chemicals, and hence, with the potential of altering male fertility. Finally, the application of a standardized quality-control filter guaranteed the quality of the studies here included.

Nevertheless, the strongest limitation of our review-paper is the reduced number of studies exploring the association of the same EDCs with a determined male fertility outcome, which was a barrier for the performance of a robust meta-analysis. Moreover, the heterogeneity among studies was moderate and substantial for some groups analyzed in our meta-analysis. However, this heterogeneity is typical for research targeting a multifactorial disease like infertility, where other known and unknown causes beyond exposure to EDCs -such as genetics or lifestyle- might determine this condition. Additionally, most of these studies addressed the role of one EDCs family -or at least a very limited number of- which underestimates the universe of chemicals to which we are daily exposed. It highlights the need of male fertility characterization by means of the last generation non-target analysis strategies. Finally, we detected publication bias for studies on BPA exposure and sperm concentration and motility.

5. Conclusions

The present systematic review revealed a high disparity between studies, making difficult a consensus on the possible detrimental effect of the 12 families of EDCs on male fertility. In the meta-analysis, we identified a significant positive association between PCB153 exposure and sperm concentration but this result is not clinically relevant. No significant positive or inverse associations were found for BPA, PCB153, and the rest of associations hereby assessed.

Because of the abovementioned limitations, as well as the related publication bias, we cannot confirm a harmful effect of EDCs on male fertility. However, we advise the population to minimize exposure to

EDCs as much as possible until more robust data are available.

Our analysis reveals a clear lack of high-quality comparable studies on EDCs and male fertility, highlighting the need of: i) more research on the field; ii) establishment of a gold standard methodology to enhance the harmonization among studies; iii) switching to the paradigm of exposome through assessment of chemical mixtures to further identify potential synergy or antagonism effects.

Further studies on this field should provide a better understanding of the epicenter of male fertility and could help to reduce related costs in public health care. They may also serve as essential reference guides for health policy makers in future measures.

Credit author statement

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Availability of the data

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114942.

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