**A systematic review: Impact of endocrine disrupting chemicals exposure on fecundity as measured by time to pregnancy**

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**Supplementary Information**

**Supplementary 1**

Quality assessment

**Supplementary 2**

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**Supplementary 3**

Review protocol

**Supplementary 4**

PRISMA Checklist

**Supplementary 1. Quality Assessment**

**1.1. Quality assessment form**

|  |  |
| --- | --- |
| Representativeness of the populations | Population-based representative = 1Not representative, selected group, volunteers, or no description = 0 |
| Ascertainment of exposure to the EDCs | Data on EDCs exposure collected prospectively = 1Data on EDCs exposure collected retrospectively = 0 |
| Selection of the non-exposed cohort/controls | Drawn from the same population = 1Drawn from a different source or no description = 0 |
| Assessment of EDCs exposure | Secure official record (medical records or professional confirmation, or laboratory confirmation) = 1Self-reported or structured interview or self-administered questions or no description = 0 |
| Case definition for fecundity measured by time to pregnancy (TTP) | Defined case for fecundity as measured by TTP = 1No description = 0 |
| Assessment of outcome | Use of structured clinical review for health outcome, blood tests or direct physical measurements = 1Questions from published health surveys/screening instruments, no system, not specified, or self-reported = 0 |
| Adequacy of follow-up of cohorts (where relevant) or response rate | Completeness good (>80%), with description of those lost to follow up = 1Completeness poor (<¸80%) or no statement = 0 |
| Appropriate statistical analysis | Yes = 1No = 0 |
| Appropriate methods to control confounding | Yes = 1 (multivariable adjusted OR )No = 0 (univariate analysis or controls for age/sex only) |
| Source of funding declared | Yes (financial disclosure, funding/support/grant declared) = 1No = 0 |

We did a comprehensive search on literature and found that a NOS score of 7 or more can be considered a “good” study (McPheeters, M.L., Kripalini, S., Peterson, N.B., Idowu, R.T. et al. (2012). Quality Improvement Interventions To Address Health Disparities. Evidence Report/ technology Assessment. Rockville (MD): Agency for Healthcare Research and Quality (US). <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0049222/pdf/TOC.pdf>). So we used this criterion as a cut off for good quality study.

The total quality score for each study is then the sum of the scores for individual assessment items. This is converted to a proportional quality score (the total quality score divided by the maximum score possible).

Data abstraction is completed independently (YR, NW, and LT). Results are reviewed (YR) and where disagreement occurs results are discussed (YR, LT, and NW) to reach consensus.

**1.2. Quality assessment results of included studies**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors/assessment contents** | **Representativeness of the populations** | **Ascertainment of exposure to the EDCs** | **Selection of the non-exposed cohort/controls** | **Assessment of EDCs exposure** | **Case definition for fecundity measured by TTP** | **Assessment of outcome** | **Adequacy of follow-up of cohorts (where relevant) or response rate** | **Appropriate statistical analysis** | **Appropriate methods to control confounding** | **Source of funding declared** | **Total score** |
| **Harley et al. 2010** | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| **Chevrier et al. 2013** | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 7 |
| **Gao et al. 2016** | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| **Den Hond et al. 2015** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 |
| **Buck Louis et al. 2013** | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| **Modigh et al. 2002** | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 6 |
| **Burdorf et al. 2011** | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |
| **Buck Louis et a. 2014** | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| **Buck Louis et a. 2018** | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| **Specht et al. 2015** | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 7 |
| **Snijder et al. 2012** | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 6 |
| **Velez et al. 2015** | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| **Jukic et al. 2016** | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 9 |
| **Tomsen et al. 2017** | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 8 |

**Supplementary 2. World Cancer Research Fund (WCRF) criteria**

**WCRF criteria for grading evidence**

**CONVINCING (STRONG EVIDENCE)**

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.

***All of the following were generally required:***

* Evidence from more than one study type.
* Evidence from at least two independent cohort studies.
* No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
* Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
* Presence of a plausible biological gradient (‘dose-response’) in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
* Strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

**PROBABLE (STRONG EVIDENCE)**

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

***All the following were generally required:***

* Evidence from at least two independent cohort studies or at least five case control studies.
* No substantial unexplained heterogeneity between or within study types in the presence or absence of an association or direction of effect.
* Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
* Evidence for biological plausibility.

**LIMITED — SUGGESTIVE**

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This judgement almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions require special explicit justification.

***All the following were generally required:***

* Evidence from at least two independent cohort studies or at least five case control studies.
* The direction of effect is generally consistent, though some unexplained heterogeneity may be present.
* Evidence for biological plausibility.

**LIMITED — NO CONCLUSION**

Evidence is so limited that no firm conclusion can be made. This category represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded ‘limited – no conclusion’ for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders) or by any combination of these factors. When an exposure is graded ‘limited – no conclusion’, this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged ‘substantial effect on risk unlikely’. There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (www.wcrf.org). However, such evidence is usually not included in the summaries. No substantial unexplained heterogeneity within or between study types or in different populations.

* Good quality studies to exclude with confidence the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
* Absence of a demonstrable biological gradient (‘dose-response’).
* Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, which typical human exposures lead to relevant cancer outcomes. Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, an insufficient range of exposure in the study population and inadequate statistical power. Defects in these and other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of ‘substantial effect on risk unlikely’. But the presence of robust evidence from appropriate animal models or in humans that a specific mechanism exists, or that typical exposures can lead to cancer outcomes, argues against such a judgement. Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure ‘substantial effect on risk unlikely’ are roughly equivalent to the criteria used with at least a ‘probable’ level of confidence. Conclusions of ‘substantial effect on risk unlikely’ with a lower confidence than this would not be helpful and could overlap with judgements of ‘limited – suggestive’ or ‘limited – no conclusion’.

**Supplementary 3. Review protocol**

**Primary database:** Three electronic databases (Scopus, Medline via Embscohost and EMBASE) were searched with the assistance of librarians.

**Search terms:**

|  |  |
| --- | --- |
| **Database** | **Search terms** |
| **Embase**  | (('endocrine disruptor'/exp OR 'endocrine disruptor' OR 'edc' OR 'ploybrominated diphenyl ether' OR 'polybrominated diphenyl ether' OR 'polybrominated diphenyl ether 47' OR 'polybrminated diphenyl ether 99' OR 'polybrominated diphenyl ether 100' OR 'polybrominated diphenyl ether 153' OR 'pbde' OR 'hexabromocyclododecane' OR 'hbcd' OR 'perfluoro compound' OR 'pfc' OR 'pfoa' OR 'pfos' OR 'organochlorine pesticide' OR 'organochlorine insecticide' OR 'organochlorine derivative' OR 'ddt' OR 'hexachlorocyclohexanes' OR 'dieldrin' OR 'chlordanes' OR 'hexachlorobenzene' OR 'phthalic acid' OR 'bisphenol' OR 'bpa' OR 'tbbpa' OR 'tetrabromobisphenol a') AND ('time to pregnancy' OR 'infertility' OR ‘fertility’ OR 'pregnancy' OR 'reproduction') AND [humans]/lim  |
| **Medline by Embscohost** | ("endocrine disruptor" OR edc OR "polybrominated diphenyl ethers" OR PBDE OR "hexabromocyclododecane" OR HBCD OR "tetrabromobisphenol A" OR TBBPA OR PFC OR "perfluorinated chemicals" OR "organocnlorine pesticides" OR OP OR phthalates OR "bisphenol A" OR BPA OR "organophosphate flame retardants" OR organophosphate OR OPFRS) AND ("reproduction" OR infertility OR "time to pregnancy" OR "fertility" OR "fecundity")  |
| **Scopus** | ('endocrine disruptor'/exp OR 'polybrominated diphenyl ether'/exp OR 'polybrominated diphenyl ether' OR edc OR 'polybrominated diphenyl ether 47'/exp OR pbde OR 'polybrominated diphenyl ether 47' OR 'polybrominated diphenyl ether 99'/exp OR 'polybrominated diphenyl ether 99' OR 'polybrominated diphenyl ether 100'/exp OR 'polybrominated diphenyl ether 100' OR 'polybrominated diphenyl ether 153'/exp OR 'polybrominated diphenyl ether 153' OR hbcd OR 'hexabromocyclododecane'/exp OR 'hexabromocyclododecane' OR pfc OR 'perfluoro compound'/exp OR 'perfluoro compound' OR 'organochlorine pesticide'/exp OR 'organochlorine pesticide' OR 'phthalic acid'/exp OR 'phthalic acid' OR bpa OR 'tetrabromobisphenol a'/exp OR tbbpa OR 'tetrabromobisphenol a') AND (infertility OR 'reproduction' OR 'fertility' OR 'time to pregnancy')OR 'fecundity') |

**Additional searching:**

Reference list review (any article pulled for possible inclusion)

Any article deemed suitable by reviewers is included for closer examination.

**Inclusion/exclusion criteria**

**Inclusion criteria:**

Studies were included if they were published in a peer-reviewed journal and reported an association between exposures to selected EDCs, including BFRs-TBBPA, PBDE, HBCD, phthalates, and OFPRs, and human fecundity and time to pregnancy.

1. *Question of interest*: Are humans exposed to EDCs, including BFRs-TBBPA, PBDE, HBCD, phthalates and OPFRs at higher risk of affecting time to pregnancy and fecundity, compared with those who are not exposed.

*Population*: females and males

*Exposure*: selected EDCs, including BFRs-TBBPA, PBDE, HBCD, phthalates and OPFRs

*Exposure Measurement* – Clinical measurement method (it is a medical measurement method to diagnose a disease or medical condition (eg. Sperm test etc), or methods or self-report by participants

*Outcome*: time to pregnancy and fecundity outcomes with standardized diagnostic criteria (clinical pregnancy confirmation) resulted from the selected EDCs exposure, including time to pregnancy, or fecundity.

*Outcome Measurement* – diagnosed by a health professional or self-reported.

2. *Study designs of interest*: Prospective and Retrospective Cohort, Cross-sectional and Case-control studies included

No limits on year of publication or language.

**Exclusion criteria:**

Articles initially excluded if they are duplicates or if the title clearly demonstrates that the exposure and outcome of interest are not the focus of the article. Articles are then excluded based on the following:

* The study is a review article or case study, an editorial, letter or commentary.
* The article does not focus on the selected EDCs exposure (other category of chemicals).
* Non-human, animal, wildlife studies or human cell lines of study population.
* The article does not explore an association between the selected EDCs exposure and infertility outcomes.
* No effect size estimate and uncertainty information reported or cannot be computed from information given.

Study inclusion/exclusion is completed independently (YR and LT). Results are reviewed (YR and LT) and any disagreement is recorded. Results are discussed (YR LT, and RP) to reach consensus.

**Data abstraction form**

**Identification of study:**

1. Record the first authors’ last names, initials

2. Record the journal name

3. Record the year of publication

4. Record the volume number

5. Record the page name

**Characteristics of study**

1. Study sample size
2. Sample size
3. Female (%)
4. Age range of the sample
5. Type of EDCs analyzed/ health effects
6. Chemical analysis/ method of assessing health outcomes
7. Matrix (blood, follicle fluid, semen samples, air or job assessment) used
8. Study results
9. Concentration of the EDCs
10. Study design
11. Sample based
12. Confounders

**Supplementary 4. PRISMA Checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #** |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | p.1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | p.3-4 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | p.5-8 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | p.5-8 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | p. 8-9 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | p. 9-10 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | p.9-10 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | p. 10-11, S1. p.2-5 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | p. 5-11 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | p. 5-11 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | p. 5-11 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | p. 12-17 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | Not given |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | p. 12-17 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #** |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | p. 12-17 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | Not given |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | p. 12-17 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | p. . 12-17 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | p. . 12-17 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | p. . 12-17 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Not given |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | p. . 12-17 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | Not given |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | p.17-22 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | p.17-22 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | p.28 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | p. 29 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.