New South Wales Government
Independent Planning Commission

LOUISE KEATS		**OBJECT**	Submission ID: 0
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Dear Secretariat of the IPC

I am writing in relation to Case Ref No SSD-9409987.

I respectfully request to lodge the following Addendum to my written submission (lodged on 25 November 2024), on the basis that a piece of critical research has only today come to my attention.

Please see the attached letter for a more detailed explanation.

Yours faithfully

Louise

Independent Planning Commission
Level 15, 135 King Street
Sydney NSW 2000

Moss Vale Plastics Recycling Facility
SSD-9409987

Dear Commissioners

I refer to my written submission lodged on 25 November 2024 in respect of application SSD-9409987.

In that submission, I discuss the impacts of microplastics and plastics-associated chemicals on human health.

I have today become aware of a 2024 umbrella review of meta-analyses that is the **first of its kind** to review the science in this field. It is a **world-leading study** that systematically reviews vast amounts of research data from thousands of scientific studies on exposure to plastic chemicals and the impacts on human health.

Additionally, there is a Full Report that accompanies this peer-reviewed scientific study.

The review was conducted by the Minderoo Foundation in collaboration with JBI at the University of Adelaide.

I believe that this is the **most critical piece of research that has been done to date exploring the links between plastics exposure and human health**.

The Minderoo Foundation has also created a website to explain this research in an accessible way: https://www.globalplastictreaty.com/umbrella-review.

I recommend that the Commission review this resource and the attached meta-analysis and report as the most pivotal research to date on the impact of exposure to microplastics on human health.

Yours faithfully

Louise Keats

BA (Hons I), LLB (Hons I), GradDipNut
(currently: Masters Human Nutrition)

An Umbrella Review of Meta-Analyses Evaluating Associations between Human Health and Exposure to Major Classes of Plastic-Associated Chemicals

Annals of Global Health

ORIGINAL RESEARCH

ubiquity press

CHRISTOS SYMEONIDES** EDOARDO AROMATARIS** YANNICK MULDERS** JANINE DIZON CINDY STERN TIMOTHY HUGH BARKER ASHLEY WHITEHORN DANIELLE POLLOCK TANIA MARIN SARAH DUNLOP

*Author affiliations can be found in the back matter of this article

**Christos Symeonides, Edoardo Aromataris and Yannick Mulders contributed equally to this work

ABSTRACT

Background: Epidemiological research investigating the impact of exposure to plastics, and plastic-associated chemicals, on human health is critical, especially given exponentially increasing plastic production. In parallel with increasing production, academic research has also increased exponentially both in terms of the primary literature and ensuing systematic reviews with meta-analysis. However, there are few overviews that capture a broad range of chemical classes to present a state of play regarding impacts on human health.

Methods: We undertook an umbrella review to review the systematic reviews with meta-analyses. Given the complex composition of plastic and the large number of identified plastic-associated chemicals, it was not possible to capture all chemicals that may be present in, and migrate from, plastic materials. We therefore focussed on a defined set of key exposures related to plastics. These were microplastics, due to their ubiquity and potential for human exposure, and the polymers that form the matrix of consumer plastics. We also included plasticisers and flame retardants as the two classes of functional additive with the highest concentration ranges in plastic. In addition, we included bisphenols and per- and polyfluoroalkyl substances (PFAS) as two other major plastic-associated chemicals with significant known exposure through food contact materials. Epistemonikos and PubMed were searched for systematic reviews with meta-analyses, meta-analyses, and pooled analyses evaluating the association of plastic polymers, particles (microplastics) or any of the selected groups of high-volume plastic-associated chemicals above, measured directly in human biospecimens, with human health outcomes.

Results: Fifty-two systematic reviews were included, with data contributing 759 meta-analyses. Most meta-analyses (78%) were from reviews of moderate methodological

CORRESPONDING AUTHOR:
Sarah Dunlop

Minderoo Foundation, Perth, Western Australia, Australia; School of Biological Sciences, The University of Western Australia, Crawley, Western Australia, Australia

sdunlop@minderoo.org
PlasticHumanHealthReviews@minderoo.org

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quality. Across all the publications retrieved, only a limited number of plastic-associated chemicals within each of the groups searched had been evaluated in relevant meta-analyses, and there were no meta-analyses evaluating polymers, nor microplastics. Synthesised estimates of the effects of plastic-associated chemical exposure were identified for the following health outcome categories in humans: birth, child and adult reproductive, endocrine, child neurodevelopment, nutritional, circulatory, respiratory, skin-related and cancers.

Bisphenol A (BPA) is associated with decreased anoclitoral distance in infants, type 2 diabetes (T2D) in adults, insulin resistance in children and adults, polycystic ovary syndrome, obesity and hypertension in children and adults and cardiovascular disease (CVD); other bisphenols have not been evaluated. Phthalates, the only plasticisers identified, are associated with spontaneous pregnancy loss, decreased anogenital distance in boys, insulin resistance in children and adults, with additional associations between certain phthalates and decreased birth weight, T2D in adults, precocious puberty in girls, reduced sperm quality, endometriosis, adverse cognitive development and intelligence quotient (IQ) loss, adverse fine motor and psychomotor development and elevated blood pressure in children and asthma in children and adults. Polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) but not other flame retardants, and some PFAS were identified and are all associated with decreased birth weight. In general populations, PCBs are associated with T2D in adults and endometriosis, bronchitis in infants, CVD, non-Hodgkin's lymphoma (NHL) and breast cancer. In PCB-poisoned populations, exposure is associated with overall mortality, mortality from hepatic disease (men), CVD (men and women) and several cancers. PBDEs are adversely associated with children's cognitive development and IQ loss. PBDEs and certain PFAS are associated with changes in thyroid function. PFAS exposure is associated with increased body mass index (BMI) and overweight in children, attention deficit hyperactive disorder (ADHD) in girls and allergic rhinitis. Potential protective associations were found, namely abnormal pubertal timing in boys being less common with higher phthalate exposure, increased high-density lipoprotein (HDL) with exposure to mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and reduced incidence of chronic lymphocytic lymphoma (a subtype of NHL) with PCB exposure.

Conclusions: Exposure to plastic-associated chemicals is associated with adverse outcomes across a wide range of human health domains, and every plastic-associated chemical group is associated with at least one adverse health outcome. Large gaps remain for many plastic-associated chemicals.

Recommendations: For research, we recommend that efforts are harmonised globally to pool resources and extend beyond the chemicals included in this umbrella review. Priorities for primary research, with ensuing systematic reviews, could include micro- and nanoplastics as well as emerging plastic-associated chemicals of concern such as bisphenol analogues and replacement plasticisers and flame retardants. With respect to chemical regulation, we propose that safety for plastic-associated chemicals in humans cannot be assumed at market entry. We therefore recommend that improved independent, systematic hazard testing for all plastic-associated chemicals is undertaken before market release of products. In addition because of the limitations of laboratory-based testing for predicting harm from plastic in humans, independent and systematic post-market bio-monitoring and epidemiological studies are essential to detect potential unforeseen harms.

INTRODUCTION

Plastic is ubiquitous in our daily lives, being used in transport, agriculture, construction, and medical and pharmaceutical products, as well as food packaging [1]. Plastics are complex compounded materials comprising a polymer backbone combined with chemical additives

such as plasticisers, flame retardants, ultra violet (UV), light and heat stabilisers, biocides and colourants. Other chemicals include processing aids and non-intentionally added substances (NIAS) such as impurities in feedstock materials, by-products of polymer production, degradation and transformation products, and contaminants from processing machinery [2–5]. Over 8,300 million metric tonnes (MMT) of virgin plastic has been produced [1] with an annual production of over 400 MMT predicted to triple by 2060 [6].

In parallel with increasing plastic production, there is increasing recognition of the health implications of 'plastic-associated chemicals' [3,7]. Additives are, for the most part, not covalently bound to the polymer [8]. Monomers may also leach from products over time as residual unreacted monomers or break down products, as may residual processing aids and NIAS as above [9]. These can then enter the human body via ingestion [10, 11], inhalation [12–15] or transdermally [15–18]. Consequently, commonly studied plastic-associated chemicals have been detected and are reliably measured in human biosamples across the human lifespan, from prenatally (amniotic fluid) through childhood to adulthood [19] and in the elderly [20].

Of the over 16,000 estimated monomers, additives and processing agents identified in regulatory databases as being used in plastics, only a minority are subject to global regulation while the majority lack hazard information [5, 21, 22]. However, where completed, pre-market in vitro or in vivo toxicological assessments have limitations regarding long-term low-dose exposure, availability of appropriate models for complex human health endpoints, suboptimal experimental animal study design and reporting with high risk of bias [23].

Nevertheless, after the introduction of plastic products to market, health effects can be directly evaluated in humans through observational research. Observational study designs, including cohort, case control and cross-sectional studies, are generally the most appropriate to assess risk of, and association with, adverse health outcomes, where controlled experimental exposure in humans would not be ethical [23]. Observational studies require reliable, sensitive methodologies to quantify individual exposure to the chemical or its metabolites in biosamples. These include availability of samples to quantify exposure at biologically relevant times, data in individuals on health outcome and potential confounding factors as well as sufficient numbers of individuals to reliably detect associations. However, there is no routine regulatory health surveillance of industrial chemicals such as those present in plastics, and the chemicals investigated by academic research studies typically cover only a small fraction of high-volume chemicals in production [24]. Indeed, a recent systematic evidence map has compiled the primary research on plastic and commonly studied plastic-associated chemicals, and revealed that only 25% of the searched chemicals have been studied in humans [25].

However, individual observational primary research studies are often limited by sample size, distribution of exposure, timing of exposure measurements (e.g., one-time urine measurements), outcome and other characteristics of the population sampled and/or difficulties in interpreting findings across multiple studies. Synthesis of findings is beneficial in evaluating the overall evidence base (e.g., for regulatory decisions). Systematic reviews with meta-analyses, meta-analyses, and pooled analyses draw on multiple primary research studies to combine statistical estimates of association for a single estimate.

A large number of systematic reviews with meta-analyses, meta-analyses, and pooled analyses have evaluated evidence of association between exposure to plastic-associated chemicals and human health outcomes such as cancer, pregnancy, and disorders of metabolic, cardiovascular and neurological systems [7]. Only a few attempts have been made to subsequently review these existing systematic reviews, and these are limited to specific plastic-associated chemicals or chemical classes, namely phthalates ('overview of reviews') and bisphenols ('umbrella review') [26, 27] and, to a very limited extent, in a broad umbrella review of all environmental risk factors for health [28].

Umbrella reviews are a recognised approach to conduct a systematic and standardised evaluation of a broad research topic for which there are multiple published systematic reviews and meta-analyses available [29]. They are regarded as one of the highest levels of evidence synthesis [30].

In setting the scope of the plastics and plastic-associated chemicals to be considered in this umbrella review, it was not possible to capture all chemicals that may be present in, and migrate from, plastic materials. Although increasingly large numbers of plastic-associated chemicals are being identified [5, 21, 22], the full extent of additional plastic-associated chemicals is unknown, especially for NIAS [9, 11, 31, 32]. In this umbrella review, we therefore focussed on a defined set of key exposures related to plastics. We included microplastics, due to their ubiquity and potential for human exposure [33] and the polymers that form the matrix of consumer plastics. We also included plasticisers and flame retardants as the two classes of functional additive with the highest concentration ranges in plastic [34]. In addition, we included bisphenols and a number of PFAS as two other major plastic-associated chemicals with significant known exposure through food contact materials [9].

Our umbrella review synthesises and presents findings from the meta-analytic literature examining associations between plastic-associated chemical exposure and human health outcomes across the lifespan.

METHODS

We followed established umbrella review methods [29] including an a priori protocol, key details of which were prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020204893) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [35]. We used vote counting and harvest plots to assimilate the large and diverse data on plastic and plastic-associated chemical exposure and human health outcomes across the lifespan. A glossary of chemical abbreviations used is available in the supplementary materials (Suppl File 1.1).

SEARCH STRATEGY

Epistemonikos, a comprehensive database of systematic reviews for health decision-making (https://www.epistemonikos.org) [36], and PubMed were searched on 26 August and 30 September 2020, respectively (JD; Suppl File 1.2). Search filters employed a combination of terms (and indexing terms in PubMed). We included broad terms such as 'plastic' alongside terms relating to functional terminology such as 'plasticiser/plasticizer' and 'flame retardant.' We also included common-use terminology and abbreviations such as 'phthalates' and 'PVC', and technical chemical terminology such as 4,4'-isopropylidenediphenol (bisphenol A) and di(2-ethylhexyl) phthalate (DEHP). Search terms encompassed microplastic particles; nanoplastics were not separately searched because reliable analytical techniques to quantify individual human exposure to these smaller particles, and therefore the opportunities for direct observational research, were not yet available. For plastic polymers, all major commodity polymers were considered: polyethylene, polypropylene, polyethylene terephthalate, polyvinyl chloride, polycarbonates, polystyrene, nylon(s) and fluoropolymers, including polytetrafluoroethylene. For plasticisers and flame retardants, our search terms were selected to capture all major chemical classes [25], including (ortho- and tere-) phthalates, cyclohexanoates, adipates, sebacates, trimellitates, dibenzoates, citrate esters, organophosphate esters (OPEs), PCBs, PBDEs and polybrominated biphenyls (PBBs). We also included a range of specific and general terms to capture other plasticisers or flame retardants not included in these major classes (decabromodiphenyl ethane, hexabromocyclododecane, any other polybrominated or polychlorinated chemicals and melamine polyphosphate). Bisphenols and PFAS were separately searched using a range of terms capturing common-use and technical terminology for these classes, and major chemicals within these classes. We also used specific search terms for flame-retardant bisphenols such as the halogenated bisphenol tetrabromobisphenol A and the organophosphate bisphenol A diphenyl phosphate. No date limits were applied; however, filters were applied to both databases to limit to systematic reviews. Grey literature was not included.

ELIGIBILITY CRITERIA

Eligibility criteria were aligned to the population, exposure, comparator and outcome (PECO) framework [37] (Table 1). We thus captured meta-analyses (i.e., systematic reviews with

COMPONENT	DESCRIPTION
Population	General population exposed through environment or poisoning. Occupational exposure to plastic-associated chemicals is included, except if the occupational exposure occurs through plastic manufacturing or fossil fuel extraction. Exposure through medical, surgical, or dental devices such as prostheses or implants was also excluded. Subgroup analyses focusing on population differences (e.g. age, gender) were included.
Exposure	Plastic-associated chemical exposure, considering comparisons of high vs. low exposure, any vs. none, and any linear or non-linear dose responses. Composite exposure to groups of chemicals (e.g. total phthalates, total polychlorinated biphenyls [PCBs]) and subgroup analyses of individual chemicals (e.g. specific phthalate diesters, specific PCB congeners) were included. Exposure measurements are required to be from human bio-samples. Indirect exposure measures (e.g. questionnaires, dust) were excluded.
Comparator	Comparisons within the general population, such as high vs. low exposure and any vs. none, without occupational, medical device-related, or indirect exposure measures.
Outcome	Health outcomes reported using statistical measures (e.g. relative risks [RR], odds ratios [OR], or regression coefficients). Meta-analyses needed to present separate analyses for different health outcomes and meet the primary or secondary analysis criteria of the reviewed articles.

Table 1 Details of the population, exposure, comparator, outcome (PECO) framework.

meta-analyses, meta-analyses, and pooled analyses) of studies that evaluated the association between exposure to plastic particles and plastic-associated chemicals and human health outcomes. This included environmental as well as occupational exposure and poisoning. We also captured any human health outcome irrespective of age. Participants could be healthy or have pre-existing illness.

Eligible exposures are shown in Suppl File 1.2. Meta-analyses examining exposure to other additives (e.g., antimicrobials, antioxidants, antistatic agents, fillers, processing agents, and UV, light and heat stabilisers) or combined exposures were not included. Meta-analyses of studies investigating endocrine-disrupting chemicals that included plastic polymers or additives were eligible for inclusion, but only if evaluated separately from chemicals that were not plastic related.

We included any analysis with comparisons of plastic-associated chemical exposure, including high versus low, any versus none, and any linear or non-linear dose responses. Meta-analyses of studies were ineligible if they included studies where measures of exposure were indirect (e.g., questionnaire-based surveys, dust), where exposure was attributable to an occupation in plastic manufacturing or fossil fuel extraction, or in the presence of a medical, surgical or dental device such as a prosthesis or implant. If an article presented separate meta-analyses for more than one health outcome (and any combination of exposures), we included each of these separately, recording whether extracted estimates related to the primary analysis (or analyses) of the paper, or related to a secondary analysis. Articles that did not present a meta-analysis or statistical combination of multiple studies for a health outcome, with a measure such as relative risks (RR), odds ratios (OR) or regression coefficients, were ineligible. Analyses of composite exposure to a group of plastic-associated chemicals were included, as well as subgroup analyses investigating individual chemicals (such as total phthalates and individual phthalate diesters or total PCBs and specific PCB congeners). Other subgroups that further investigated population differences (age, gender) and differences in measurement of exposure (e.g., serum, urine) aligned to the main analyses of the included reviews were also included. Only reviews and analyses published in English were included.

SELECTION AND ASSESSMENT OF METHODOLOGICAL QUALITY

Citations from database searching were uploaded into EndNote v9 (Clarivate Analytics) and duplicates removed. Titles and abstracts of remaining records were subsequently screened independently by two reviewers (JD, DP) considering the eligibility criteria. Full text of potentially

relevant reviews and syntheses were retrieved and reviewed (JD, DP); where necessary, inclusion was determined by discussion between reviewers.

Methodological quality of eligible systematic reviews with meta-analyses, meta-analyses, and pooled analyses was independently assessed by two reviewers (JD, TB, DP, TM, AW). Umbrella review methodology appraises the quality of reporting of the systematic review, and not directly the quality of the primary research included therein. We used the 'A MeaSurement Tool to Assess systematic Reviews' (AMSTAR) tool [38], an 11-item checklist designed to assess methodological quality of systematic reviews of interventions. AMSTAR has been shown to be a reliable and valid tool for quality assessment of systematic reviews and meta-analyses of observational research [39]. AMSTAR was selected due to more rapid completion and greater inter-rater reliability to mitigate multiple appraisers involved (JD, TB, DP, TM, AW) rather than other tools [40]. A pilot appraisal was undertaken on a subset of eligible reviews (10%) to maximise the reliability of the process between members of the review team (JD, TB, DP, TM, AW). A third reviewer (EA) resolved any disagreements. We established an arbitrary categorisation system to convey the appraisal findings: AMSTAR scores of 9–11 were rated as high quality (low risk of bias), 5–8 as moderate quality and less than 5 as low quality (high risk of bias). Rules used for consistency for each question are available in Suppl File 1.3. For expedience, the AMSTAR tool was also used to assess the quality of included pooled analyses. Because pooled analyses lack many design features inherent in a systematic review [41], we therefore scored them universally as 'low' in the quality appraisal.

DATA EXTRACTION

Data were extracted from the included reviews using a structured form in MS Excel (Microsoft) tailored to prompt retrieval of relevant information. Data extraction was performed independently by a member of the review team (JD, TB, AW, TM, DP) and all data extractions subsequently verified independently by the remaining team members (CSy, EA, CSt, YM). Extracted descriptive details were citation details, conflict of interest declaration, date of last search, included study designs, number of studies included (in the review and in the meta-analyses), critical appraisal tool used and results of appraisal, participants (characteristics and total number), plastic exposure (type, route, measure and time), health outcome(s) and measures reported and authors' conclusions. Effect estimates (EE) from included meta-analyses (main findings or subgroup analyses) were extracted as OR, RR or standardised mortality ratios (SMR) for dichotomous data. Standardised, unstandardised, or z-transformed (z), beta (β) coefficients, correlation coefficients (r) or standardised (SMD) or unstandardised mean differences (MD) were extracted for continuous data. All data were extracted exactly as reported in the source publications, making no adjustments for number of decimal points or suspected extraction errors from the primary literature.

DATA SUMMARY AND PRESENTATION

Health outcomes assessed with meta-analyses were aligned to corresponding chapters in the International Classification of Diseases, ICD-11 (https://icd.who.int/en). Considering the wide range of exposures, outcomes and outcome measures identified, it was not possible to estimate overall EE and therefore no further statistical meta-analysis of findings was considered [29, 42].

To synthesise data and establish evidence of effect across a large heterogeneous data set, we used vote counting with harvest plots [42]. In rare instances where the same exposure/outcome has been reported, the range of EE has been presented. The bars in the harvest plots represent individual EE (main or subgroup), placed on a matrix to indicate whether exposure to the plastic-associated chemical had a negative (decreased, left-hand column) or positive (increased, right-hand column) influence on the outcome based on the EE (point) reported. Where there was no influence, the direction of any non-significant effect is indicated as an increase (>), no change (–), or a decrease (<) in the measure or risk estimate (centre column) (Suppl File 1.4) [42]. Effect size is not portrayed within the harvest plots but is presented in the narrative and Suppl File 2.

The outcome or outcome measure reported is indicated in the first column of the harvest plot matrix, including whether outcomes were continuous (‡) or dichotomous (†). Given the

heterogeneity of outcomes as well as methods of measurement and reporting, harvest plots were constructed as follows. Bars representing dichotomous outcome measures (relative estimates of risk) or continuous outcomes (regression coefficients, mean differences in measure between exposed versus low/non-exposed groups) were assigned as an increase or decrease in the measure where the change is statistically significant ($p < 0.05$). Where articles presented sensitivity analyses based on a meta-analytical model, considering the heterogeneity in study designs, populations, exposures and level of exposure, random effects were selected preferentially over fixed effects. Dark filled bars indicate the main analysis for each review, and light filled bars indicate subgroup analyses of the same participants within reviews. Reviews are indicated by the citation number (see Table 2 for included reviews). Within each column, bars are organised left to right by chemical class (bisphenols, phthalates, PCBs, PBDEs, PFAS) and then within each chemical class from low to high molecular weight (for phthalates and PFAS), or congener (for PCBs and PBDEs; Suppl File 1.4).

RESULTS

REVIEW IDENTIFICATION, SELECTION AND INCLUSION

Database searching returned 3,641 unique records which were screened for eligibility, after electronic deduplication (Figure 1). Searching of PubMed offered only those reviews most recently published, not yet indexed in Epistemonikos. Following screening, 156 potentially eligible reviews were retrieved and the full text assessed. Sixty-two systematic reviews with meta-analyses, meta-analyses, and pooled analyses, were deemed eligible for inclusion. The predominant reason for exclusion of the remaining 94 reviews was lack of statistical meta-analysis and presentation of narrative synthesis only (Figure 1, Suppl File 1.5.1). During the conduct of this umbrella review, a further ten reviews were excluded where reporting of the EE was identified to have used data from the same studies (participants) repeatedly. This was most common for different plastic-associated chemical exposures (e.g., phthalate metabolites and PCB congeners) measured in the same participants, or where there were repeated measures over time from the same cohort, thereby introducing a unit of analysis error [43] (Figure 1, Suppl File 1.5.2). Ultimately, 52 systematic reviews with meta-analyses, meta-analyses, and pooled analyses were included (Figure 1).

There were no systematic reviews with meta-analyses addressing the health effects of plastic polymers, nor microplastics. We found meta-analysed data for only a very small number of plastic-associated chemicals: BPA, but no other bisphenols; certain ortho-phthalate diesters but no other plasticisers such as terephthalates, cyclohexanoates, adipates, trimellitates or benzoates; PCBs and PBDEs but no other flame retardants such as organophosphate esters; and only a small number of PFAS. Fifty-two eligible reviews and pooled analyses (46 reviews, 6 pooled analyses) reported on the following outcome categories: birth, child and adult reproductive, endocrine, child neurodevelopment, nutritional, circulatory, respiratory, skin-related, cancer and cancer-related mortality, hepatic disease mortality and all-cause mortality.

REVIEW CHARACTERISTICS

Characteristics of included reviews are presented in Table 2 and further details including all outcome data extracted are available in Suppl File 2. A total of 759 meta-analyses, including main analyses and subgroup analyses, were identified. Participants included infants, children and adults, including pregnant mothers, and were mostly general population samples, but also including highly exposed populations in some cases of PCB exposure. Plastic-associated chemicals included bisphenol A (BPA) for bisphenols, diester phthalates and monoester metabolites for plasticisers (e.g., DEHP, di-n-butyl phthalate [DnBP], and metabolites: monomethyl phthalate [MMP], monoethyl phthalate [MEP], mono(2-ethylhexyl) phthalate [MEHP], monobenzyl phthalate [MBzP]), PCBs and PBDEs for flame retardants, and PFAS (perfluorooctanoic acid [PFOA], perfluorooctane sulfonate [PFOS], perfluorohexane sulfonate [PFHxS], perfluorononanoic acid [PFNA]; Table 2).

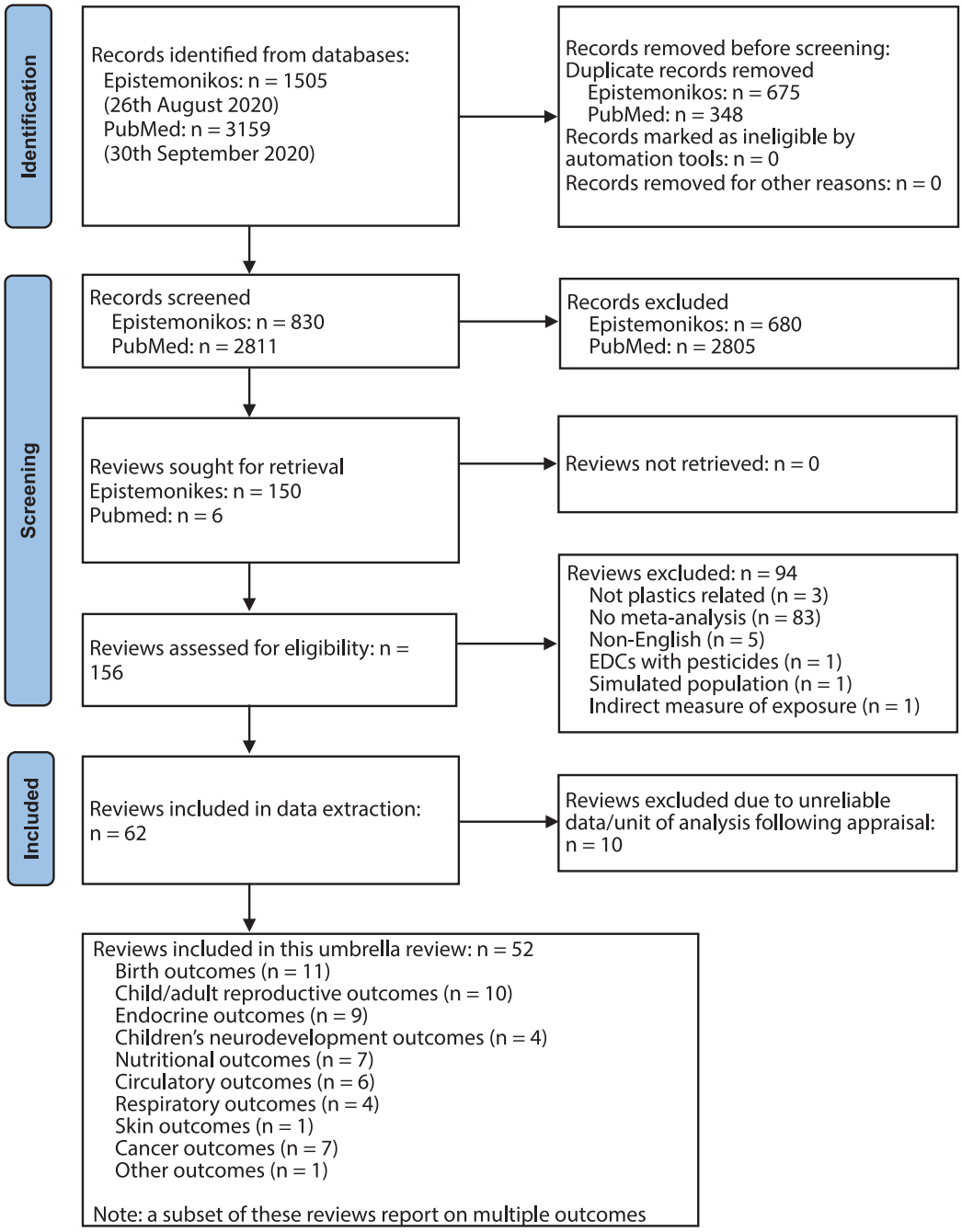

Figure 1 PRISMA flow diagram [35] presenting process of study identification, selection and final inclusion in the review project and the outcomes reported in this manuscript.

SUMMARY OF THE EVIDENCE

Birth Outcomes

There were seven birth outcomes reported across ten systematic reviews with meta-analyses and one pooled analysis. Of these, evidence from available analyses suggests an association with a decrease in infant birth weight, and an increase in spontaneous pregnancy loss (SPL; i.e., miscarriage) by mothers across the plastic-associated chemical exposures that have been evaluated (Figure 2). Birth outcomes were addressed for BPA, phthalates, flame retardants and PFAS. Anthropometric measures including birth weight were the most commonly reported in eight reviews and one pooled analysis, followed by birth length and head circumference in three reviews. Other child outcomes, including ponderal index, gestational age, sex ratio and SPL, were each reported in one review. Where outcomes were measured in infants, exposure to plastic-associated chemicals was prenatal and details of type of samples measured are provided in Table 2.

REVIEW DETAILS (AUTHOR AND YEAR AND NUMBER OF META-ANALYSES/EE)	OUTCOMES REPORTED	POPULATION (DESCRIPTION)	PLASTIC-ASSOCIATED CHEMICAL(S) INVESTIGATED	SUBGROUPS BY STUDY CHARACTERISTICS	BIOSPECIMEN AND EXPOSURE TIMING	AMSTAR SCORE (/11)
Birth outcomes (Fig 2)						
Hu et al., 2018a [46] EE = 4	Birth weight	Infants	BPA	Pregnancy stages	Urine, blood, or amniotic fluid; prenatal	8
Golestanzadeh et al., 2019 [54] EE = 10	Birth weight	Infants	MMP, MEP, MnBP, MiBP, MBzP, ΣDEHP, MEHP, MEHHP, MEOHP, MECPP		Urine; prenatal	5
*Govarts et al., 2012 [50] EE = 1	Birth weight	Infants	PCB 153		Cord plasma or serum; maternal serum or breast milk; prenatal	3
Zou et al., 2019 [53] EE = 6	Birth weight	Infants	Total PCBs	Pregnancy stages, samples analysed	Cord blood; maternal serum; prenatal	4
Negri et al., 2017 [47] EE = 26	Birth weight	Infants	PFOA, PFOS	Transformed data, pregnancy stages, samples analysed	Cord serum; maternal serum or plasma or breast milk; prenatal	8
Steenland et al., 2018 [51] EE = 5	Birth weight	Infants	PFOA	Pregnancy stages, samples analysed	Maternal or cord blood; prenatal	4
Zhong et al., 2020 [52] EE = 4	Birth length, birth weight, head circumference, gestational age	Infants	BPA		Urine; prenatal	5
Zhao et al., 2017 [45] EE = 10	Birth length, birth weight, head circumference	Infants; with subgroup of girls and boys	Total PBDEs, BDE 47, BDE 99, BDE 100, BDE 153		Serum; prenatal	9
Johnson et al., 2014 [44] EE = 4	Birth length, birth weight, head circumference, ponderal index	Infants	PFOA		Cord blood; maternal serum; prenatal	10
Nieminen et al., 2013 [49] EE = 1	Sex ratio	Infants	Total PCBs		Maternal blood or breast milk; paternal blood; cord blood; prenatal	3
Zhang et al., 2020 [48] EE = 10	Spontaneous pregnancy loss	Adult reproductive women	MMP, MEP, MnBP, MiBP, MBzP, ΣDEHP, MEHP, MEHHP, MEOHP, MECPP		Urine	7
Child Reproductive outcomes (Fig 3)						
Bigambo et al., 2020 [55] EE = 1	Onset of puberty/early puberty	Girls	BPA		Urine; prenatal and postnatal	5
Wen et al., 2015 [57] EE = 2	Precocious puberty	Girls from 0.5 to 11.3 years of age	DnBP, DEHP	Samples analysed	Urine or serum; postnatal	7
Golestanzadeh et al., 2020 [56] EE = 27	Abnormal timing of breast development (thelarche), abnormal timing of pubic hair development (pubarche) in girls and boys, abnormal age of menarche, testicular volume in boys	Adolescent boys and girls from 7 to 19 years of age	MMP, MEP, MnBP, MEHP, MEHHP, MEOHP		Urine; prenatal and postnatal	6
Dorman et al., 2019 [58] EE = 1	Anogenital distance	Male infants	ΣDEHP		Urine; prenatal	8

(Contd.)

REVIEW DETAILS (AUTHOR AND YEAR AND NUMBER OF META-ANALYSES/EE)	OUTCOMES REPORTED	POPULATION (DESCRIPTION)	PLASTIC-ASSOCIATED CHEMICAL(S) INVESTIGATED	SUBGROUPS BY STUDY CHARACTERISTICS	BIOSPECIMEN AND EXPOSURE TIMING	AMSTAR SCORE (/11)
Nelson et al., 2020 [59] EE = 2	Anoclitoral and anofourchette distance	Female infants	BPA		Urine, cord serum or plasma; prenatal	7
Adult reproductive outcomes (Fig 4)						
Wen et al., 2019 [64] EE = 1	Endometriosis	Women	BPA		Urine	7
Cai et al., 2019 [60] EE = 5	Endometriosis	Women	MEP, MBzP, MEHP, MEHHP, MEOHP		Urine or plasma	7
Cano-Sancho et al., 2019 [61] EE = 5	Endometriosis	Women	Total PCBs	Samples analysed, type of endometriosis	Serum or adipose tissue	8
Roy et al., 2015 [62] EE = 1	Endometriosis	Women	Total PCBs		Serum	3
Cai et al., 2015 [63] EE = 93	Low sperm concentration, Low sperm morphology	Subfertile men	MMP, MEP, MnBP, MBzP, ΣDEHP, MEHP, MEOHP, MEHP + MEOHP (combined); with different concentration levels		Urine	6
	Low sperm motility	Subfertile men	MMP, MEP, MnBP, MBzP, DnBP, ΣDEHP, DEHP, MEHP, MEOHP; with different concentration levels		DnBP and DEHP in seminal fluid; phthalate metabolites in urine	6
	Sperm motion (straight-line velocity, curvilinear velocity, linearity), sperm DNA (comet extent, %DNA in tail, tail distributed moment)	Subfertile men	MMP, MEP, MnBP, MBzP, MEHP; with different concentration levels		Urine	6
	Low semen volume	Subfertile men; with subgroup of men in their reproductive age	MnBP		Urine	6
Endocrine outcomes (Fig 5)						
Kim et al., 2019a [70] EE = 36	Thyroid function (free thyroxine [ft4], total thyroxine [TT4], thyrotropin [TSH])	Adults and children; with subgroups of children, adults, pregnant women	MEHP, MEHHP, MEOHP		Urine	5
Zhao et al., 2015 [72] EE = 2	Thyroid function (total thyroxine [TT4], thyrotropin [TSH])	Adults and children	Total PBDEs		Serum (ng/g lipid)	9
Kim et al., 2018 [71] EE = 66	Thyroid function (free thyroxine [ft4], total thyroxine [TT4], thyrotropin [TSH], triiodothyronine [T3])	Adults; with subgroups of pregnant and non-pregnant adults	PFOA, PFOS, PFHxS; with different concentration levels		Blood	7
Hwang et al., 2018 [65] EE = 3	Type 2 diabetes	Adults	BPA	Samples analysed	Serum or urine	6
Rancière et al., 2015[66] EE = 1	Type 2 diabetes	Adults	BPA		Urine	7

(Contd.)

REVIEW DETAILS (AUTHOR AND YEAR AND NUMBER OF META-ANALYSES/EE)	OUTCOMES REPORTED	POPULATION (DESCRIPTION)	PLASTIC-ASSOCIATED CHEMICAL(S) INVESTIGATED	SUBGROUPS BY STUDY CHARACTERISTICS	BIOSPECIMEN AND EXPOSURE TIMING	AMSTAR SCORE (/11)
*Wu et al., 2013 [68] EE = 5	Type 2 diabetes	Adults; majority women; one included study with PCB poisoning	Total PCBs, PCB 118, PCB 138, PCB 153, PCB 180		Serum	4
Song et al., 2016 [67] EE = 18	Type 2 diabetes, insulin resistance, fasting insulin, fasting glucose, 2-hour glucose, 2-hour insulin	Adults; with subgroups of men and women	BPA, total phthalates, MEP, MiBP, total PCBs		Serum (total PCBs) or urine	6
Shoshtari-Yeganeh et al., 2019 [69] EE = 10	Insulin resistance	Adults and children	MMP, MEP, MiBP, MBzP, ΣDEHP, MEHP, MEHHP, MEOHP, MECPP, MCPP		Serum or urine	4
Children's neurodevelopmental outcomes (Fig 6)						
Lam et al., 2017 [74] EE = 1	Intelligence Quotient (IQ) using the Full Scale Intelligence Quotient (FSIQ) or McCarthy Scale	Children from 4 to 7 years of age	BDE-47		Cord blood or maternal serum (ng/g lipid); prenatal	11
Lee et al., 2018 [75] EE = 4	Cognitive development or Intelligence Quotient (IQ) using Wechsler Intelligence Scale for Children (WISC), Bayley Scales of Infant Development (BSID) and subscale of BSID, Mental Development Index (MDI) and Full-scale intelligence quotient (FSIQ); psychomotor development using Psychomotor Development Index (PDI)	Children from 6 months to 12 years of age	DEHP metabolites (mDEHP)		Urine or plasma; prenatal and postnatal	7
Radke et al., 2020 [76] EE = 30	Cognitive development or Intelligence Quotient (IQ) using Bayley Scales of Infant Development, Mental Development Index (MDI), Bayley III Cognitive Development Scale and fine motor using Bayley III Fine Motor Scale	Children ≤ 4 years of age	MEP, MnBP, MiBP, MBzP, ΣDEHP	Girls and boys	Urine or plasma; prenatal and postnatal	8
*Forns et al., 2020 [77] EE = 30	Attention Deficit Hyperactivity Disorder (ADHD) using Attention Syndrome Scale of the Child Behavior Checklist (CBCL-ADHD), Hyperactivity/Inattention Problems subscale of the Strengths and Difficulties Questionnaire (SDQ-Hyperactivity/ Inattention) and ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th ed.	Children 4 to 11 years of age	PFOA, PFOS	Girls and boys; estimated PFAS levels from birth to 24 months	Maternal serum/ plasma or breast milk; prenatal except for breast milk	3

(Contd.)

REVIEW DETAILS (AUTHOR AND YEAR AND NUMBER OF META-ANALYSES/EE)	OUTCOMES REPORTED	POPULATION (DESCRIPTION)	PLASTIC-ASSOCIATED CHEMICAL(S) INVESTIGATED	SUBGROUPS BY STUDY CHARACTERISTICS	BIOSPECIMEN AND EXPOSURE TIMING	AMSTAR SCORE (/11)
Nutritional outcomes (Fig 7)						
Ribeiro et al., 2019 [81] EE = 17	BMI, BMI z-score, obesity, waist circumference	Adults and children	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCPP		Urine; postnatal	6
Rancière et al., 2015 [66] EE = 7	Obesity, overweight (or generalised overweight), elevated waist circumference	Adults and children; with subgroup of adults and children	BPA		Urine; postnatal	7
Ribeiro et al., 2020 [80] EE = 7	Obesity, overweight (or generalised overweight), elevated waist circumference	Adults and children; with subgroup of adults and children	BPA		Urine; postnatal	7
Kim et al., 2019b [78] EE = 4	Obesity	Children; with subgroups of obese vs. normal-weight children	BPA; with subgroup of high exposure		Urine; postnatal	6
Wu et al., 2020a [79] EE = 3	Abdominal obesity, generalised obesity, overweight (or generalised overweight)	Adults and children	BPA		Urine; postnatal	5
Liu et al., 2018 [82] EE = 6	Obesity or overweight, BMI	Children	PFOA	Exposure timing, girls and boys	Maternal serum or plasma; cord blood; prenatal and postnatal	7
Golestanzadeh et al., 2019 [54] EE = 22	BMI, BMI z-score, waist circumference	Children	MMP, MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MnOP, MCPP		Urine; postnatal	5
Circulatory outcomes (Fig 8)						
*Dunder et al., 2019 [84] EE = 30	Serum lipids (low-density cholesterol [LDL-C], high-density cholesterol [HDL-C], total cholesterol [TC], triglycerides [TG] and apolipoprotein B [ApoB])	Adults and children	BPA	Adults (men and women) and children (girls and boys)	Urine; postnatal	4
Golestanzadeh et al., 2019 [54] EE = 24	Systolic blood pressure, diastolic blood pressure, high-density cholesterol (HDL), triglycerides (TG)	Children	MMP, MBzP, ΣDEHP, MEHP, MEHHP, MEOHP, MCPP		Urine; postnatal	5
Park et al., 2016 [85] EE = 4	Hypertension	Adults	PCB 118, 153, dioxin-like PCBs, non-dioxin-like PCB		Serum (lipid) or adipose tissue	7
Rancière et al., 2015 [66] EE = 1	Hypertension	Adults	BPA		Urine	7
Fu et al., 2020 [87] EE = 13	Cardiovascular disease	Adults and children	BPA, MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, Total PCBs, PCB 138, 153, 180		Urine, serum, plasma or adipose tissue; children, postnatal	6

(Contd.)

REVIEW DETAILS (AUTHOR AND YEAR AND NUMBER OF META-ANALYSES/EE)	OUTCOMES REPORTED	POPULATION (DESCRIPTION)	PLASTIC-ASSOCIATED CHEMICAL(S) INVESTIGATED	SUBGROUPS BY STUDY CHARACTERISTICS	BIOSPECIMEN AND EXPOSURE TIMING	AMSTAR SCORE (/11)
*Li et al., 2015 [83] EE = 7	Cardiovascular disease, cerebrovascular disease and hypertension deaths	Adults; with subgroups of men and women with cerebrovascular disease and hypertension deaths	Special PCB exposure (poisoning)		Blood	4
Respiratory outcomes (Fig 9)						
Wu et al., 2020b [90] EE = 80	Asthma	Adults and children	MEP, MnBP, MiBP, MBzP, DEHP or ΣDEHP, MEHP, MEHHP, MEOHP, MECPP, MCOP, MCNP, MCPP	Exposure timing prenatal and postnatal, adult men and women	Urine	5
Luo et al., 2020 [89] EE = 28	Asthma, allergic rhinitis, wheeze	Children	PFOA, PFOS, PFHxS, PFNA	Exposure timing, prenatal and postnatal	Infant's/ children's cord blood or plasma or serum; maternal serum or plasma	7
Li et al., 2017 [88] EE = 8	Asthma	Children	MnBP, MiBP, MBzP, DEHP or ΣDEHP, MCOP	Exposure timing, prenatal and postnatal	Urine	9
*Gascon et al., 2014 [91] EE = 14	Bronchitis, wheeze and bronchitis and/or wheeze	Infants/children	PCB 153	Infants < 18 months and 18 to 49 months of age, prenatal and postnatal	Maternal blood or serum or breast milk; infant's/ children's cord, plasma or serum; prenatal	3
Skin disorder outcomes (Fig 10)						
Luo et al., 2020 [89] EE = 8	Atopic dermatitis and eczema, with subgroups of skin disorder	Children	PFOA, PFOS, PFHxS, PFNA		Infant's/ children's cord blood or plasma or serum; maternal serum or plasma;	7
Cancer and cancer related mortality (Fig 11)						
Roy et al., 2015 [62] EE = 1	Breast cancer	Women	Total PCBs		Serum, plasma or adipose tissue	3
Zhang et al., 2015 [93] EE = 1	Breast cancer	Women	Total PCBs	Serum and adipose sample only	Serum, plasma or adipose tissue	8
Leng et al., 2016 [94] EE = 17	Breast cancer	Women	PCB 187, 118, 138, 156, 170, 99, 153, 180, 183. Including analyses of two studies for only PCB 28, 52, 74, 77, 101, 105, 126, 167		Serum, plasma or adipose tissue	8
Zani et al., 2013 [92] EE = 6	Breast cancer	Women	Total PCBs		Serum, plasma or adipose tissue	2
	Non-Hodgkin's lymphoma	Adults and children	Total PCBs, PCB 118, PCB 138, PCB 153, PCB 180		Blood, serum or adipose tissue	2

(Contd.)

REVIEW DETAILS (AUTHOR AND YEAR AND NUMBER OF META-ANALYSES/EE)	OUTCOMES REPORTED	POPULATION (DESCRIPTION)	PLASTIC-ASSOCIATED CHEMICAL(S) INVESTIGATED	SUBGROUPS BY STUDY CHARACTERISTICS	BIOSPECIMEN AND EXPOSURE TIMING	AMSTAR SCORE (/11)
Catalani et al., 2019 [96] EE = 8	Non-Hodgkin's lymphoma (NHL), subtypes of NHL (chronic lymphocytic leukaemia, diffuse large B-cell lymphoma, follicular lymphoma	Adults and children	Total PCBs, PCB 118, PCB 138, PCB 153, PCB 180, PCB 170,		Blood, serum or adipose tissue	7
Zani et al., 2017 [95] EE =3	Non-Hodgkin's lymphoma	Adults and children	Total PCBs		Blood, serum or adipose tissue	5
	Non-Hodgkin's lymphoma mortality, melanoma mortality	Adults	Special PCB exposure (occupational)		Blood, serum or adipose tissue	5
*Li et al., 2015 [15] EE = 12	All-cancer mortality and cancer-specific mortality (breast cancer, leukaemia, liver cancer, lung cancer, pancreatic cancer, rectal cancer, stomach cancer, uterine cancer)	Adults; with subgroups of men and women in some cancer types	Special PCB exposure (poisoning)		Blood	4
Other outcomes (Fig 12**)**						
*Li et al., 2015 [83] EE = 6	Hepatic disease mortality, all-cause mortality	Adults; with subgroups of men and women	Special PCB exposure (poisoning)		Blood	4
Case control studies (Supplementary Fig S1**)**						
Wen et al., 2015 [57] EE = 7	Precocious puberty	Girls from 0.5 to 11.3 years of age	MEP, DnBP, MnBP, MBzP, DEHP, MEHP	Samples analysed	Urine or serum; postnatal	7
Hu et al., 2018b [73] EE = 3	Polycystic ovarian syndrome (PCOS)	Women; with subgroups with different age, method of measurement	BPA	Serum samples, age	Serum	9

Table 2 Characteristics of included reviews.

Legend:

**pooled analysis.*

EE: number of effect estimates (from main and subgroup analyses) included from the systematic review or pooled analysis.

Superscript number indicates the reference number in the harvest plot figures.

Total phthalates: composite measure of phthalate metabolite exposure which is the total concentration of all phthalate metabolites measured.

ΣDEHP: sum of the DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, MCMHP).

Total PCBs: composite measure of PCB exposure which is the total concentration of all PCB congeners measured Total PBDEs: composite measure of PBDE exposure which is the total concentration of all PBDE congeners measured.

Bisphenol A (BPA), Di-n-butyl phthalate (DnBP), Di(2-ethylhexyl) phthalate (DEHP), Monomethyl phthalate (MMP), Monoethyl phthalate (MEP), Mono-n-butyl phthalate (MnBP), Monoisobutyl phthalate (MiBP), Monobenzyl phthalate (MBzP), Mono(2-ethylhexyl) phthalate (MEHP), Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), Mono(2-carboxymethyl-5-hexyl) phthalate (MCMHP), Mono-n-octyl phthalate (MnOP), Mono(carboxyoctyl) phthalate (MCOP), Mono(carboxynonyl) phthalate (MCNP), Mono(3-carboxypropyl) phthalate (MCPP), Polychlorinated biphenyls (PCBs), Polybrominated diphenyl ethers (PBDEs) Perfluorooctanoic acid (PFOA), Perfluorooctanesulfonic acid (PFOS), Perfluorohexane sulfonate (PFHxS).

The reviews that informed this outcome category ranged from low to high quality, scoring between 3 and 10 on the AMSTAR tool (Table 2; Figure 2; Suppl File 1.6). Only two reviews were informed by an a priori protocol and included searching for grey literature [44, 45]; duplicate selection and extraction could be confirmed for only five reviews [44–48]. Transparent reporting of included and excluded studies was provided by only two reviews [46,49], whereas all reviews provided detailed study characteristics and assessment of publication bias. Half of the included

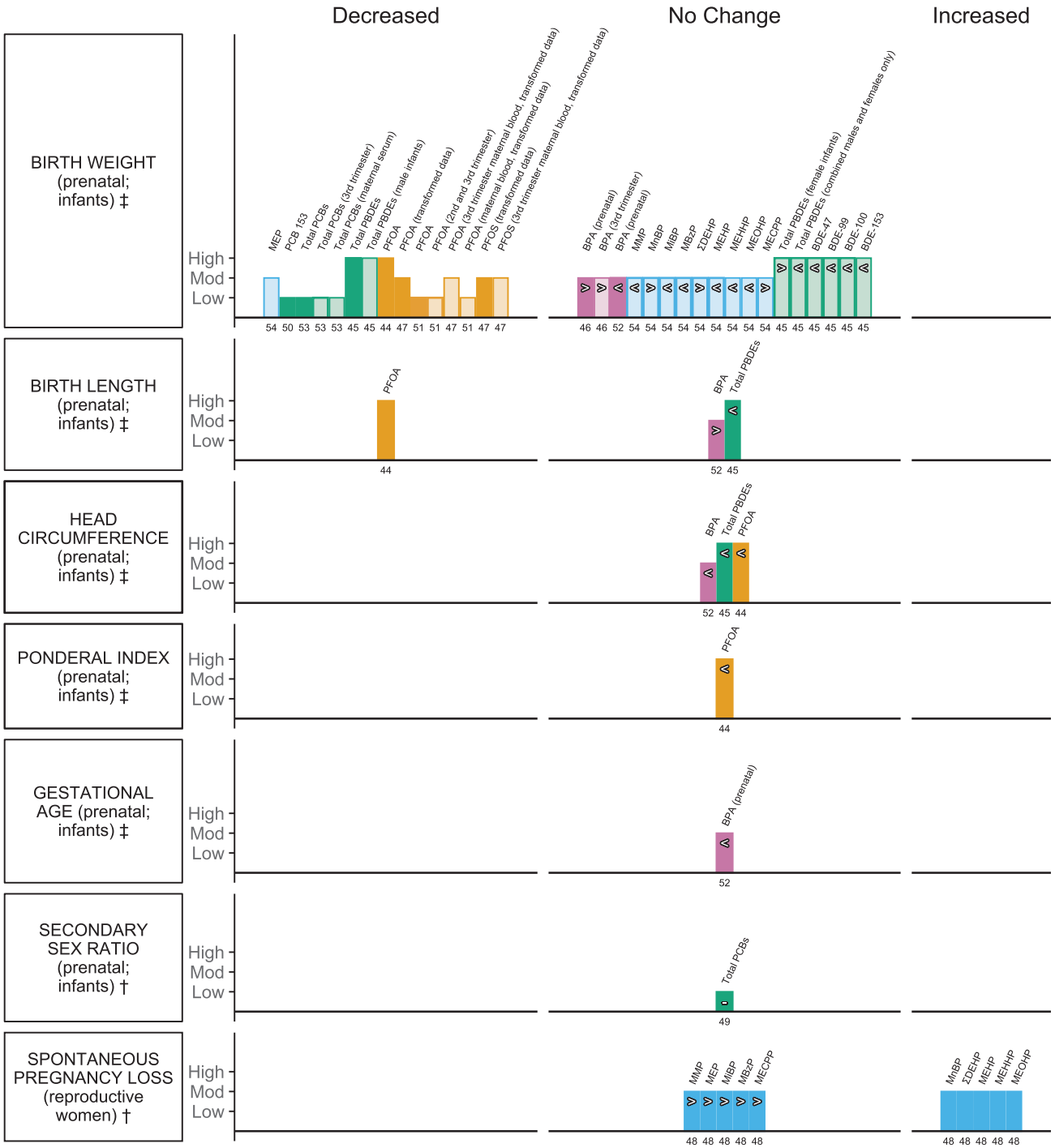

Figure 2 Harvest plot of exposure to plastic-associated chemicals and birth outcomes.

Plastic-associated chemicals included are bisphenol A (BPA) (pink); phthalate monoester metabolites (blue), encompassing monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and molar sum of the di(2-ethylhexyl) phthalate metabolites (∑DEHP); flame retardants (green) encompassing polychlorinated biphenyl (PCB), polybrominated diphenyl ethers (PBDEs), 2,2',4,4'-tetrabromodiphenyl ether (BDE-47), 2,2',4,4',5-pentabromodiphenyl ether (BDE-99), 2,2',4,4',6-pentabromodiphenyl ether (BDE-100), 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153); and per- and polyfluoroalkyl substances (PFAS) (orange), encompassing perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS).

Outcomes are either dichotomous (†) or measured on a continuous scale (‡). Outcome measures include ‡birth weight, ‡birth length, ‡head circumference, ‡ponderal index, ‡gestational age, †secondary sex ratio and †spontaneous pregnancy loss.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4, moderate quality a score of 5–8 and high quality a score of 9–11. Dark filled bars represent the main analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no clear trend (–) (the estimate of relative risk was 1 or regression coefficient or mean difference was 0), or decrease (<) in the measure or risk estimate.

reviews provided no assessment of the quality of the included studies [49–53] and even fewer reviews considered quality further in their analyses [45, 46, 54]. One review investigating phthalates had problematic main analyses, as findings from the same sample of the population were used repeatedly within sub-analyses for each metabolite [54]. Overall, reviews of highest methodological quality informed flame retardant (PDBE) and PFAS (PFOA) exposure (Table 2; Figure 2; Suppl File 1.6).

Birth weight

All of the plastic-associated chemical classes included in this umbrella review were considered for this outcome. Fifty-two meta-analyses, including both main analyses and subgroup analyses, informed the association between plastic-associated chemical exposure and change in birth weight. The majority of effect estimates informing PFAS (10/13 EE) and flame retardants (PCBs and PDBEs; 9/15 EE) suggested a decrease in birth weight with exposure. One phthalate plasticiser (1/10 EE) was associated with a decrease in birth weight, and BPA exposure was not significantly associated with any change (5/5 EE) (Figure 2).

Two main analyses showed no significant association with a change in birth weight with exposure to BPA, ES 4.42g, 95%CI −8.83 to 17.67 (highest vs lowest exposure) [46] and β −0.049g, 95%CI −0.199 to 0.101 (untransformed) [52] respectively (Figure 2). Similarly, no association with a change in birth weight was observed irrespective of which trimester exposure was analysed (3/3 EE; Figure 2; first and second trimester not plotted; Suppl File 2.1) [46].

Ten meta-analyses from one review assessed the association of birthweight with prenatal phthalate metabolites (Figure 2) [54]. Results for the main analysis for this review were excluded due to unit of analysis error (see Section 3.3.1). A significant decrease in birth weight was observed for higher MEP, z −10.1g, 95%CI −18.57 to −1.6, with no significant change in estimates of association for all the remaining metabolites investigated, including ∑DEHP, though the majority tended towards a decrease (6/9 EE; Figure 2; Suppl File 2.1) [54].

One meta-analysis reported a significant association between higher exposure to PCBs (total) and reduced birth weight of β −0.59g, 95%CI −0.852 to −0.343 (untransformed). This association was consistent with measurement of exposure also in maternal serum, cord serum and across all trimesters of pregnancy (5/5 EE; Figure 2; cord serum, first and second trimester not plotted; Suppl File 2.1) [53]. Similarly, a significant association of β −0.15, 95%CI −0.24 to −0.05, was reported in a pooled analysis investigating the single congener, PCB 153 (Figure 2) [50]. Considering PDBEs, the association with reduced birth weight was statistically significant for the composite measure of exposure, β −50.56g, 95%CI −95.91 to −5.28, and for the subgroup analysis that included just male infants. Where studies included male and female infants, the reduction in birth weight was no longer significant and likely tempered by the observation that birth weight trended towards an increase when only female infants were analysed (Figure 2; Suppl File 2.1) [45]. Analyses of the individual congeners BDE-47, −99, −100 and −153 were not significantly associated with a change in birth weight, although there was a trend towards decreased birth weight for each congener (4/4 EE; Figure 2; Suppl File 2.1) [45].

Of the main analyses that investigated PFOA exposure in infants, all reported a statistically significant decrease in birth weight, with a range of β from −10.5 to −18.9g (Figure 2; Suppl File 2.1) [44, 47, 51]. The significant association was also observed in subgroup analyses where measure of exposure was determined from cord serum (1/3 EE; data not plotted; Suppl File 2.1) [47, 51] and maternal blood during the second (3/4 EE) and third trimester (2/2 EE) of pregnancy (Figure 2; Suppl File 2.1) [47, 51]. No changes were observed with exposure measured in the first trimester (2/2 EE; data not plotted; Suppl File 2.1) [47, 51]. Similarly, whilst exposure to PFOS was significantly associated with a decrease in birth weight of β −46.09g, 95%CI −80.33 to −11.85 in infants and when exposure was measured in mothers (also in cord serum; 1/2 EE; transformed; data not plotted; Suppl File 2.1) during the third trimester of pregnancy (1/2 EE) [47], no significant changes were observed with measures of exposure during the first two trimesters (2/2 EE; data not plotted; Suppl File 2.1) [47].

Birth length, head circumference and ponderal index

Seven meta-analyses addressed the remaining anthropometric measures pertinent to birth outcomes; three informed the association of plastic-associated chemical exposure with birth length and three meta-analyses from the same reviews informed the association with head circumference, while one analysis assessed ponderal index. Higher prenatal exposure to PFOA was associated with a significant decrease in birth length of β −0.06 cm, 95%CI −0.09 to −0.02, and non-significant decreases were observed for the majority of remaining outcome estimates (5/6 EE, Table 2; Figure 2) [44]. The remaining analyses reported no significant association of birth length with prenatal BPA exposure, β 0.058cm, 95%CI −0.072 to 0.188, nor head circumference, β −0.004cm, 95%CI −0.119 to 0.111 (Figure 2) [52]. Similarly, prenatal exposure to composite measures of PBDEs resulted in no significant decrease in birth length, β −0.33 cm, 95%CI −0.74 to 0.07 nor head circumference, β −0.175 cm, 95%CI −0.42 to 0.07, respectively (Figure 2) [45] and no significant change in head circumference, β −0.03cm, 95%CI −0.08 to 0.01 with PFOA exposure (Figure 2) [44]. No change was reported in ponderal index of infants with higher exposure to PFOA β −0.01 95%CI −0.08 to 0.01 (Figure 2) [44].

Gestational age and sex ratio

No changes were observed in two meta-analyses investigating the association with gestational age and BPA exposure, β −0.032 weeks, 95%CI −0.163 to 0.10 [52], nor secondary sex ratio 0.5, 95%CI 0.45 to 0.551 with higher exposure to PCBs (2/2 EE, Figure 2) [49].

Spontaneous pregnancy loss (SPL)

Ten meta-analyses for individual phthalate metabolites from one review reported the association of exposure to phthalate plasticisers in pregnant women and SPL (Figure 2) [48]. A significant increase in risk of SPL was observed for higher concentrations of mono-n-butyl phthalate (MnBP) and DEHP metabolites MEHP, mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), as well as ∑DEHP, with a range in risk estimates from OR 1.34 to 1.79 (5/10 EE; Figure 2; Suppl File 2.1) [48]. The phthalate metabolites MMP, MEP, monoisobutyl phthalate (MiBP), MBzP and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) were not significantly associated with any change in risk of SPL, though all tended towards an increase (5/10 EE; Figure 2; Suppl File 2.1) [48].

CHILD REPRODUCTIVE HEALTH OUTCOMES

There were eight child reproductive health outcome measures evaluated across five systematic reviews with meta-analyses. Of these, the evidence suggests an association with changes in markers of the timing of puberty and adolescent development, and decreases in anogenital distance (AGD), in children with exposure to BPA and some phthalate plasticisers (Figure 3). Outcomes indicative of timing of puberty and adolescent development following prenatal and postnatal plastic-associated chemical exposure, including measures of abnormal timing of puberty- thelarche (breast development), menarche (first menstrual cycle) and pubarche (development of pubic hair; girls and boys) and precocious puberty (appearance of secondary sex characteristics before eight years of age) -were reported in three reviews (Table 2) [55–57]. Markers of AGD, including anoclitoral and anofourchette distance in girls and anoscrotal and anopenile distance in boys, were reported in two reviews following prenatal exposure (Table 2) [58, 59].

The reviews that informed this outcome category were all rated as moderate quality, scoring 5–8 on the AMSTAR tool (Table 2; Figure 3; Suppl File 1.6). Only one review was informed a priori [58] or included searching for grey literature [57]; duplicate selection and extraction could be confirmed for only two reviews [58, 59]. No reviews provided transparent records of included and excluded studies, whereas all reviews provided detailed study characteristics and details of assessment of quality of included studies (Table 2; Figure 3; Suppl File 1.6).

Onset of puberty

Thirty meta-analyses from three reviews informed the association between both pre- and postnatal plastic-associated chemical exposure and measures indicative of pubertal timing in girls and boys [55–57]. Measures included abnormal (early or delayed) timing of thelarche, abnormal age of pubarche and abnormal age of menarche, and a selection of these same measures was also used to report precocious puberty in girls. Measures in boys included abnormal timing of pubarche and testicular volume.

Two reviews investigated pre- and postnatal exposure and puberty outcomes in girls [55, 57] and one in adolescents [56] (Table 2). Onset of puberty before 8 or after 13 years of age was considered as abnormal timing across the measures considered. BPA exposure was not associated with the risk of precocious puberty in girls, ES 1.09, 95%CI 0.88 to 1.35 (Figure 3) [55]. Higher serum DEHP was significantly associated with an increased risk in precocious puberty in girls, OR 4.09, 95%CI 2.3 to 7.3; however, the increase was not statistically significant with exposure to DnBP, OR 3.26, 95%CI 0.69 to 15.42 (Figure 3) [57]. Seventeen meta-analyses addressed various measures indicative of onset of puberty with six phthalate metabolites in girls. An increased risk of abnormal timing of thelarche was observed with higher concentrations of the DEHP metabolites MEHHP, OR 1.48, 95%CI 1.11 to 1.85, and MEOHP, OR 1.52, 95%CI 1.15 to 1.88 (Figure 3) [56]. The majority of the remaining analyses suggested decreases with phthalate metabolites for age of thelarche (2/3 EE), menarche (3/6 EE) and pubarche (6/6 EE) though no changes were statistically significant (Figure 3;

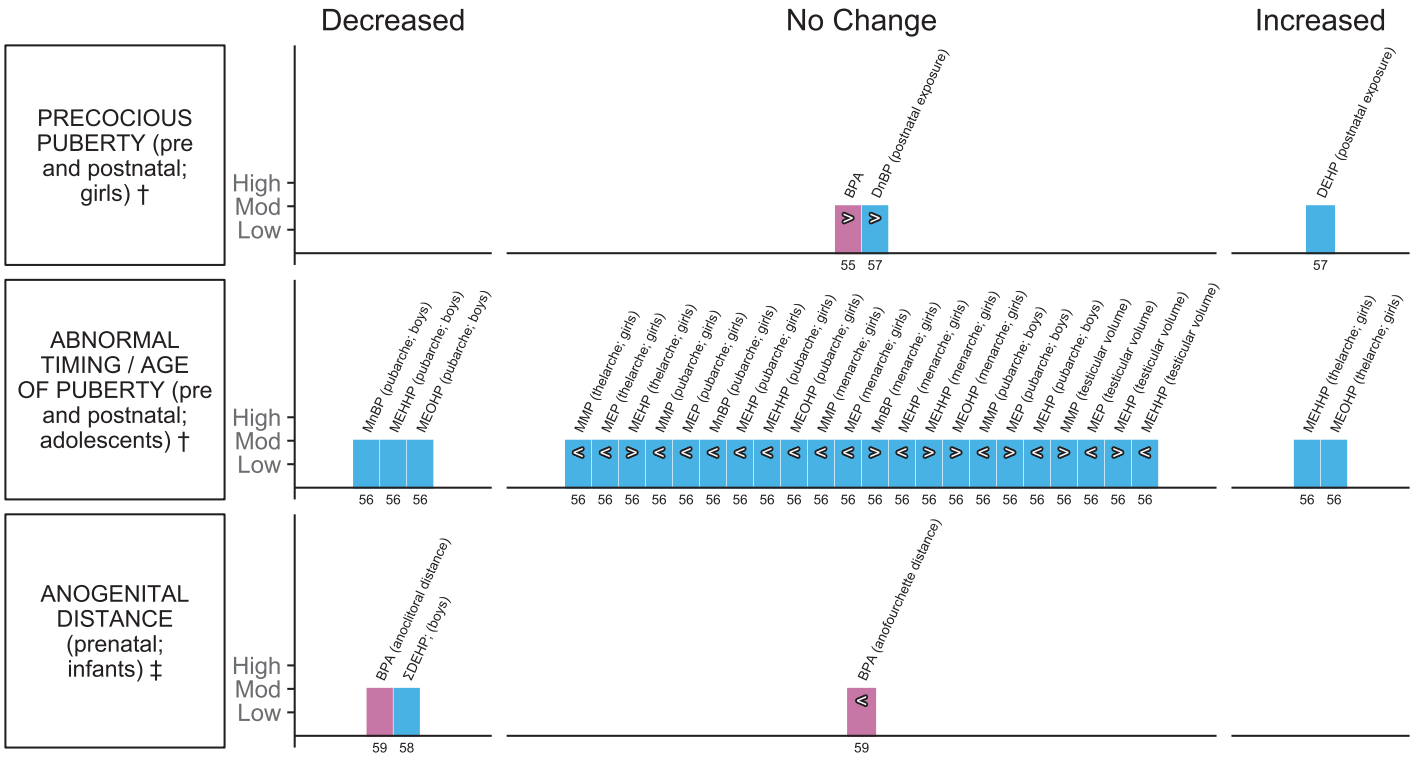

Figure 3 Harvest plot of exposure to plastic-associated chemicals and child reproductive outcome measures.

Plastic-associated chemicals included are bisphenol A (BPA) (pink); and phthalate diesters diethylhexyl phthalate (DEHP) and di-n-butyl phthalate (DnBP) and monoester metabolites (blue), including monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono (3-carboxypropyl) phthalate (MCPP).

Outcomes are either dichotomous (†) or measured on a continuous scale (‡). Outcomes measured include †precocious puberty, ‡anogenital distance measured by anoclitoral and anofourchette distance in girls and anoscrotal and anopenile distance in boys, †abnormal timing/age of puberty/early puberty measured by pubarche, menarche, thelarche and testicular volume.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Moderate quality reflects a score of 5–8. Dark filled bars represent the main analyses of each review. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), or decrease (<) in the measure or risk estimate.

Suppl File 2.2) [56]. In boys, a decreased risk of abnormal age of pubarche (premature or delayed) with higher phthalate metabolites was observed for MnBP, OR 0.66, 95%CI 0.39 to 0.93, MEHHP, OR 0.61, 95%CI 0.32 to 0.91, and MEOHP, OR 0.61, 95%CI 0.26 to 0.97, while for the remaining metabolites meta-analysed (MMP, MEP, MEHP), no association was observed (2/3 EE decreased; Figure 3; Suppl File 2.2) [56]. Similarly, for testicular volume, no association was reported with any of the phthalate metabolites analysed (2/4 EE decreased; Figure 2; Suppl File 2.2) [56].

One review of case control studies also reported seven meta-analyses of the differences in phthalate metabolites detected in serum or urine between girls with precocious puberty and those without (Table 2; Suppl File 2.2) [57]. The serum concentration of DEHP, SMD 1.73, 95%CI 0.54 to 2.91, and DnBP, SMD 4.31, 95%CI 2.67 to 5.95, was greater in girls with precocious puberty than those without (Suppl Figure S1) [57]. No association was observed for the remaining metabolites (5/5 EE), three of which indicated an increased (non-significant) phthalate concentration in girls with precocious puberty (3/5 EE) assessed (Suppl File 2.2) [57].

Anogenital distance (AGD)

Three meta-analyses from two reviews informed the association between plastic-associated chemical exposure and measures of AGD in both female and male infants [58, 59]. Of the two analyses that investigated BPA exposure and AGD in female infants (Table 2), one reported a statistically significant decrease in anoclitoral distance, β −1.37, 95%CI −2.48 to −0.27, whereas the decrease in anofourchette distance was non-significant, β −1.07, 95%CI −3.65 to 1.51 (standardised % change per $\log_{10}$ change in BPA; Figure 3) [59]. One meta-analysis reported a statistically significant decrease in AGD (predominantly anoscrotal distance) in male infants with phthalate plasticiser exposure in utero, β −4.07, 95%CI −6.49 to −1.66 (standardised % change per $\log_{10}$ change in ∑DEHP or MEHP; Figure 3) [58].

ADULT REPRODUCTIVE HEALTH OUTCOMES

Ten adult reproductive health outcome measures were reported in five systematic reviews with meta-analyses. Of these, the evidence available suggests an association with an increased risk of endometriosis in women, and reduction in sperm concentration and changes to motility, motion and increased sperm DNA damage in men with exposure to plastic-associated chemicals (Figure 4). Risk of endometriosis was the most commonly reported outcome addressed for BPA, phthalates and flame retardants in three reviews (Table 2) [60–62], while multiple measures of semen quality, semen motion and sperm DNA damage with phthalate metabolites were addressed in one review (Table 2) [63].

The majority of reviews that informed this outcome category were of moderate quality, scoring between 6 and 8 on the AMSTAR tool; one review was rated as low quality, scoring 3 (Table 2; Figure 4; Suppl File 1.6) [62]. Only one review was informed a priori [61], whereas the review by Wen et al. [64] had the most complete conduct and reporting of searching to identify studies. No reviews provided transparent recordings of included and excluded studies, whereas all reviews provided detailed study characteristics and details of assessment of quality of included studies as well as appropriate statistical analyses (Table 2; Figure 4; Suppl File 1.6). All reported outcomes for this outcome domain, except risk of endometriosis, were derived from one moderate quality review (Figure 4) [63].

Endometriosis

Twelve meta-analyses, including both main and subgroup analyses, from four reviews informed the association between plastic-associated chemical exposure and risk of endometriosis. Exposure to BPA was not significantly associated with an increase in endometriosis, OR 1.4, 95%CI 0.94 to 2.08 (Figure 4) [64]. A statistically significant increase in risk of endometriosis with higher exposure to PCBs was reported in two main analyses with a range of risk estimates between OR 1.70 and 1.91 (Figure 4; highest versus lowest exposure categories; Suppl File 2.3) [61, 62]. Subgroup analyses revealed significant increased association with deep endometriosis, endometriosis

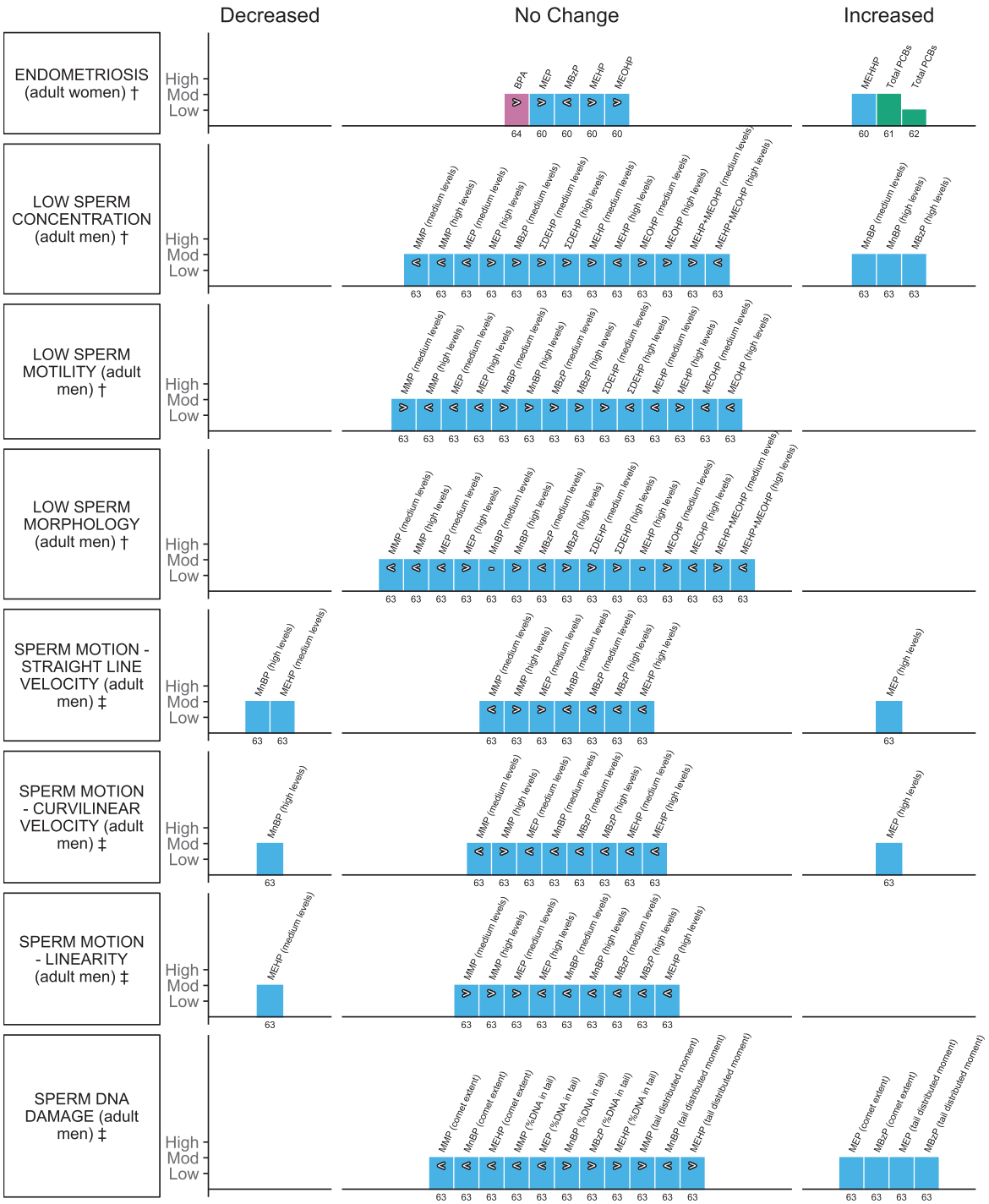

Figure 4 Harvest plot of exposure to plastic-associated chemicals and adult reproductive outcome measures.

Plastic-associated chemicals included are bisphenol A (BPA) (pink); phthalate monoester metabolites (blue), including monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), molar sum of the di(2-ethylhexyl) phthalate metabolites (∑DEHP), and mono (3-carboxypropyl) phthalate (MCPP); and flame retardants (green) encompassing polychlorinated biphenyl (PCB).

Outcomes are either dichotomous (†) or measured on a continuous scale (‡). Outcomes measured include †endometriosis, †sperm concentration, ‡†sperm motility, †sperm morphology, †sperm volume, ‡sperm motion measured via straight line velocity, curvilinear velocity, linearity, and ‡sperm DNA damage measured via comet assay (comet extent), comet assay (percentage [%] DNA in tail) and comet assay (tail distributed moment).

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4 and moderate quality a score of 5–8. Dark filled bars represent the main analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no clear trend (–) (the estimate of relative risk was 1 or regression coefficient or mean difference was 0), or decrease (<) in the measure or risk estimate.

without peritoneal form (total), and serum samples; however, not those from adipose tissue (3/4 EE; data not plotted—Suppl File 2.3) [61]. Five meta-analyses from one review [60] assessed the association with phthalates and endometriosis in women (Figure 4). A significant association for endometriosis was observed for higher concentrations of MEHHP, OR 1.25, 95%CI 1.003 to 1.549, but no significant change in estimates of association for all of the remaining metabolites investigated (3/4 EE), with all (MEP, MEHP, MEOHP) except MBzP, tending towards an increase in risk (Figure 4; Suppl File 2.3) [60].

Semen quality

One review reported 93 meta-analyses pertinent to sperm production, sperm quality and sperm DNA damage with urinary phthalate metabolites (Suppl File 2.3; medium and high phthalate exposure categories) [63]. Measures included sperm concentration, motility (additionally reported for seminal DEHP and DnBP) and morphology, as well as semen motion parameters (straight-line velocity [VSL], curvilinear velocity [VCL] and linearity [LIN]) and indicators of sperm DNA damage (comet assay parameters—comet extent [CE], percent of DNA in tail [Tail%] and tail distributed moment [TDM]). Risk of low sperm concentration, motility and morphology was determined compared to predefined reference values in men (Suppl File 2.3) [63].

Sixteen meta-analyses assessed the association between phthalate metabolite levels in urine and low sperm concentration. Two metabolites, MnBP (medium and high levels, OR 2.39, 95%CI 1.26 to 4.53) and MBzP (high levels only, OR 2.23, 95%CI 1.16 to 4.3), were associated with an increased risk of reduced sperm concentration (3/16 EE; Figure 4), while eight of the remaining analyses tended towards an increase in risk (7/16 EE; Figure 4). There was inconsistency in the direction of effect for many of the metabolites, dependent on the level of exposure (medium vs. high; Figure 4; Suppl File 2.3). Considering the other classical semen parameters that were assessed for urinary phthalates, no significant association with low sperm motility or decreased morphology was observed for any of the metabolites investigated across 29 meta-analyses assessing varying levels of exposure (29/29 EE; Figure 4; Suppl File 2.3). Seven analyses (7/14 EE; Figure 4) tended towards an increased risk of low sperm motility and seven towards an increasing risk of low sperm morphology (7/15 EE; Figure 4). MnBP concentrations in the highest category were not associated with low semen volume (trend decrease; Suppl File 2.3; data not plotted). Conversely, both seminal DEHP, β −0.21, 95%CI −0.3 to −0.12 and DnBP, β −0.19, 95%CI −0.28 to −0.1 levels were significantly associated with low sperm motility (2/2 EE; data not plotted; Suppl File 2.3).

Thirty meta-analyses assessed the association between five urinary phthalate metabolites (MBP, MBzP, MMP, MEP and MEHP; medium and high levels) and the sperm motion parameters VSL, VCL and LIN (Figure 4; Suppl File 2.3) [63]. MnBP (high levels) was associated with decreased VSL, β −2.51 95%CI −4.44 to −0.59, and VCL, β −3.81 95%CI −6.74 to −0.87, while MEHP (medium levels) was similarly associated with decreased VSL, β −1.06 95%CI −1.99 to −0.12 (Figure 4). All remaining analyses suggested a tendency for VSL and VCL to decrease (12/20 EE) with phthalate metabolites, except for VSL and VCL with MMP (high levels) and VSL for MEP (medium levels; Figure 4, Suppl 2.3) [63]. Conversely, urinary MEP (high levels) was significantly associated with an increased VSL, β 2.36, 95%CI 0.28 to 4.45, and VCL, β 5.23, 95%CI 1.67 to 8.80, and a non-significant decrease in LIN (Figure 4). Of the remaining analyses, the majority (6/10 EE) tended towards a decrease in LIN (Figure 4).

Comet assay parameters indicative of sperm DNA damage, including, CE, Tail%, and TDM were each analysed for the five urinary phthalate metabolites (MBP, MBzP, MMP, MEP and MEHP; medium and high levels; 15 EE; Figure 4). An interquartile range increase in MEP (449.4 ug/L), β 4.22, 95%CI 1.66 to 6.77, and MBzP (11.35 ug/L), β 3.57, 95%CI 0.89 to 6.25, was associated with an increase in CE and also TDM, MEP β 1.64, 95%CI 0.24 to 3.03, MBzP β 1.72, 95%CI 0.33 to 3.12 (Figure 4; Suppl File 2.3) [63]. No significant associations were observed for the remaining metabolites, which tended to decrease for CE (3/3 EE); however, the majority tended to increase for Tail% (3/5 EE) and TDM (2/3 EE; Figure 4) [63].

ENDOCRINE OUTCOMES

Ten endocrine outcome measures were reported in eight systematic reviews with meta-analyses and one pooled analysis. Evidence suggests an association with changes in measures of thyroid function, an increasing risk of type 2 diabetes (T2D) and other measures of blood glucose regulation, including insulin resistance using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and fasting glucose, as well as polycystic ovary syndrome (PCOS) in women across the plastic-associated chemical exposures that have been evaluated (Figure 5; Suppl Figure S1). Endocrine outcomes were addressed for BPA, phthalates, flame retardants and PFAS. Risk of T2D was the most commonly reported endocrine outcome in three reviews and one pooled analysis [65–68], followed by HOMA-IR in two reviews [67, 69], while the remaining measures indicative of insulin regulation in the body, including fasting insulin and glucose, as well as 2-hr insulin and 2-hr glucose were reported in one review (Table 2) [67]. Measures of thyroid function were reported in three reviews, with thyroid stimulating hormone (TSH) and total thyroxine (TT4) reported in three reviews [70–72], free thyroxine (fT4) in two reviews [70, 71] and triiodothyronine (T3) in one review (Table 2) [71]. Additionally, one review reported on PCOS (Table 2) [73].

The reviews that informed this outcome category ranged from low to high methodological quality, scoring between 4 and 9 on the AMSTAR tool (Table 2; Figure 5; Suppl File 1.6). Overall, thyroid function was informed by higher-quality reviews than those informing diabetes and glucose homeostasis (Table 2; Figure 5; Suppl File 1.6). Only two reviews were informed by an a priori protocol [67, 72] and few included considerations of grey literature [69, 72, 73]. Duplicate selection and extraction could be confirmed for all but two reviews [65, 71] Transparent reporting of included and excluded studies was provided by only two reviews [66, 72], whereas all reviews provided detailed study characteristics. Almost half of the included reviews provided no assessment of the quality of the included studies [67–70] nor considered quality further in their analyses [65]. Two reviews had problematic main analyses, as findings from the same sample of the population were used repeatedly within sub-analyses for each metabolite [69] or congener [72]. These analyses were excluded.

Thyroid function

Phthalates, flame retardants and PFAS were considered in 104 analyses of thyroid hormone levels to inform the impact of plastic-associated chemical exposure on thyroid function. Decreases in estimates of association were observed for DEHP phthalate metabolites (MEHP, MEHHP, MEOHP) across the majority of population groups investigated for TSH (9/12 EE), fT4 (8/12 EE) and TT4 (4/12 EE), including children, adults and pregnant women (Figure 5; Suppl File 2.4) [70].

MEHHP was significantly associated with a decreased fT4 in the general population, r –0.03, 95%CI –0.05 to –0.01, and adults alone r –0.08, 95%C –0.14 to –0.01, though this association was reversed in children, r 0.06, 95%CI: 0.01 to 0.10. MEOHP was associated with TT4 in children, r 0.05, 95%CI 0.01 to 0.10 (Figure 5; Suppl File 2.4) [70]. DEHP exposure was not significantly associated with any change in TSH (Figure 5; Suppl File 2.4) [70]. In the sub-population of pregnant women, no associations were observed for DEHP exposure or any of the thyroid hormones measured (9/9 EE; data not plotted; Suppl File 2.4) [70].

One review reported 66 main and subgroup analyses investigating exposure to PFAS, including PFOA, PFOS and PFHxS and thyroid function [71]. Of the main analyses, one presented a weak significant positive association for exposure to PFOS and fT4 concentration in adult blood, z 0.05, 95%CI 0.03 to 0.08; this weak association between PFOS and fT4 was maintained when pregnant women were excluded from the analysis, z 0.06, 95% CI 0.02 to 0.09 (Figure 5; Suppl File 2.4) [71]. A significant negative association was also observed with exposure to PFHxS and TT4 when pregnant women were excluded from the analysis, –0.04, 95%CI –0.07 to –0.01 (Figure 5; Suppl File 2.4) [71]. Of the remaining 11 main analyses, increasing PFAS exposure showed a decrease in thyroid function in four (4/11 EE), an increase in five (5/11 EE) and no change in three (3/11 EE; Figure 5; Suppl File 2.3) [71]. Associations appeared independent of the level (low, intermediate, high; random effects) of mean concentration of PFAS in the blood (30 EE; data not plotted) [71].

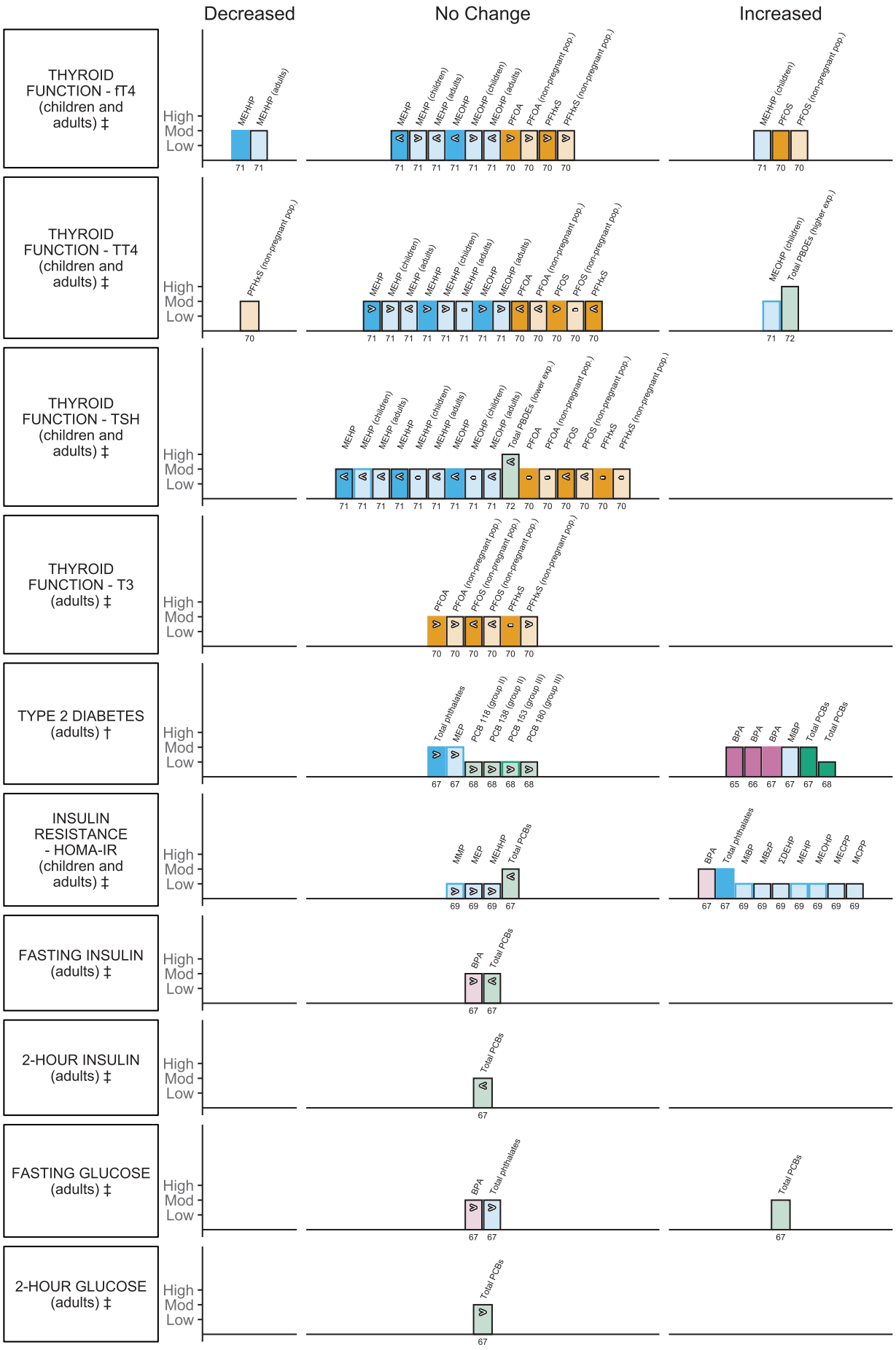

Figure 5 Harvest plot of exposure to plastic-associated chemicals and endocrine outcome measures. *(Continued on next page)*

Figure 5 continued Plastic-associated chemicals included are bisphenol A (BPA) (pink); phthalate monoester metabolites (blue), encompassing monomethyl phthalate (MMP), monoethyl phthalate (MEP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(3-carboxypropyl) phthalate (MCPP) and molar sum of the di(2-ethylhexyl) phthalate metabolites (∑DEHP); flame retardants (green) encompassing polychlorinated biphenyl (PCB), 2,3',4,4',5-pentachlorobiphenyl (PCB 118) group (gp) II, 2,2',3,4,4',5'-hexachlorobiphenyl (PCB 138) (gp II), 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) (gp III), 2,2',3,4,4',5,5'-heptachlorobiphenyl PCB 180) (gp III), polybrominated diphenyl ethers (PBDEs); and per- and polyfluoroalkyl substances (PFAS) (orange), encompassing perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), and perfluorooctane sulfonate (PFOS).

Outcomes are either dichotomous (†) or measured on a continuous scale (‡). Outcomes measured include thyroid function measured by levels of ‡free thyroxine (fT4), ‡thyroxine (TT4), ‡thyroid-stimulating hormone (TSH), and ‡triiodothyronine (T3), †type 2 diabetes (T2D), ‡insulin resistance (HOMA-IR), ‡fasting insulin, ‡2-hour (hr) insulin, ‡fasting glucose and ‡2-hour glucose.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4, moderate quality a score of 5–8 and high quality a score of 9–11. Dark filled bars represent the main analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no clear trend (–) (the estimate of relative risk was 1 or regression coefficient or mean difference was 0), or decrease (<) in the measure or risk estimate.

Of the remaining analyses of the sub-populations, when pregnant women were excluded, seven were showing a decreasing trend or no change (7/12 EE), whilst five showed an increasing trend (5/12 EE; Figure 5; Suppl File 2.4) [71]. Considering pregnant women only, six analyses of thyroid outcome measures (6/12 EE) showed some increase in measure, whilst three showed no change (3/12 EE; data not plotted; Suppl File 2.4) [71].

Two meta-analyses from one review informed the association between flame-retardant exposure and thyroid function (Figure 5) [72]. Results for the main analysis for this review were excluded due to unit of analysis errors (see endocrine outcomes main section above). Comparing serum PBDE levels, exposure to total PBDE levels between 35 and 100 ng/g lipid was associated with TT4, z 0.15, 95%CI 0.06 to 0.24 (Figure 5; Suppl File 2.4) [72]. No association was observed with total PBDE exposure <30 ng/g lipid and TSH, z –0.07, 95%CI –0.14 to 0.00 (Figure 5; Suppl File 2.4) [72].

Type 2 Diabetes

BPA, phthalate plasticisers and flame retardants were considered in 16 meta-analyses of plastic-associated chemical exposure and risk of T2D. An increase in risk estimate was observed for all analyses informing PCB (8/8 EE), phthalates (3/3 EE) and BPA (5/5 EE) exposure; for the majority of analyses the association was statistically significant (Figure 5, Suppl File 2.4).

Three main analyses reported a statistically significant increased risk of T2D with exposure to BPA (3/3 EE; Figure 5). Two analyses reported a range from OR 1.28 to 1.47 [65, 66] and a third a RR 1.45, 95%CI 1.13 to 1.87 (highest versus lowest exposure, Figure 5; Suppl File 2.4) [67]. The significant association was also observed with subgroup analyses irrespective of whether the measure of exposure was determined from either urine or serum (2/2 EE; data not plotted; Suppl File 2.4) [65]. Considering phthalates, MiBP was significantly associated with higher risk of T2D, RR 1.90, 95%CI 1.17 to 3.09, while one main analysis of total phthalates and additional subgroup analysis of MEP suggested similar though non-significant increase of T2D in adults (Figure 5; Suppl File 2.4) [67].

Of the main analyses that investigated total PCB exposure in adults (Table 2), both reviews reported a statistically significant increase in risk of T2D (2/2 EE; Figure 5) with OR 1.7 [68] and RR 2.39 (highest versus lowest exposure) [67]. The review by Song et al. [67] included all of the studies that were included in the review by Wu et al. [68], as well as other retrospective studies (Suppl File 2.4). The significant association was also observed in subgroup analyses of females, but not males (2/2 EE; data not plotted; Suppl File 2.4) [67]. All analyses of total PCBs included some cohorts with either poisoning due to ingestion or instances of exposure to contaminated areas. Estimates of individual group II (PCB 118, 138) and group III (PCB 153, 180) congeners all increased with higher relative exposure, though non-significantly (4/4 EE; Figure 5; Suppl File 2.4) [68].

Diabetes-related metabolic traits

The same plastic-associated chemicals (BPA, phthalates and flame retardants) were considered in 20 meta-analyses investigating other diabetes-related metabolic traits; 13 informed the association with HOMA-IR from two reviews [67, 69], while the remaining analyses of other diabetes related measures were all derived from the same review (7/7 EE; highest to lowest exposure; Table 2; Figure 5) [67].

Higher BPA concentrations were significantly associated with higher HOMA-IR, MD 0.80 mg/dL, 95%CI 0.36 to 1.25 (Figure 5) [67]. Similarly, higher total phthalates concentrations were significantly associated with HOMA-IR, MD 0.71 mg/dL, 95% CI 0.30 to 1.12 (Figure 5) [67]. This relationship was maintained consistently when individual metabolites were examined (10/10 EE), with multiple metabolites showing significant associations (β range of 0.02 to 0.26), including MiBP, MBzP, MCPP as well as ∑DEHP and the individual DEHP metabolites, MEHP, MEOHP, MECPP (7/10 EE), while MMP, MEP and one DEHP metabolite, MEHHP, showed non-significant increases (3/10 EE; Figure 5; Suppl File 2.4) [69]. Results for the main analysis for this review were excluded due to unit of analysis error (see endocrine outcomes main section above) [69]. Conversely, total PCB exposure tended to decrease HOMA-IR, MD −2.05 mg/dL, 95%CI −4.65 to 0.56 (highest versus lowest exposure; Figure 5) [7]. Neither higher BPA nor higher total PCB exposure were significantly associated with fasting insulin (2/2 EE; Figure 5; Suppl File 2.4), nor was higher total PCB exposure significantly associated with lower 2hr insulin (Figure 5; Suppl File 2.4) [67].

Four meta-analyses from one review analysed blood glucose measures [67]. Exposure to higher total PCBs was significantly associated with an increase in fasting glucose, MD 3.27 mg/dL, 95%CI 1.87 to 4.67, and although neither higher BPA nor higher total phthalate concentrations were associated, both tended to increase non-significantly (Figure 5; Suppl File 2.4) [67]. Two-hour glucose increased with higher total PCB concentration (Figure 5; Suppl File 2.4) [67].

Polycystic ovary syndrome

One review of case control studies also reported meta-analyses of the differences in BPA levels detected in serum and follicular fluid (Table 2; Suppl File 2.4) [73]. Women with PCOS were found to have significantly higher BPA levels than women without PCOS, SMD 2.44, 95%CI 1.27 to 3.61 (Suppl Figure S1) [73]. This association was maintained when assessing serum samples only and when limited to women over 19 years of age (Suppl Figure S1; Suppl File 2.4) [73].

CHILD NEURODEVELOPMENT OUTCOMES

There were three domains of neurodevelopmental outcome reported in children up to 12 years of age across three systematic reviews with meta-analyses and one pooled analysis. Of these, the evidence suggests an association with a decrease in children's cognitive development and intelligence quotient (IQ), a decrease in fine motor development, and no change in attention deficit hyperactive disorder (ADHD) with exposure to plastic-associated chemicals evaluated (Figure 6). Child neurodevelopment outcomes were addressed for phthalates, flame retardants and PFAS (Table 2; Figure 6). Meta-analyses included separate consideration of prenatal and postnatal exposure to plastic-associated chemicals (Table 2).

The reviews that informed this outcome category ranged from moderate to high quality and scored between 7 and 11 on the AMSTAR tool, whilst the pooled analysis scored 3 (Table 2; Figure 6; Suppl File 1.6). The review by Lam et al. [74] informing the impact of flame-retardant exposure (BDE-47) on children's IQ, fulfilled all of the AMSTAR criteria (11/11). Neither of the other reviews considered grey literature sources, nor transparent reporting of included and excluded studies [75, 76]. The reviews by Lam et al. [74] and Radke et al. [76] were informed by an a priori protocol. All of the reviews and pooled analysis provided detailed characteristics of included studies [74–77].

Cognitive development or intelligence quotient (IQ)

Eighteen meta-analyses, including both main and subgroup analyses, from two reviews informed the association between prenatal phthalate exposure and measures of cognitive development or IQ in children [75, 76]. The phthalate metabolites MEP, MnBP, MiBP, MBzP and DEHP metabolites, measured in urine or plasma, were investigated (18 EE). Of the main analyses, the majority reported a non-significant decrease in measures of cognitive development or IQ with increasing phthalates (6/7 EE), including ∑DEHP metabolites, β −0.1, 95%CI −0.8 to 0.5; DEHP metabolites, β −0.36, 95%CI −1.05 to 0.32; MnBP, β −0.2, 95%CI −0.7 to 0.4; MiBP, β −0.1, 95%CI −0.6 to 0.4, MBzP; β −0.1, 95%CI −0.8 to 0.5; except the phthalate metabolite MEP, β 0.3, 95%CI −0.3 to 0.9 (Figure 6) [75, 76]. Considering subgroups of girls and boys, in girls the majority of analyses similarly reported a non-significant, inverse association (4/5 EE; data not plotted; Suppl File 2.5) [76]. Whilst in boys, small, non-significant improvements in cognitive development or IQ were observed (4/5 EE, one EE no change; data not plotted; Suppl File 2.5) [76]. One meta-analysis evaluated the association

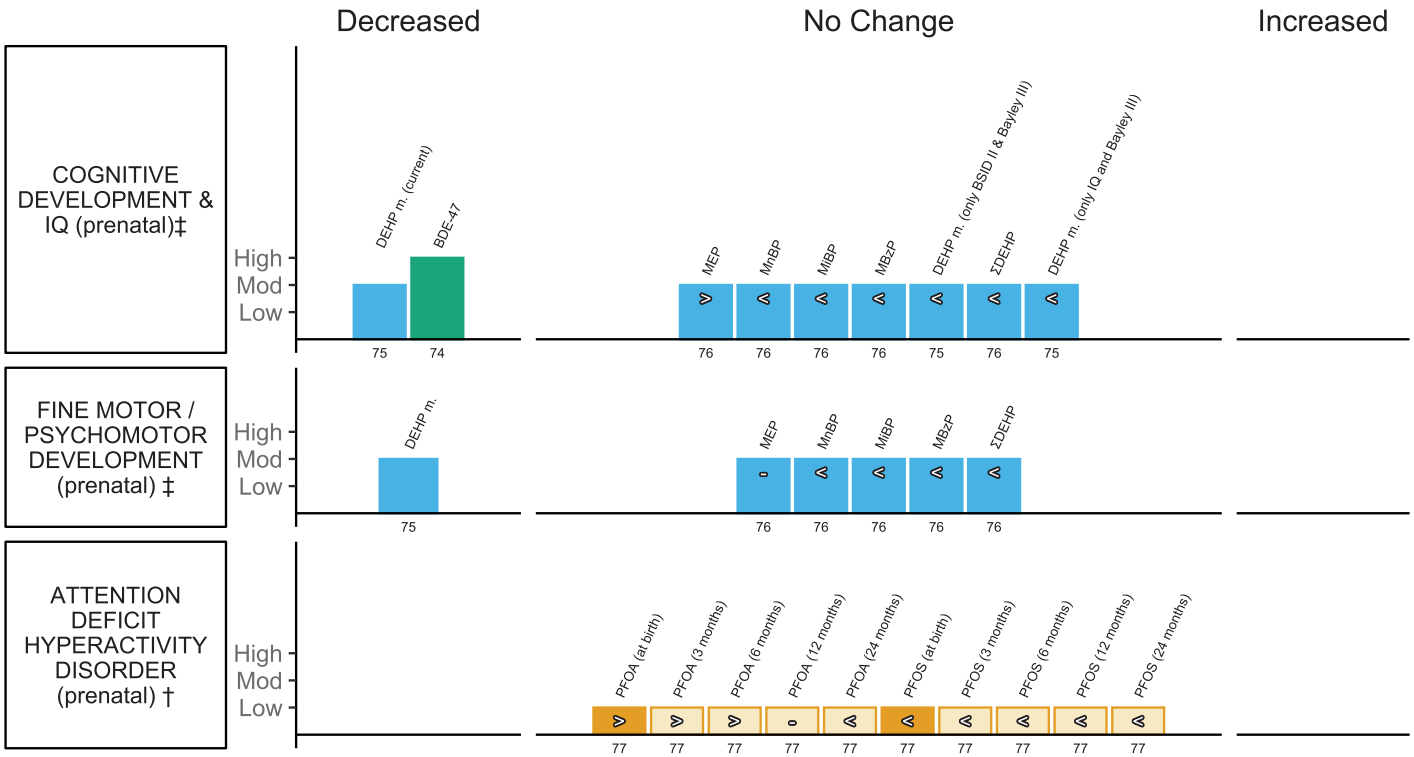

Figure 6 Harvest plot of exposure to plastic-associated chemicals and children's neurodevelopmental outcome measures.

Plastic-associated chemicals included are phthalates (blue) where exposure was determined based on monoester metabolites monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), molar sum of all di(2-ethylhexyl) phthalate metabolites measured (∑DEHP), and best single measure of metabolite(s) of di(2-ethylhexyl) phthalate (DEHP m.); flame retardants (green) including polybrominated diphenyl ethers (PBDEs) where exposure was determined based on a prevalent congener 2,2',4,4'-tetrabromodiphenyl ether (BDE-47); and per- and polyfluoroalkyl *substances* (PFAS) (orange) including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS).

Outcome measures are either dichotomous (†) or measured on a continuous scale (‡). Outcomes include ‡Cognitive Development and Intelligence Quotient (IQ) (measured on the Mental Development Index (MDI) of the Bayley Scales of Infant Development, 2nd ed. (BSID-II), Cognitive Development subscale of the Bayley Scales of Infant and Toddler Development, 3rd ed. (Bayley-III), General Cognitive Scale (GCS) of the McCarthy Scales of Children's Abilities (MSCA), and Full Scale IQ (FSIQ) of the Wechsler Preschool & Primary Scale of Intelligence (WPPSI) or Wechsler Intelligence Scale for Children (WISC)); ‡Fine Motor/Psychomotor Development (measured on the Psychomotor Development Index (PDI) of BSID-II, and Fine Motor subscale of Bayley-III) and †Attention Deficit Hyperactive Disorder (ADHD) (measured with the Attention Problems Syndrome Scale of the Child Behaviour Checklist (CBCL), the Hyperactivity/Inattention subscale of the Strengths and Difficulties Questionnaire (SDQ) and the ADHD Diagnostic and Statistical Manual of Mental Disorder 4th ed (DSM-IV)).

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4, moderate (mod) quality a score of 5–8 and high quality a score of 9–11. Dark filled bars represent the primary analyses of each review; unfilled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no clear trend (–) (the estimate of relative risk was 1 or regression coefficient or mean difference was 0), or decrease (<) in the measure or risk estimate.

between postnatal (current) phthalate exposure and measures of children's cognitive development or IQ [75], with measures including the General Cognitive Scale (GCS) of the McCarthy Scales of Children's Abilities (MSCA) and Full Scale IQ (FSIQ) of the Wechsler Preschool & Primary Scale of Intelligence (WPPSI) or Wechsler Intelligence Scale for Children (WISC) (Table 2). A significant reduction in cognitive performance or IQ, β −1.03, 95%CI −1.88 to 0.18, was found with postnatal exposure to DEHP metabolites (Figure 6; Suppl File 2.5) [75].

One meta-analysis informed the association between prenatal flame-retardant exposure and children's IQ, assessed on the WPPSI or MSCA [74]. A significant inverse association was found with prenatal BDE-47 exposure and cognitive development or IQ, β −3.7 points, 95% CI: −6.56 to −0.83 (Figure 6; Suppl File 2.5) [74].

Fine motor or psychomotor development

Sixteen meta-analyses, including both main and subgroup analyses, from two reviews informed the association between prenatal phthalate exposure and measures of fine motor or psychomotor development in children, measured using Bayley Scales of Infant Development, 2nd ed. (BSID-II) or Bayley Scales of Infant and Toddler Development, 3rd ed. (Bayley-III) [75, 76]. There were four phthalate metabolites (MEP, MnBP, MiBP and MBzP) as well as DEHP metabolites investigated, measured in urine or plasma. Of the main analyses, prenatal DEHP metabolite exposure was associated with a decrease in psychomotor development in children, β −0.80, 95%CI −1.48 to −0.12 (1/6 EE; Figure 6). However, there were no significant changes with the other metabolites investigated, nor with ∑DEHP (5/6 EE; Suppl File 2.5; Figure 6) [75]. Considering girls and boys separately, higher prenatal MBzP exposure was also associated with a significant decrease in fine or psychomotor development (1/5 EE; data not plotted; Suppl File 2.5) [76], and non-significant inverse associations were observed for MnBP and MiBP in girls (2/5 EE; data not plotted; Suppl File 2.5) [76]. In boys, a small, non-significant, positive association was observed in the majority of analyses, as with cognitive development and IQ (4/5 EE; data not plotted; Suppl File 2.5) [76].

Attention Deficit Hyperactive Disorder (ADHD)

Thirty meta-analyses from one pooled analysis [77] reported the association of prenatal exposure to PFOA and PFOS and ADHD in children 4–11 years of age. A pharmacokinetic model was used to generate estimates of PFOS and PFOA levels from birth until 24 months of age. No significant risk was observed with exposure to either PFOA (inter-quartile range –IQR increase 3–7ng/ml) or PFOS (IQR increase 1–5 ng/ml) at birth, 3, 6, 12 and 24 months and ADHD (10/10 EE; Figure 6; Suppl file 2.5) [77], with double the number of estimates indicating a decreased risk (6/10 EE; Figure 6) compared to an increased (3/10 EE; Figure 6) risk. Considering subgroups of girls and boys, in girls, risk of ADHD tended to increase with PFOA and PFOS exposure at all time points assessed (10/10 EE; data not plotted; Suppl File 2.5) [77]; the association was significant for PFOA exposure at birth and also at three months for ADHD (2/10 EE; data not plotted; Suppl file 2.5) [77]. Conversely, in boys, findings include both slight decreases (7/10 EE) and increases (3/10 EE) in risk estimates (data not plotted; Suppl File 2.5) [77].

NUTRITIONAL OUTCOMES

There were multiple nutritional outcomes reported in seven systematic reviews with meta-analyses. The available evidence suggests an increased risk of obesity and related anthropometric measures—overweight, BMI and elevated waist circumference—with exposure to plastic-associated chemicals (Figure 7). Nutritional outcomes were addressed for BPA, phthalates and PFAS. Exposure to plastic-associated chemicals was postnatal in the majority of included meta-analyses for both children and adults, with prenatal exposure also assessed for PFAS (Table 2).

The reviews that informed this outcome category were all of moderate quality, scoring between 5 and 7 on the AMSTAR tool (Table 2; Suppl File 1.6). None of the included reviews were informed by an a priori protocol, and it was unclear in three reviews if duplicate extraction of data was

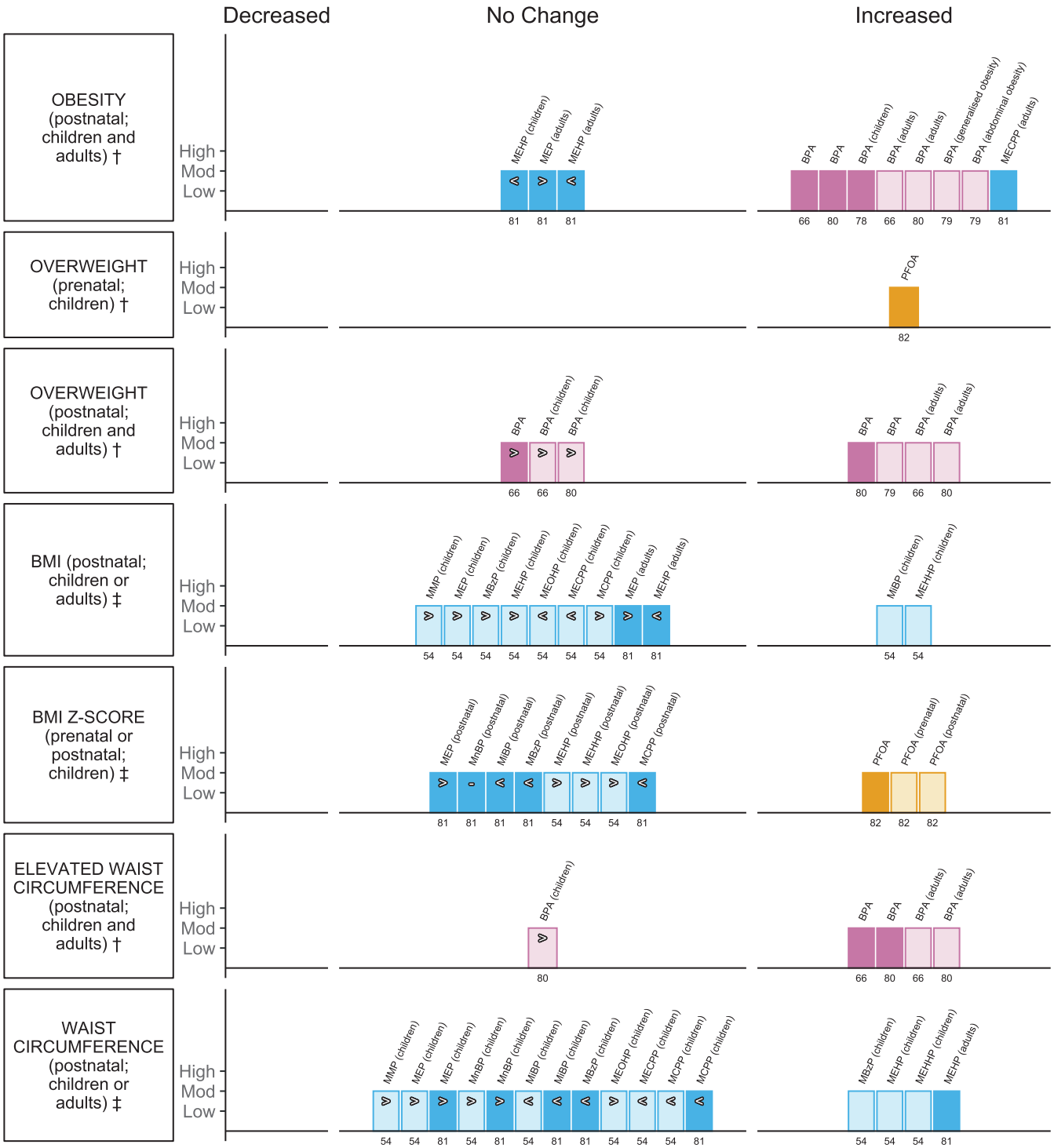

Figure 7 Harvest plot of exposure to plastic-associated chemicals and nutritional outcome measures.

Plastic-associated chemicals included are bisphenol A (BPA) (pink) and phthalate monoester metabolites (blue), including monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-n-octyl phthalate (MnOP) and mono (3-carboxypropyl) phthalate (MCPP).

Outcome measures are either dichotomous (†) or measured on a continuous scale (‡). Outcomes measured include †obesity including abdominal obesity and generalized obesity, †overweight including generalized overweight, ‡Body Mass Index (BMI) and ‡BMI z score, †elevated waist circumference and ‡waist circumference.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Moderate quality reflects a score of 5–8. Dark filled bars represent the primary analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no change (–) (the estimate of relative risk was 1 or regression coefficient or mean difference was 0), or decrease (<) in the measure or risk estimate.

performed [66, 78, 79]. Only one of the reviews that informed this outcome category provided a complete list of excluded as well as included studies [66], whereas two reviews out of the five included considered the results of critical appraisal in the analysis. It was unclear in two of the included reviews if statistical analysis was appropriate [79, 80].

Obesity

Fifteen meta-analyses, including both main and subgroup analyses, from five systematic reviews informed the association between BPA and phthalates and risk of obesity [66, 78–81]. None of the included reviews used a reference standard for categorisation of obesity.

Two meta-analyses reported a significantly increased risk of obesity with higher BPA exposure in the general population with an OR range of 1.57 to 1.67 (2/2 EE; Figure 7; highest versus lowest category; Suppl File 2.6) [66, 80]. This finding was maintained in subgroup analyses considering different patterns of obesity, with significant associations reported for both generalised obesity, OR 1.83, 95% CI 1.59 to 2.12, and abdominal obesity, OR 1.43, 95%CI 1.27 to 1.62 (2/2 EE; Figure 7; highest versus lowest category) [79], as well as in a dose response analyses for these two outcomes (2/2 EE; per 1ng/mL increase in BPA; data not plotted; Suppl File 2.6) [79]. A significant association was also maintained in an analysis of postnatal exposure in children alone, OR 1.57, 95%CI 1.09 to 2.23 (Figure 7; Suppl File 2.6) [78], and in adults alone, an OR range of 1.50 to 1.60 (2/2 EE; Figure 7; Suppl File 2.6) [66, 80], although an alternative meta-analytical approach applied to studies of children did not find a statistically significant difference in urinary BPA concentration in obese and non-obese children (Suppl File 2.6; 2 EE, data not plotted) [78].

One review assessed the association of three phthalate metabolites, MEP, MEHP and MECPP, and risk of obesity (Figure 7) [81]. A significant increase in risk of obesity in adults was observed with the DEHP metabolite MECPP, OR 1.67, 95%CI 1.3 to 2.16, and was also observed for MEP, though non-significant (Figure 7; high versus low exposure; Suppl File 2.6) [80]. A non-significant reduction in the risk estimate was observed with the DEHP metabolite MEHP (Figure 7; Suppl File 2.6) [80]. The only meta-analysis of childhood obesity was for MEHP, with a similar non-significant inverse association (Figure 7; Suppl File 2.6) [80].

Overweight

Eight meta-analyses including both main and subgroup analyses from four systematic reviews informed the association between risk of overweight and exposure to BPA and PFOA [66, 79, 80, 82]. No reference standard for overweight was provided by any of the included reviews.

Of three analyses including both children and adults, two reported a significant increase in risk of overweight with higher exposure to BPA, OR range of 1.24 to 1.32 (Figure 7) [79, 80], while a similar increase was reported, though non-significant, in the other meta-analysis, OR 1.21, 95%CI 0.98 to 1.50 (Figure 7) [66]. This relationship with higher BPA exposure was maintained in a dose response analysis (per 1ng/mL increase in BPA; data not plotted; Suppl File 2.6. [79] Similarly, this significant risk of overweight was also observed in meta-analyses from two reviews including only adults (same studies included), OR 1.25, 95%CI 1.01 to 1.56 (Figure 7; 2/2 EE; Suppl File 2.6) [66, 80], while only the positive trend in the association was maintained in children (2/2 EE; Figure 7; Suppl File 2.6) [66, 80].

Similar to the effects reported with exposure to BPA, in a main analysis investigating prenatal PFOA exposure, a significant association with risk of overweight was observed in children, ES 1.25, 95%CI 1.04 to 1.50 (Figure 7; Suppl File 2.6) [82].

BODY MASS INDEX

Twenty-four meta-analyses, including both main and subgroup analyses, from three systematic reviews informed the association between exposure to phthalates or PFAS, and BMI or BMI z-score [54, 81, 82]. The majority of phthalates assessed showed a positive association with increased BMI in children with increasing concentrations of phthalate metabolites (10/12 EE) [54]. Of these, two metabolites, MiBP and MEHHP, showed a statistically significant increase in BMI, whereas a small,

non-significant reduction in BMI was reported with increasing MEOHP and MECPP (Figure 7; Suppl File 2.6) [54]. Similar trends were observed when considering BMI z-score in children, with all metabolites assessed by one review (3/3 EE; MEHP, MEHHP and MEOHP) showing a small, non-significant increase in BMI z-score with increasing urinary phthalate concentration (Figure 7; Suppl File 2.6) [54]. In another review, however, no change was reported with MnBP exposure in children, while a small, non-significant, positive association was reported for MEP and small, non-significant reductions in BMI z-score with increasing concentration of MiBP, MBzP and MCPP (Figure 7; 3/5 EE; Suppl File 2.6) [81]. Only two metabolites were assessed in adults for BMI small positive association with MEP, and a small negative association with MEHP (Figure 7; Suppl File 2.6) [81].

One systematic review presented one main analysis and four subgroup analyses investigating BMI z-score and the association with PFOA exposure in children. A significant increase in BMI z-score was observed with increasing PFOA exposure in children, β 0.10, 95%CI 0.03 to 17.00 (Figure 7) [82], a relationship that was maintained irrespective of whether exposure was prenatal, β 0.09, 95%CI 0.02 to 0.17, or postnatal, β 0.16, 95%CI 0.01 to 0.30 (Figure 7; 3/3 EE) [82]. This small, positive association with PFOA exposure was maintained in girls; however, not in boys (Figure 7; data not plotted; Suppl File 2.6) [82].

Waist circumference

Twenty-one meta-analyses, including both main and subgroup analyses, from four reviews informed the association between BPA, phthalates and waist circumference [54, 66, 80, 81].

Two meta-analyses from two reviews found a consistent association between elevated waist circumference and BPA exposure with an OR range of 1.48 to 1.49 (Figure 7; Suppl File 2.6) [66, 80]. No reference for elevated waist circumference was provided in either review. This significant association with BPA exposure, as observed with other anthropometric measures related to obesity, was maintained in adults, OR range of 1.50 to 1.52 (Figure 7; Suppl File 2.6) [66, 80]. In children, a similar positive association was also observed; however, this was not statistically significant, OR 1.62, 95%CI 0.97 to 2.72 (Figure 7) [80].

Two reviews reported 15 meta-analyses assessing the association of increasing phthalate levels with waist circumference in children [54, 81]. A positive association was reported for MEP and MnBP (4/4 EE) from both reviews, whilst a negative association was reported for MiBP and MCPP from both reviews (4/4 EE). For MBzP, the results were inconsistent, with a negative association found in one (Figure 7; Suppl File 2.6) [81], but a statistically significant positive association in the other (Figure 7; Suppl File 2.6) [56]. For the remaining phthalate metabolites assessed, including MMP, MEP, MEHP, MEHHP and MEOHP, positive associations were observed with waist circumference, which were statistically significant for MEHP and MEHHP (Figure 7; Suppl File 2.6) [56]. Only one metabolite, MEHP, was assessed for adults, with a finding of a significant positive association with increased waist circumference, β 0.58, 95%CI 0.55 to 0.62 (Figure 7) [81], consistent with that found for children.

CIRCULATORY OUTCOMES

There were seven circulatory outcomes reported in four systematic reviews with meta-analyses and two pooled analyses. Of these, the evidence suggests an association with increased systolic blood pressure (SBP) and increased high-density lipoprotein (HDL) levels in children, increased risk of hypertension in adults and increased risk of CVD and CVD mortality with exposure to the plastic-associated chemicals evaluated (Figure 8). Circulatory outcomes were addressed for BPA, phthalates and flame retardants. Exposure to plastic-associated chemicals was measured in children and adults, and outcome measures included serum lipids (HDL, low-density lipoprotein [LDL], total cholesterol [TC], triglycerides [TG] and apolipoprotein B [ApoB]), blood pressure (SBP and diastolic [DBP]), risk of CVD and hypertension and mortality attributable to CVD, cerebrovascular disease and hypertension (Table 2).

The reviews that informed this outcome category were of moderate quality, scoring between 5 and 7 on the AMSTAR tool, whereas the pooled analysis ranged from low to moderate quality,

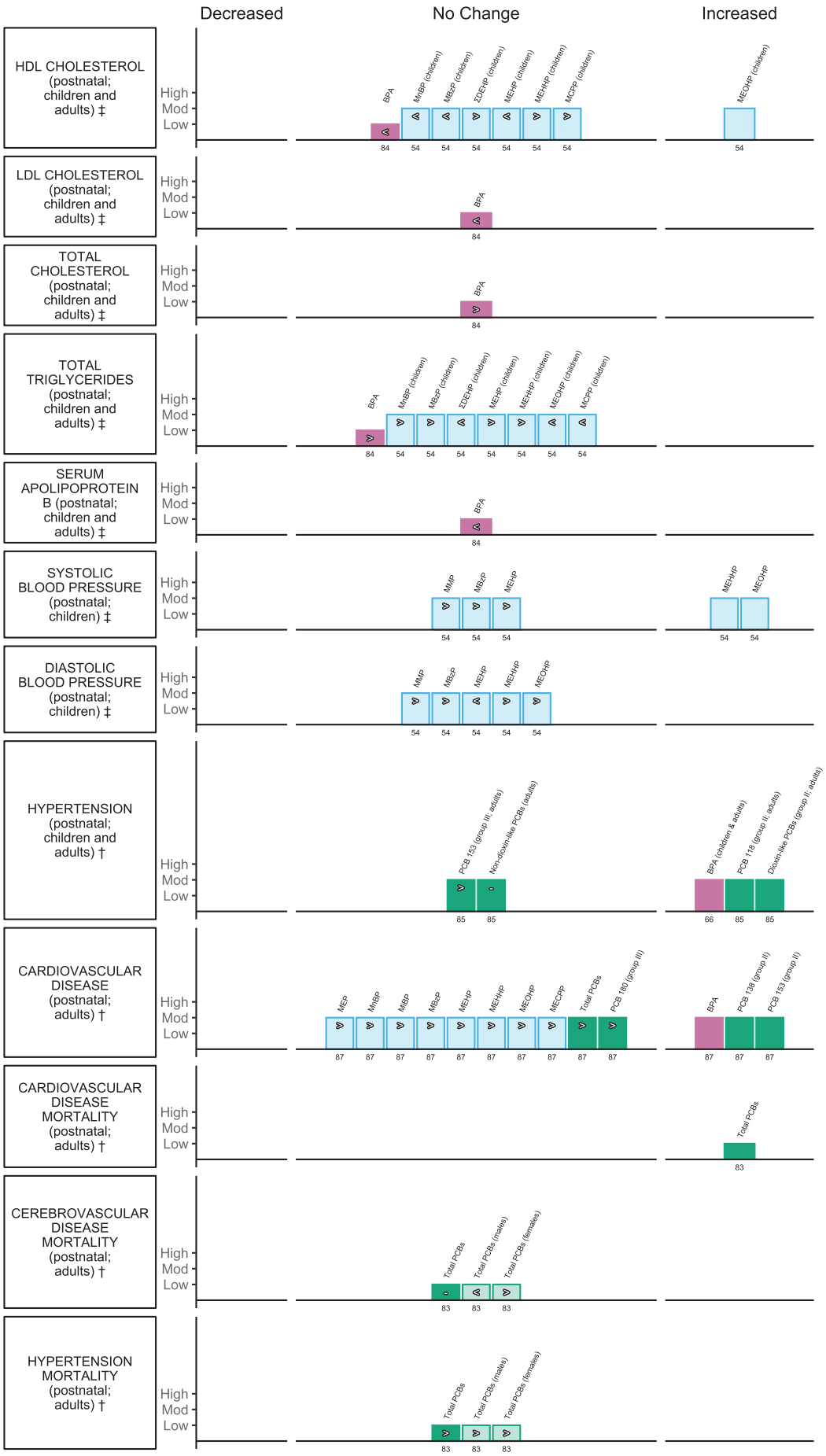

Figure 8 Harvest plot of exposure to plastic-associated chemicals and circulatory outcome measures. *(Continued on next page)*

Figure 8 continued The plastic-associated chemicals included are bisphenol A (BPA) (pink); phthalate monoester metabolites (blue), including monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(3-carboxypropyl) phthalate (MCPP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and the molar sum of the di(2-ethylhexyl) phthalate metabolites (∑DEHP); and flame retardants (green) including polychlorinated biphenyl (PCB).

Outcome measures are either dichotomous (†) or measured on a continuous scale (‡). Outcomes measured include serum lipids encompassing concentrations in low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG) and apolipoprotein B (ApoB); child systolic blood pressure (SBP); child diastolic blood pressure (DBP); cardiovascular disease (CVD; for BPA and phthalates children also included with sampling frame [17]); CVD mortality; cerebrovascular disease mortality; hypertension and hypertension mortality.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4 and moderate (mod) quality a score of 5–8. Dark filled bars represent the primary analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no change (–) (the estimate of relative risk was 1 or regression coefficient or mean difference was 0), or decrease (<) in the measure or risk estimate.

scoring 4 [83] and 6 [84] respectively (Table 2; Suppl File 1.6). Consistent with many of the other outcomes reported here, reviews that informed this category failed to provide any evidence of an a priori protocol. In one review [85] and one pooled analysis [83] it was clear that data extraction was performed in duplicate. None of the reviews considered grey literature, and only one review provided clarity regarding study inclusion and exclusion and adequate details to completely assess the methods of synthesis used [66].

Serum lipid levels

Forty-nine meta-analyses, including both main and subgroup analyses from one systematic review and one pooled analysis, informed the association between BPA or phthalate metabolites exposure and measures of serum lipids in children and adults [54, 84]. Of the five main meta-analyses of children and adults, there was no significant association with BPA exposure and changes in HDL, LDL, TC, TG and ApoB; however, the majority of estimates tended to decrease, an undesirable effect in the case of HDL cholesterol, with increased exposure (3/5 EE; Figure 8; Suppl File 2.7) [84]. Similarly, in the 30 subgroup analyses of children and adults separately, including analyses for males and females for each outcome measure, the majority of serum lipid measures also tended to decrease, though not significantly (25/30 EE; data not plotted; Suppl File 2.7) [84].

One review presented 14 subgroup meta-analyses investigating the association between phthalate metabolites and HDL and TG in children [54]. Results for the main analysis for this review were excluded due to unit of analysis error. A beneficial increase in serum HDL levels was observed with increasing concentration of one DEHP metabolite, MEOHP, z 0.31, 95%CI 0.25 to 0.37, but with non-significant findings in each direction for two other DEHP metabolites, MEHHP and MEHP, and a much-attenuated overall finding for ∑DEHP, z 0.09, 95%CI –0.26 to 0.44. Of the other phthalate metabolites evaluated, there were non-significant decreases in serum HDL (undesirable) for MnBP and MBzP (2/3 EE), but an increase for the nonspecific phthalate metabolite MCPP (1/3 EE; Figure 8; Suppl File 2.7) [54]. The observed profile was largely inversed for serum TG, with non-significant beneficial decreases observed for increasing concentration of ∑DEHP, MEOHP and MCPP, and a non-significant undesirable increase in circulating TG with the remaining metabolites investigated (4/4 EE; Figure 8; Suppl File 2.7) [54].

Blood pressure and hypertension

One systematic review with ten subgroup meta-analyses informed the association between phthalates and SBP and DBP in children [54]. Results for the main analysis for this review were excluded due to unit of analysis error. All meta-analyses reported a positive association with SBP (5/5 EE) with increasing postnatal phthalate metabolites. For two metabolites, the association was significant: MEHHP, β 0.16, 95%CI 0.09 to 0.23, and MEOHP, β 0.12, 95%CI 0.12 to 0.24 (Figure 8; Suppl File 2.7) [54]. Similarly, positive associations were observed for DBP for the majority of metabolites investigated, (4/5 EE) except MEHP, where DBP decreased slightly with increasing concentration (Figure 8; Suppl File 2.7) [54].

Two reviews, including five meta-analyses informed the association between BPA and flame retardant exposure and hypertension [66, 85]. A significant increase in hypertension (SBP >140mmHg and/or DBP >90mmHg) was reported with exposure to BPA, OR 1.41, 95%CI 1.12 to 1.79 in adults (Figure 7; highest vs lowest exposure) [66]. Similarly, in the analyses investigating flame retardant exposure and hypertension (SBP >140mmHg and/or DBP >90mmHg; receiving medication or doctor diagnosed), a significant positive association with hypertension was observed with the sum of group II dioxin like PCBs (following the Wolff et al. classification [86]), OR 1.45 95%CI 1.00 to 2.12, and the individual group II PCB 118, OR 1.26, 95%CI 1.00 to 1.58 (highest to lowest exposure; Figure 8; Suppl File 2.7) [85]. A non-significant positive association was also reported with exposure to the non-dioxin-like group III PCB 153, but not with combined exposure to non-dioxin-like PCBs (Figure 8; Suppl File 2.7) [85].

Cardiovascular disease (CVD)

One systematic review comprising 13 main and subgroup meta-analyses informed the association between BPA, phthalate and flame retardant exposure and risk of CVD in children and adults [87]. Results for the two overall analyses for phthalates and PCBs were excluded due to unit of analysis errors. Of the main analyses evaluating BPA and three individual PCBs (138, 153, 180), 3/4 reported an increased risk of CVD with exposure to BPA OR 1.19, 95%CI 1.03 to 1.37, and the flame retardants PCB 138, OR 1.35, 95%CI 1.10 to 1.66, and PCB 153, OR 1.35, 95%CI 1.13 to 1.62 (Figure 8; highest vs. lowest or per unit increase) [87]. Non-significant increased risk was observed for total PCBs and PCB 180 (Figure 8; Suppl File 2.7) [87]. Similarly, risk of CVD tended to increase, though non-significantly, with all eight phthalate metabolites investigated in subgroup meta-analyses (8/8 EE; Figure 8; Suppl File 2.7) [87].

Mortality—cardiovascular disease, cerebrovascular disease and hypertension

One pooled analysis of two highly exposed cohorts presented seven meta-analyses investigating mortality attributable to CVD, cerebrovascular disease and hypertension respectively, following incidents of PCB poisoning [83]. An increased risk of CVD deaths was observed with PCB poisoning with a reported a SMR of 1.3, 95%CI 1.0 to 1.7, though no significant change was observed for cerebrovascular disease deaths SMR 1.0, 95%CI 0.8 to 1.29, which was consistent in sub-group meta-analysis for males and females (Figure 8; 2/2 EE increase; Suppl File 2.7) [83]. A non-significant increase in deaths attributable to hypertension was similarly reported in exposed adults, SMR 1.6, 95%CI 0.9 to 2.9 (Figure 8) [83], a trend maintained in the sub-analyses for both males and females (Figure 8; 2/2 EE; Suppl File 2.7) [83].

RESPIRATORY OUTCOMES

There were four respiratory outcomes reported in three systematic reviews with meta-analyses and one pooled analysis. Of these, the evidence suggests an association with increased risk of asthma with some phthalate metabolites, MBzP in particular, bronchitis in children with exposure to PCBs and allergic rhinitis with exposure to PFOA (Figure 9). Respiratory outcomes were addressed for phthalates, flame retardants and PFAS. Outcomes included asthma in three reviews [88–90], wheeze in two reviews [89, 91], and bronchitis [91] and allergic rhinitis [89] in one review each (Table 2). Exposure to plastic-associated chemicals included both prenatal and postnatal for children (Table 2). The majority of the included reviews assessed categorical, high versus low, exposure.

The reviews that informed this outcome category scored between 5 and 9 on the AMSTAR tool, whereas the pooled analysis [91] scored 3 (Table 2; Suppl File 1.6). The evidence informing the impact of phthalates and PFAS was all high to moderate quality. None of the included studies searched grey literature, nor provided complete indication of study inclusion and exclusion, nor considered the results of appraisal (which was performed by all except in the pooled analysis) in the analysis. This was with the exception of one review by Li et al. [88], which was also the only review to be informed by an a priori protocol. Where it could be adequately determined, the statistical analysis appeared appropriate in all of the studies that informed this outcome.

Asthma

Two systematic reviews and one published meta-analysis presenting 88 main and subgroup meta-analyses informed the association between plastic-associated chemical exposure and asthma (highest versus lowest exposure) [88–90]. Main analyses presented by Wu et al. [90]

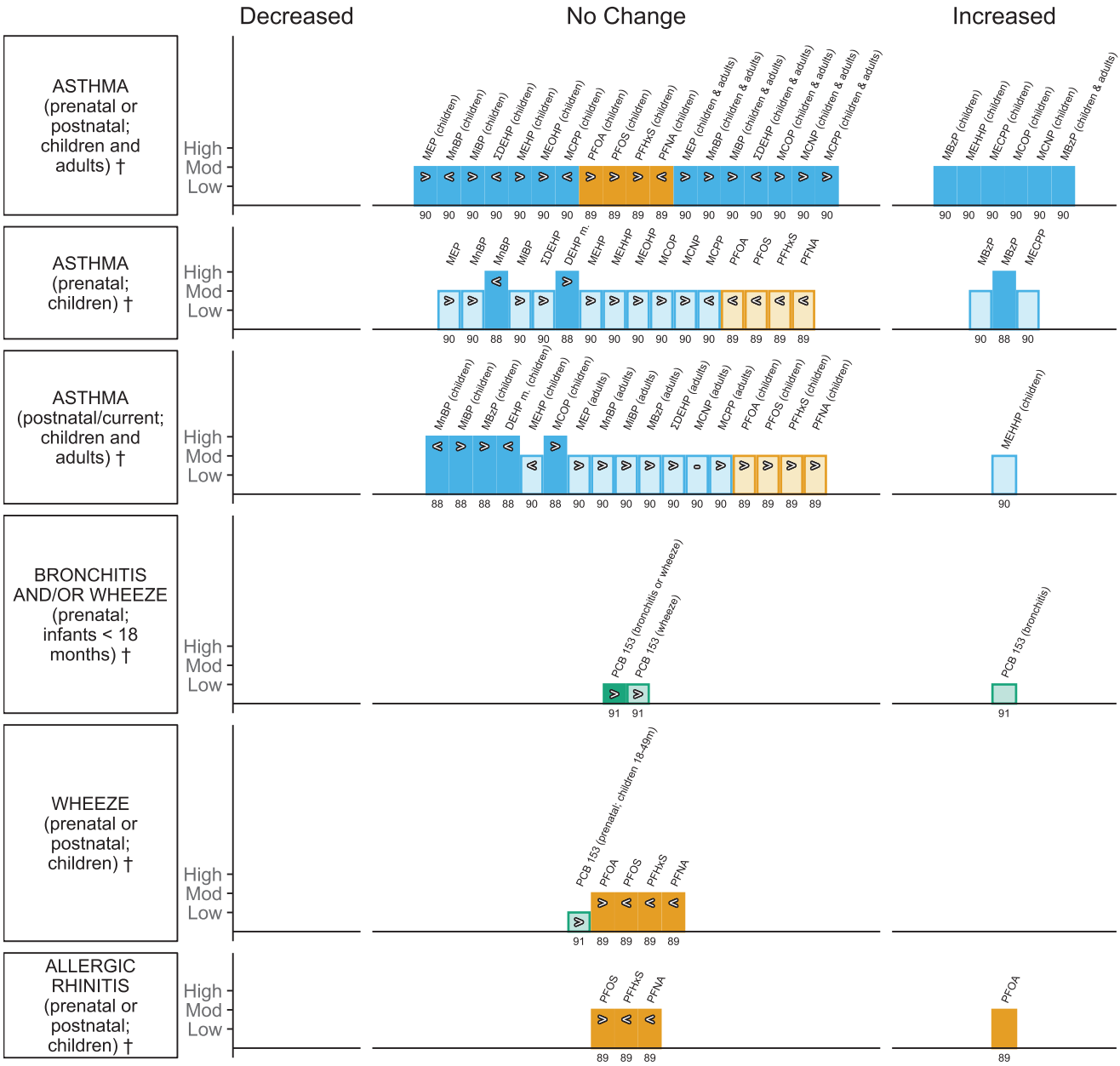

Figure 9 Harvest plot of exposure to plastic-associated chemicals and respiratory outcomes.

Plastic-associated chemicals included are phthalate monoester metabolites (blue), encompassing monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), molar sum of the di(2-ethylhexyl) phthalate metabolites (∑DEHP), mono(carboxyisooctyl) phthalate (MCOP), monocarboxyisononyl phthalate (MCNP), and mono (3-carboxypropyl) phthalate (MCPP); flame retardants (green) including polychlorinated biphenyl (PCB); and per- and polyfluoroalkyl *substances* (PFAS) (orange) including perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFNA).

Outcomes are dichotomous (†) and include risk of asthma, bronchitis, wheeze and allergic rhinitis.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4, moderate (mod) quality a score of 5–8 and high quality a score of 9–11. Dark filled bars represent the primary analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no change (–) (the relative estimate was 1), or decrease (<) in the estimate.

considered 11 urinary phthalates as well as ∑DEHP. In both main and subgroup analyses investigating phthalate metabolites in children (Figure 9; Table 2), a statistically significant increase in risk of asthma with MBzP was reported OR 1.17, 95%CI 1.05 to 1.29 [90]. In further main analyses, significant associations with asthma in children were also observed with DEHP metabolites MEHHP, OR 1.13, 95%CI 1.03 to 1.24, and MECPP, OR 1.20, 95%CI 1.00 to 1.42, as well as with metabolites of related higher molecular weight phthalates, including mono (carboxy-isooctyl) phthalate (MCOP), OR 1.19, 95%CI 1.02 to 1.37, and mono (carboxynonyl) phthalate (MCNP) OR 1.15, 95%CI 1.00 to 1.31 (Figure 9; Suppl File 2.8) [90]. Similarly, risk of asthma in children tended to also increase though not significantly, with some remaining metabolites investigated, except for MnBP, MCPP and ∑DEHP (Figure 5; 4/7 EE; Suppl File 2.8) [90]. This relationship remained consistent when timing of exposure was explored in children, with significant associations observed with prenatal MBzP, showing an OR range of 1.15 to 1.38 and MECPP, OR 1.23, 95%CI 1.03 to 1.47 (Figure 9; Suppl File 2.8) [90]. The positive trend with phthalates was maintained across the majority of remaining analyses (11/13 EE; Figure 9; Suppl File 2.8) [90]. Results were less equivocal with postnatal phthalates in children. One metabolite exposure, MEHHP, resulted in a significant increase in risk of asthma, OR 1.30, 95%CI 1.09 to 1.65 (Figure 9) [90], and three of the remaining six analyses showed non-significant increases (3/6 EE; Figure 9; Suppl File 2.8) [90]. The majority of further sub-analyses in the general population showed a trend to towards an increase in risk of asthma with phthalate metabolites when restricted to postnatal assessment and also in adults only (13/15 EE; Figure 9; postnatal only, data not plotted; Suppl File 2.8) [90]; a significant association was observed for postnatal exposure to MBzP (Figure 9; Suppl File 2.8) [90]. No significant associations were reported with subgroups of males or females with over half of analyses tending towards positive association (7/12 EE) and the remainder negative (5/12 EE; data not plotted; Suppl File 2.8) [90].

Four meta-analyses from one review assessed the association between exposure to PFAS and risk of asthma in children up to 19 years old (Table 2) [89]. No statistically significant risk of asthma was reported; however, small increases were observed with exposure to PFOA, PFOS, PFHxS (3/4 EE) though not PFNA (Figure 9; Suppl File 2.8) [89]. Similar non-significant increases were observed when only postnatal exposure was included for each analysis (4/4 EE; Figure 9; Suppl File 2.8) [89]. However, this trend was reversed with prenatal exposure (4/4 EE; Figure 9; Suppl File 2.8) [89].

Bronchitis and/or wheeze

One pooled analysis with six meta-analyses informed the association between flame retardants and bronchitis in children less than 18 months [91]. Increasing PCB 153 exposure was associated with an increased risk of bronchitis in these children, RR per doubling exposure 1.06, 95%CI 1.01 to 1.12 (Figure 9; Suppl File 2.8) [91]. This positive association was no longer significant when exposure was analysed categorically (2/2 EE; highest, medium versus lowest; data not plotted; Suppl file 2.8) [91]. Similarly, three main analyses assessing risk of bronchitis and/or wheeze in infants reported a small increase in RR per doubling of exposure 1.02, 95%CI 0.96 to 1.12 (Figure 9; Suppl File 2.8) [91], whereas the direction of this association was reversed with categorical analysis (highest, medium vs. lowest), though neither risk estimates were statistically significant (2/2 EE; Figure 9; Suppl File 2.8; data not plotted) [91]. Similar results were reported in the cohorts analysed when considering wheeze alone, with small positive associations observed per doubling of exposure in children under 18 months old and also in the cohort with an average age over 18 months (2/2 EE; Figure 9; Suppl File 2.8) [91]. Similar, non-significant positive associations were observed for these outcomes with categorical analyses, comparing high and medium versus low PCB exposure (3/4 EE; data not plotted; Suppl File 2.8) [91]. Exposure to PFAS and risk of wheeze in children was also assessed in four meta-analyses from one review (Table 2) [89]. No significant risk of wheeze was reported. However, small decreases in risk were observed with exposure to PFOS, PFHxS, PFNA (3/4 EE) though not PFOA (Figure 9; Suppl File 2.8) [89]. An identical trend for each PFAS was observed when prenatal exposure was considered alone (4/4 EE; data not plotted; Suppl File 2.8) [89].

Allergic rhinitis

Eight meta-analyses from one review assessed the association between exposure to PFAS and risk of allergic rhinitis in children up to 19 years old (Table 2) [89]. A significant association with increased risk of allergic rhinitis was observed with exposure to PFOA, OR 1.32, 95%CI 1.13 to 1.55, while exposure to PFOS only increased risk minimally. Conversely, PFHxS and PFNA exposure led to small decreases in the observed risk estimates (Figure 9; Suppl File 2.8) [89]. A similar trend for each PFAS, including significant risk with PFOA was maintained with prenatal exposure only (4/4 EE; data not plotted; Suppl File 2.8) [89].

SKIN-RELATED OUTCOMES

One skin related outcome was reported in one systematic review with meta-analyses [89]. In this review, a distinction was made between studies of atopic dermatitis and eczema, and these were meta-analysed separately. However, no justification was provided for the distinction between these two closely related terms and a combined analysis is not provided. The data as analysed suggest prenatal exposure to PFNA may have a protective effect against risk of eczema in children (Figure 10); however, this is unclear as this significant effect was not replicated in the analysis of atopic dermatitis studies. Exposure to plastic-associated chemicals was prenatal and details of type of samples measured are provided in Table 2.

The review that informed the evidence regarding the impact of PFAS on this outcome category was rated as moderate quality, scoring 7/11 on the AMSTAR tool (Table 2; Suppl File 1.6). As with other reviews in this field, there was no evidence of an a priori protocol, grey literature was not considered, nor was a complete list of included and excluded studies provided. While appraisal of the included studies was performed, nowhere was it apparent that these results were then considered further in the analysis presented.

Atopic dermatitis and eczema

Eight meta-analyses from one systematic review informed the association between prenatal PFAS exposure and atopic dermatitis and eczema (Table 2; high versus low exposure) [89]. Exposure to PFNA appeared to result in a statistically significant decrease in risk of eczema, OR 0.89, 95%CI 0.80 to 0.99, and a similar non-significant decrease in risk of atopic dermatitis (2/2 EE; Figure 10). A reduction in the risk of eczema was also observed with PFOS and PFOA (2/2 EE; Figure 10; Suppl File 2.9) [89]. Risk of eczema tended to increase with exposure to PFHxS (1/4 EE) and atopic dermatitis

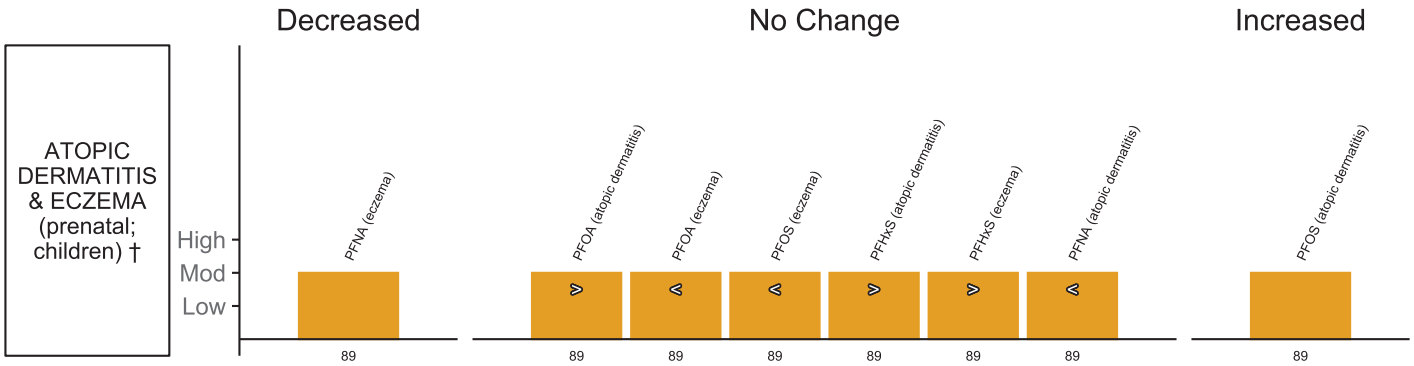

Figure 10 Harvest plot of prenatal exposure to plastic-associated chemicals and skin-related outcomes in children.

Plastic-associated chemicals included are per- and polyfluoroalkyl *substances* (PFAS) (orange), encompassing perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFNA).

Outcomes are dichotomous(†) and include atopic dermatitis and eczema.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Moderate (mod) quality reflects a score of 5–8. Dark filled bars represent the primary analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>) or decrease (<) in the measure or risk estimate.

with PFOA, PFOS and PFHxS exposure (3/4 EE) Figure 10; Suppl File 2.9) [89]. However, only PFOS was significantly associated with atopic dermatitis (Figure 10; Suppl File 2.9) [89].

CANCER OUTCOMES

The association between plastic-associated chemical exposure and occurrence of three different types of cancer was reported in six systematic reviews with meta-analyses and one pooled analysis. Of these, the evidence suggests an association with an increased risk of non-Hodgkin's lymphoma (NHL) with occupational PCB exposure, as well as increased risk of breast cancer with exposure to four individual PCB congeners (Figure 11). There was, however, also evidence of a protective effect for chronic lymphocytic leukemia—a subtype of NHL. A further 11 cancer-related mortality outcomes were evaluated in one systematic review with meta-analyses and one pooled analysis. Evidence was found of an increased risk for all cancer-related mortality in males, liver cancer mortality in females and mortality attributable to lung cancer and malignant melanoma. Flame retardants, specifically PCBs, were the only plastic-associated chemicals evaluated for cancer outcomes. Breast cancer was the most commonly investigated type of cancer reported in four reviews [62, 92–94], followed by NHL and its subtypes in three reviews [92, 95, 96]. Cancer specific mortality was reported in one review [95] and one pooled analysis [83] and all cancer mortality in one pooled analysis [83]. Cancer-related mortality was predominantly assessed in highly exposed cohorts arising from occupational exposure or incidents of PCB poisoning (Table 2).

The reviews that informed the impact of PCBs on this outcome category ranged from moderate to low quality scored between 2 and 8 on the AMSTAR tool (Table 2; Suppl File 1.6). Only one review was informed by an a priori protocol [96], whereas only two of the included studies provided clear indication of duplicate data extraction [83, 93]. Consistent with most of the reviews informing this project, grey literature searching was not performed by any review and clear reporting of excluded studies in particular was also poor, with only one review [94] and the pooled analysis [83] informing this outcome providing the expected details. Half of the reviews critically appraised the included studies and of those that did [93, 94, 96], only the review by Zhang et al. [93] considered the results of the appraisal further in the analysis, which was appropriate in most studies (Suppl File 1.6).

Breast cancer

Twenty-two meta-analyses informed the association between flame retardant exposure and risk of breast cancer. Three reviews presented main analyses indicating non-significant associations between total PCB exposure and breast cancer, range of OR 1.09 to 1.33 (highest versus lowest exposure) [62, 92, 93]. This statistically non-significant positive association was maintained in subgroup analyses restricted to the samples taken from serum and adipose tissue only (2/2 EE; Table 2; data not plotted; Suppl File 2.10) [93]. The remaining main and subgroup analyses assessed exposure to 17 individual PCB congeners (Table 2; Figure 11) [94]. A significant increased risk of breast cancer was reported with exposure to PCB 187 (Group I), OR 1.18, 95%CI 1.01 to 1.39, PCB 105 (Group II), OR 2.22, 95%CI 1.18 to 4.17, PCB 99 (Group III), OR 1.36, 95%CI 1.02 to 1.80, and PCB 183 (Group III), OR 1.56, 95%CI 1.25 to 1.95 (Figure 11; Suppl File 2.10) [94]. Small, statistically non-significant increases were observed for most of the remaining congeners investigated (10/13 EE; Group I 1/2 EE; Group II 6/8 EE; Group III 2/2 EE; Figure 10; Suppl File 2.11) [94].

Non-Hodgkin's lymphoma (NHL)

Fourteen meta-analyses, including main and subgroup analyses, informed the association between flame-retardant exposure and risk of NHL in the general population. A significant increased risk of NHL with exposure to total PCBs was reported in the two available main analyses, OR range of 1.4 to 1.5 (Figure 11) [92, 95]. Five individual PCB congeners were assessed in two reviews; both reviews reported increased risk estimates for NHL with exposure to Group III PCBs 153, RR/OR range of 1.1 to 1.5 (2/2 EE) and PCB 180, RR/OR range of 1.07 to

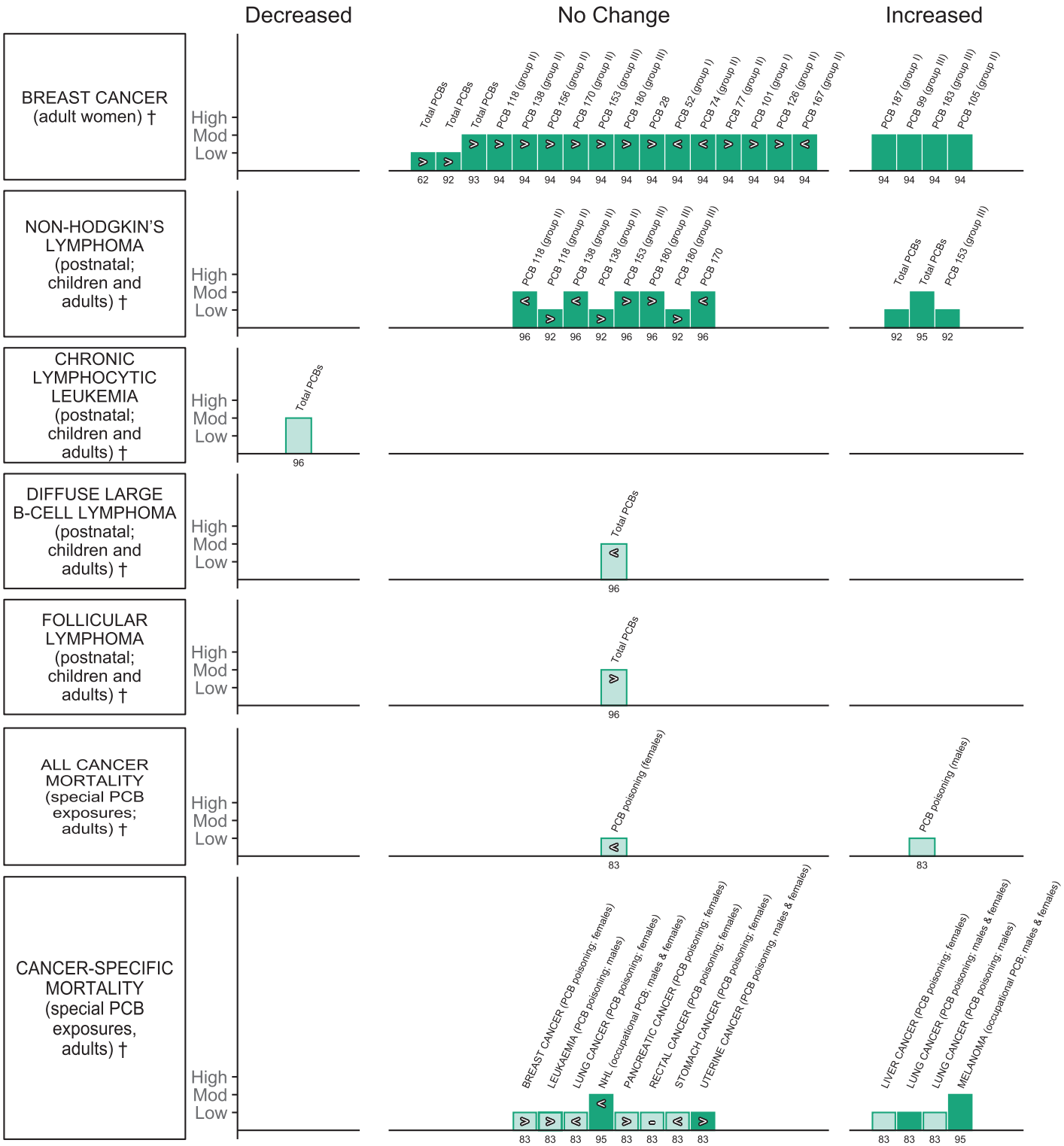

Figure 11 Harvest plot of exposure to plastic-associated chemicals and cancer outcomes.

Plastic-associated chemicals included are flame retardants (green), including polychlorinated biphenyl (PCB) further organised by group – gp I (44, 52, 101, 107, 187, 201), gp II (105, 118, 138, 156, 167, 170) and gp III (99, 153, 180, 183, 203) as well as PCB 28.

Outcomes are dichotomous (†) and include breast cancer, non-Hodgkin's lymphoma (NHL), NHL subtypes—chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL)—and cancer-specific mortality: all cancer, breast cancer, leukaemia, liver cancer, lung cancer, melanoma, NHL, pancreatic cancer, rectal cancer, stomach cancer and uterine cancer. PCB poisoning refers to populations exposed to PCB-contaminated food and PCB occupational refers to populations occupationally exposed to PCBs.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4 and moderate (mod) quality a score of 5–8. Dark filled bars represent the primary analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>) or decrease (<) in the measure or risk estimate.

1.4 (2/2 EE; Figure 11; Suppl File 2.10) [92, 96], which was found to be statistically significant in one (Figure 11; Suppl File 2.10) [92]. Results were equivocal for the remaining congeners, with one review reporting statistically non-significant increases for PCB 118 and 138 (2/2 EE; Group II; OR range of 1.08 to 1.32; Figure 11; Suppl File 2.10) [92] and the other, non-significant decreased risk estimates for these same congeners and also PCB 170 (3/3 EE; Group II; Figure 11; Suppl File 2.10) [96]. Of three subgroup analyses investigating subtypes of NHL, one estimate corresponded to a significant protective effect for chronic lymphocytic leukemia (CLL) with exposure to total PCBs, RR 0.63, 95%CI 0.39 to 0.87 (Figure 11) [96]. A reduction in risk of diffuse large B-cell lymphoma (DLBCL), though non-significant, was also reported, whereas a non-significant positive association was observed for follicular lymphoma (FL) with exposure to PCBs (Figure 11; Suppl File 2.10) [96].

Cancer mortality

Fourteen meta-analyses informed the association between flame-retardant exposure and risk of cancer mortality in adults, with the majority reported according to gender. The majority of analyses were provided by a pooled analysis assessing two cohorts with high incident exposure from poisoning [83]. A significant association with mortality attributable to cancer and exposure to PCBs was reported for all cancer mortality in males, SMR 1.3, 95%CI 1.1 to 1.6, liver cancer mortality in females, SMR 2.0, 95%CI 1.1 to 3.6, lung cancer mortality in both males and females, SMR 1.5, 95%CI 1.1 to 2.1 and also lung cancer mortality among males only, SMR 1.2, 95%CI 1.2 to 2.3 (Figure 11) [83]. Increased risk of malignant melanoma mortality in males and females was also significant, SMR 1.32, 95%CI 1.05 to 1.64 (Figure 11) [95]. No significant risk in cancer mortality was observed with PCB exposure by poisoning in eight other meta-analyses; however, a trend to increased risk of mortality from breast cancer and uterine cancer in women, leukaemia and pancreatic cancer was reported (4/8 EE). Conversely, mortality in women attributable to all cancers, lung cancer and stomach cancer, decreased with PCB poisoning, though not significantly. No change was observed in rectal cancer mortality in females (Figure 11; Suppl File 2.10) [83]. A non-significant decreased risk in NHL mortality was observed in workers occupationally exposed to PCBs, SMR 0.94, 95%CI 0.73 to 1.23 (Figure 11) [95].

OTHER OUTCOMES

Two additional mortality outcomes, hepatic disease mortality and all-cause mortality, were reported in one pooled analysis, each in relation to flame retardants following poisoning incidents in two cohorts (Table 2) [83]. Evidence suggests an association with increased risk of death attributable to hepatic disease and increased death from all causes in adults exposed to flame retardants (Figure 12).

The pooled analysis investigating hepatic disease mortality and all-cause mortality with PCB exposure scored 4/11, low quality, with the AMSTAR tool (Table 2; Suppl file 1.6). The pooled analysis provided clear indication of duplicate data management, in which cohorts were included and their details. Appropriate statistical analysis was performed.

Hepatic disease mortality

A statistically significant increase in mortality attributable to hepatic disease with PCB exposure was reported in a main analysis of males and females with SMR 1.5, 95%CI 1.0-2.4, and in the subgroup of males only, SMR 1.9, 95%CI 1.3 to 2.8; however, not in females, SMR 1.0, 95%CI 0.5–1.9 (Figure 8; Suppl File 2.7) [83].

All-cause mortality

A statistically significant increase in mortality with PCB exposure was reported in a main analysis of with SMR 1.1, 95%CI 1.1 to 1.2, and in the subgroup of males only, SMR 1.2, 95%CI 1.1 to 1.3, but not in females, SMR 1.1, 95%CI 0.9 to 1.2 (Figure 12; Suppl File 2.11) [83].

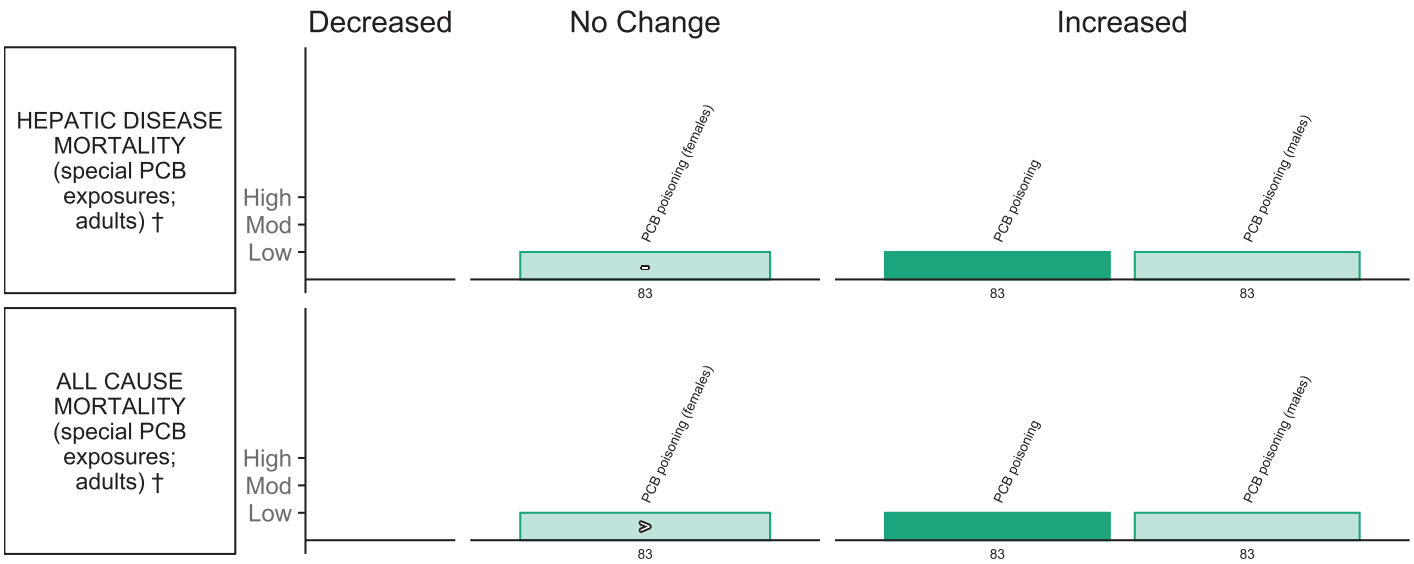

Figure 12 Harvest plot of exposure to plastic-associated chemicals and other outcomes.

Plastic-associated chemicals included are flame retardants (green), including polychlorinated biphenyls (PCB) in populations exposed to contaminated food.

All outcomes are dichotomous (†). Outcomes measured include mortality attributable to hepatic disease and all-cause mortality.

Each bar represents an individual effect estimate from the corresponding review, which is indicated by the number below each bar. The height of the bar represents the quality score of the review assessed using the AMSTAR tool. Low quality reflects a score of 1–4 and moderate quality a score of 5–8. Dark filled bars represent the primary analyses of each review; light filled bars represent sub-group analyses. Bars have been assigned as an increase or decrease (columns) in the measure where the change is statistically significant. Remaining bars appearing under 'no change' indicate direction of effect as an increase (>), no change (–) (the relative estimate was 1), or decrease (<) in the measure or risk estimate.

DISCUSSION

ASSOCIATIONS BETWEEN PLASTIC-ASSOCIATED CHEMICAL EXPOSURE AND HEALTH OUTCOMES

For each of the chemical groups for which meta-analytical data were retrieved (i.e., BPA, phthalate plasticisers, PCBs and PBDEs flame retardants, as well as some PFAS), significant association was established for at least one adverse human health outcome. Despite a multitude of chemicals that are used to make plastic [5, 21, 22], and an exponential increase in plastic production [1], there are limited epidemiological data meta-analysed to evaluate the safety of these chemicals in humans. For our search period, we found only a total of 62 systematic reviews with meta-analyses meeting our initial eligibility criteria, with 10 of these excluded due to unit of analysis errors [43]. We report on 759 meta-analyses related to a range of health outcomes.

Direction of association is not anticipated to be consistent across different chemical classes captured within this umbrella review, but consistency of findings within a chemical class provides additional evidence of association reflecting an underling biological causal pathway. Considering the regulatory implications of this work, action would be at a chemical level, not a health-outcome specific level. Here, we therefore reframe and summarise the key findings aggregated by chemical class.

BPA exposure was found to be significantly associated with adverse child reproductive, endocrine, nutritional and circulatory outcomes. This is seen in the anoclitoral distance in girls with prenatal exposure, T2D in adults, insulin resistance measured as HOMA-IR in both adults and children, PCOS in women, increased risk of obesity (separately established in both children and adults), elevated waist circumference and overweight status in adults (with a consistent trend in children for each), hypertension (on evaluation of children and adults combined) and CVD.

Exposure to phthalates is significantly associated with adverse birth, child reproductive, endocrine, child neurodevelopment and circulatory outcomes. This presents as SPL in pregnant women (with strongest evidence for DnBP and DEHP, but with consistent trends for all others meta-analysed),

decreased AGD in newborn boys with prenatal exposure (specifically evaluated for DEHP exposure) and insulin resistance measured as HOMA-IR in both adults and children (with strongest evidence for diisobutyl phthalate [DiBP], butyl benzyl phthalate [BBP] and DEHP, but with consistent trends for all others meta-analysed and association established for total phthalate exposure). Furthermore, certain phthalates are associated with decreased birth weight of newborns with prenatal exposure (diethyl phthalate [DEP]), T2D in adults (DiBP), precocious puberty in adolescent girls (DEHP), a number of measures of reduced sperm quality in men (DnBP and BBP with decreased sperm concentration, DnBP and DEHP with decreased sperm velocity, DEP and BBP with DNA damage as measured by increased CE and TDM) and endometriosis in women (DEHP when measured as its metabolite MEHHP and with similar trends for all other DEHP metabolites meta-analysed). However, for these, association for individual phthalates was not established across all other phthalates evaluated and does not therefore establish adverse associations for phthalates as a group. In addition, associations were seen for decreased fine motor and psychomotor development after prenatal exposure, and increased SBP in children following postnatal exposure. There were additional concerning findings for child neurodevelopment, nutritional and respiratory outcomes. These presented as decreased cognitive development and IQ loss in children, with strong evidence for postnatal exposure to DEHP, but inconsistent findings for prenatal exposure to MEP specifically. Additionally, certain phthalates (BBP) are associated with asthma, but lacking consistent trends for other individual phthalates, preventing any conclusions on phthalates as a group. A recent narrative review on phthalates and allergic diseases such as asthma and rhinoconjunctivitis, also reports a reason for concern [97]. Furthermore, a consistent trend of association with CVD is also found for all phthalates evaluated, although no individual finding was statistically significant.

PCBs, PBDEs and PFAS are each significantly associated with adverse birth outcomes, which is seen in the decreased birth weight of newborns with prenatal exposure, and additionally with decreased birth length for PFAS. PCBs also show significant associations with adverse adult reproductive and endocrine outcomes. This is reflected in T2D in adults and endometriosis in women. Of concern within endocrine outcomes, exposure to PBDEs and certain PFAS are also associated with changes in measures of thyroid function (increased TT4 for high exposure to PBDEs, increased fT4 for PFOS and decreased TT4 for PFHxS). However, similar association was not established for lower exposure to PBDEs, or for other PFAS, and we cannot draw conclusions of adverse associations for PDBEs and PFAS as a group. For PCB exposure, significant associations were also found for adverse circulatory, respiratory, cancer and other outcomes. This is due to increased CVD and hypertension after PCB exposure, mortality from CVD after PCB poisoning as well as bronchitis in infants following prenatal exposure. Additionally, there were significant associations for multiple types of cancer in the general population and cancer mortality in special risk populations (i.e., occupationally exposed or poisoning). Lastly, PCB poisoning was significantly associated with mortality from hepatic disease in males, and from all-cause mortality for men and women combined. While not significant, there is also a trend for increased hypertension mortality after PCB poisoning. It is important to note that many of these studies are based on PCB poisoning which occurred through the ingestion of contaminated rice bran that had been contaminated during processing [83, 92]. While exposure in these circumstances was at high levels and not directly through use in plastics, studies of special exposure populations give highly relevant information on potential health impacts of chemicals at higher exposure and complement separate findings of studies in the general population. PBDE exposure is significantly associated with adverse child neurodevelopment outcomes, seen as reduced children's cognitive development and IQ loss after prenatal exposure to BDE-47. Furthermore, exposure to PFAS is significantly associated with adverse nutritional outcomes. This is reflected in the increased risk for overweight status after prenatal exposure and BMI after pre- or postnatal exposure in children. While there was a significant increase of allergic rhinitis after PFOA exposure, this association was not seen for other PFAS analysed. Furthermore, while prenatal exposure to PFOA was associated with ADHD in girls, inconsistent findings were reported for boys, as well as for exposure to PFOS.

There was evidence for only three protective effects. One was seen for associations between phthalate exposure and timing of puberty. However, while the abnormal timing of puberty was less

common in boys with higher phthalate exposure, adverse associations were found in girls for this class of chemicals. Higher DEHP exposure when measured as its metabolite MEOHP is associated with increased (beneficial) HDL levels. However, there was an inconsistent trend in the opposite direction when measured as either of two other DEHP metabolites (MEHHP or MEHP). Additionally, increased PCB exposure is associated with reduced incidence of chronic lymphocytic leukemia, a subtype of NHL, but there was and increased incidence of NHL as a whole. Therefore, none of these specific exposure outcome associations provide reassurance regarding safety.

CHEMICALS IDENTIFIED

Due to the hierarchal relationship between of primary publications and systematic reviews, considering both volume and timing, it is not surprising that this umbrella review captured a narrow range of chemicals that are, or were, common high production volume plastic-associated chemicals and have been suspected to be harmful to human health for some time, namely BPA, phthalates, PCBs, PBDEs, and PFAS. BPA is primarily (95%) used in the production of polycarbonate plastics and polymer resins [98]. Similarly, ortho-phthalate diesters comprise 85% of the total plasticiser market; as a specific example, ~97% of DEHP is used as a plasticizer, with the remainder being predominantly used as solvents [99]. PCB flame retardants had an application in plastics alongside their major application in electrical capacitors and heat exchangers [100–102]. They are still present in modern recycled plastics as legacy chemicals [103] and are included in key comprehensive lists of plastic-associated chemicals [5, 21, 22]. PBDEs were used in substantial quantities in the manufacture of plastic components of electronic devices and in polyurethane furniture [104]. PFAS are a large family of chemicals with applications including protective coatings for food packaging, textiles and furniture, and the production of fluoropolymers used in non-stick cookware and waterproof fabrics [77, 105]. PFAS may also form during surface fluorination of plastic packaging containers [106, 107].

In addition, there is a paucity of systematic and meta-analysed data for the plastic-associated chemicals that are replacing those that have been shown to be harmful to human health but are increasing in production volumes. For example, due to health concerns [108] and concomitant regulation [109, 110], BPA is being replaced by bisphenol analogues such as Bisphenol F and Bisphenol S despite emerging concerns about their safety [111]. Such replacement, or "regrettable substitution" [112] is similarly occurring for PDBEs with replacement by OPEs [113], and for phthalates with phthalate substitutes [99]. Furthermore, there is a gap in the primary literature on micro- and nanoplastic exposure and human health outcomes [25, 114], which explains the absence of systematic reviews and meta-analyses.

COMPARISON WITH OTHER STUDIES

To our knowledge, this study is first to investigate the complete, high-level, evidence for human health effects of plastics and plastic-associated chemicals across a broad range of plastic chemical groups. However, there have been other overviews with narrower focus or alternative systematic methodologies.

Eales et al. [26] recently presented a structured overview of human health effects of phthalate plasticisers. That review was narrower in scope than our umbrella review in terms of the breadth of plastic-associated chemicals considered, but broader in including narrative reviews. Allowing for this, findings are highly consistent. As with our umbrella review, the authors find a consistent pattern of association between prenatal phthalate exposure and decreased AGD in boys, and moderate evidence for an association between phthalate exposure and low birth weight, endometriosis and T2D. Somewhat stronger findings for abnormal sperm-quality measures (evaluated to meet their criteria for robust evidence) are likely to reflect the conclusions of several reviews without meta-analysis and therefore omitted in our umbrella review, including in particular a high-quality review by Radke et al. [113] applying the United States Environmental Protection Agency's Integrated Risk Information System (IRIS) systematic review methods. Findings of some evidence of associations with decreased gestational age at birth (prematurity), changes in sex hormones, decreased anofourchette distance in girls, and lower antral follicle count in women are similarly

based on reviews without meta-analysis excluded in our umbrella review. Whilst omitted from our umbrella review by design, these narrative findings must not be dismissed; in the absence of meta-analysis, they may reflect the best available evidence for these exposure-outcome combinations. Furthermore, Eales et al. included a meta-analysis of association with anofourchette distance [114] that we excluded here due to unit of analysis errors [43]. Conversely, we additionally report association between phthalate exposure and SPL evaluated in a 2020 review [48], which may have been published after the search undertaken by Eales et al. [26]. Our findings for an association between phthalate exposure and precocious puberty similarly reflect two additional systematic reviews that were published in 2020 [55, 56].

Consistent with our umbrella review, Eales et al. [26] also find robust association between postnatal phthalate exposure and adverse child cognitive development / lower IQ, robust association between exposure to the phthalate BBP and childhood asthma and mixed evidence of association with obesity, BMI and waist circumference, which was strongest for DEHP and adult obesity. Stronger conclusions from Eales et al. [26] in relation to prenatal exposure are likely to reflect the findings of an additional review without meta-analysis that was omitted in our umbrella review [115]. A finding of moderate evidence of association of phthalate exposure with ADHD, and some evidence of association with autism spectrum disorder (ASD), are similarly based on reviews without meta-analysis excluded here due to unit analysis errors [116, 117]. Eales et al. [26] similarly finds some evidence of association with atopic dermatitis [118] and, in addition, hearing disorders [119] and markers of oxidative stress [120]. A finding of moderate evidence of association with breast cancer is based on a study excluded here due to the statistical approach in the meta-analyses [121]. Whilst omitted from our umbrella review by design, findings without meta-analysis must not be dismissed since they may reflect the best available evidence for these exposure-outcome combinations. Conversely, we additionally report association between phthalate exposure, specifically DEHP, and increased SBP based on the 2019 meta-analysis by Golestanzadeh et al. [54], the details of which were in supplementary material that may not have been reviewed by Eales et al. [26], although Golestanzadeh et al. [54] do also confirm their findings of association between various phthalate and increased blood pressure in the main body of their publication.

Similarly, Lin et al. [27] recently published an umbrella review of human health outcomes of BPA exposure. That umbrella review is confined to a single plastic-associated chemical, BPA, selects only the most recently published meta-analysis for each exposure-outcome association, in contrast to the vote-counting approach here, and is based on a search strategy which extended to mid 2023. Allowing for these differences, the authors findings are highly consistent with those presented here. With respect to birth outcomes, a finding of significant association with preterm delivery and reduced gestational age at birth is based on a meta-analysis published outside our search dates [122]. On the one hand, a review the year prior, presented here, had found a trend in that direction which was not statistically significant [52]. On the other hand, with respect to child reproductive outcomes, AGD in girls is omitted as an outcome by Lin et al. [27], where a statistically significant association was found by Nelson et al. [59]. The reason for this omission by the authors is unclear as Nelson et al. [59] is referenced elsewhere in their review. Finally, two additional endocrine outcomes are evaluated within very recently published meta-analyses captured by Lin et al. [27]. Although beyond the range of our study, we note that there were no new statistically significant findings for either gestational diabetes or neonatal thyroid hormones. Other differences similarly do not impact our key findings. While Lin et al. [27] do not include findings for insulin resistance, fasting insulin and glucose, they do report on the clinical outcomes of T2D with the same findings as ours with statistically significant association on meta-analysis. A meta-analysis of BPA exposure and endometriosis [64], reported here, is also omitted by Lin et al. [27], but again with no significant association with BPA exposure. Study quality is assessed against AMSTAR 2 by Lin et al. [27], which is similar to our preferred measure of the original AMSTAR tool, but details of scoring are not presented to allow for any comparison.

In addition, statistically significant adverse associations that we find in this umbrella review are replicated in the findings of Lin et al., including evidence of association between exposure to BPA

and each of obesity, overweight status, increased wait circumference, CVD and hypertension. An additional finding by Lin et al. [27] of association between BPA and decreased HDL is reported based on a meta-analysis by Fu et al. [87]. No statistically significant findings are reported for any other lipid parameters, consistent with our own findings. While Fu et al. [87] do report finding correlation between BPA and lower HDL, details of that meta-analysis are not available in either the paper or associated supplementary material. Our findings for lipid parameters are instead based on an analysis by Dunder et al. [84] the previous year, who do not find statistically significant association with HDL. There are no other differences in findings with respect to other papers within the scope of both umbrella reviews, although there are a number of additional findings by Lin et al. [27] based on very recently published meta-analyses beyond the scope of this study, notably including statistically significant adverse associations with allergic respiratory and skin disease, immunological and renal parameters [123, 124].

STRENGTHS OF THE UMBRELLA REVIEW

Strengths of our review's eligibility criteria and search strategy include searches across two databases, including a major database indexing systematic reviews. In addition, given the large number of plastics and plastic-associated chemicals, we evaluated a broad scope of common polymers and high-volume plasticisers, flame retardants, bisphenols and PFAS, against all outcomes reported—an approach not undertaken to date. Moreover, we present our findings in qualitative harvest plots, complemented by the quantitative effect size estimates in the narrative of the results section, and supplementary material. This provides the audience with the full picture of the evidence base covered. Additional strengths include the combination of experimental and epidemiological evidence, the assessment of methodological quality against objective criteria (AMSTAR), and concomitant evaluation of statistical methodology for possible unit of analysis errors, which we found to be prevalent and were excluded.

LIMITATIONS OF THE UMBRELLA REVIEW

Source Systematic Reviews

The overall scope of our findings is limited by the availability of meta-analyses, reflecting, but not accounted for, by gaps in availability of primary research [25]. In addition, there are a number of limitations in the source systematic reviews.

First, methodological and statistical issues led to the exclusion of 10 systematic reviews otherwise within the scope of this paper (Suppl File 1.5.2), as well as individual meta-analyses from 12 systematic reviews in which other meta-analyses were not impacted and are included (Suppl File 2). Reasons for exclusion are listed for each excluded review paper in Supplementary Information (Suppl File 1.5.2). Underlying statistical issues are explored in a separate publication [43].

Second, a number of limitations in methodology of meta-analysis or reporting of the methodology was identified against AMSTAR criteria for included meta-analyses and pooled analyses. This is reported in detail within our results. Of particular note, limitations relate to risk of bias in the primary literature itself. Although meta-analysis is a beneficial tool to combine estimates of relationships across different studies, the reliability of estimates from the included primary studies can also impact the reliability of meta-analysis. These risks can be evaluated with risk-of-bias assessments. It was notable that across the 52 studies in this umbrella review, AMSTAR scores for the 36 studies that did report use of a risk-of-bias tool (ranging from 5 to 11) tended to be higher than the score for the 16 that did not (range 2-6). It is recommended that future reviews report on risk-of-bias assessment of the primary studies included.

Overall, 28 of the meta-analyses and pooled analyses in this umbrella review were assessed to be derived from reviews of high quality (AMSTAR score 9–11), 595 of moderate quality (AMSTAR 5–8), and 136 from reviews of low quality (AMSTAR <5) and, from the available information presented, should be interpreted with some caution. That said, all exposure-outcome associations evaluated within a review assessed to be of low quality by their AMSTAR rating were separately evaluated in at least one other review of moderate quality or above, with the exception of associations

between in utero PCB exposure and birth weight and sex ratio. Reassuringly, in all cases where the exposure-outcome combination had been separately evaluated in a review assessed to be of moderate or high quality, the findings were consistent with that in the review assessed to be of low quality. Specifically, meta-analyses in other reviews confirm association between total PCB exposure and both breast cancer and NHL. However, additional meta-analyses were not found for a number of other exposure-outcome combinations: association between PCB poisoning and mortality statistics; risk of ADHD with PFAS exposure [77]; lipid levels with BPA exposure [84] and bronchitis and wheeze in children following PCB exposure [91]. Without further detail on methodology, these associations should be treated with caution but not dismissed; lower AMSTAR scores indicate only risk of bias, not that bias is present, and in the absence of additional meta-analyses these lower-scoring reviews may reflect the best available evidence synthesis for these exposure-outcome combinations.

Conflict of interest (COI) is a known source for risk of bias. Using AMSTAR, we were only able to evaluate COI of the included studies, of which the majority declared no COI (n = 48) and only a few did not report on COI (n = 4). In addition, evaluation at the systematic review level as we did here, precluded assessing whether there was any COI in the primary literature underpinning the findings of our included studies. As such, COI is another aspect where there is a potential risk of bias that we could not explore, but which does not indicate that bias was present.

Process

Beyond limitations in the source systematic reviews, there are a number of limitations in the process employed in this umbrella review.

First, we selected outcomes for which data had been meta-analysed. Meta-analysis has some distinct advantages when considering an evidence base: it can increase the statistical power of the analysis, increase the generalisability of the results overall and increase the confidence in the results where marked heterogeneity is absent (be it methodological, clinical or statistical). However, meta-analysis is not always the most suitable approach for synthesising evidence. Our approach omitted a large number of reviews, including narrative, and their included studies that were either too heterogenous to combine statistically, or where only one study was identified to inform the outcome. Second, our method of synthesis used vote counting, harvest plots and narrative. With this method, the direction of effect and its significance is readily accommodated whereas the effect size, number of included studies, sample size and heterogeneity are not. However, we have provided this information in the supplementary materials (Suppl File 2). Additionally, the source review literature generally does not cover detailed findings such as dose-response modeling, disease burden, or effects of all covariates. As these detailed findings need a study designed specifically to address them, primary research is better suited than systematic or umbrella reviews.

Second, we used the original AMSTAR tool to assess the quality of all included reviews, including the pooled analyses of large cohorts of participants [50, 68]. Despite AMSTAR 2 being designed to better accommodate reviews with inclusion of non-randomised studies, as mentioned (see Methods section), AMSTAR has performed adequately for review of observational research, is faster to complete and has high inter-rater reliability and hence was selected [39, 40]. Furthermore, pooled analysis methodology does not necessarily include specific criteria for undertaking systematic reviews, such as a comprehensive search and screening of the literature. Therefore, the small subset of pooled analyses that met the inclusion criteria for this umbrella review expectedly scored low in the quality appraisal with AMSTAR. In this umbrella review, a low-scoring pooled analysis is different from a low-scoring systematic review with meta-analysis.

FRAMEWORKS FOR ASSESSING EPIDEMIOLOGICAL STUDIES

Formal frameworks have been developed for the systematic evaluation of epidemiological toxicology data. These include the United States National Toxicology Program's Office of Health Assessment and Translation (OHAT) [125, 126], IRIS [113, 127] and the Navigation Guide

Systematic Review Methodology [23]. These frameworks provide guidance on all steps in the conduct of systematic reviews of observational studies of aetiology: problem formulation and shaping the research question, defining exposure and outcomes, literature search strategy, evaluating risk of bias, planning the statistical analyses and translation of findings. Frameworks such as these were rarely used across the reviews identified in this umbrella review, with just five reviews following one of the three frameworks above [44, 58, 61, 74, 76].

There was more widespread use of reporting guidelines such as PRISMA and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [128] (the former recently revised [35]) which were used in an additional 20 included reviews. Notably, all 5 reviews which had followed a formal framework were evaluated to score 8 or higher on AMSTAR (range 8–11) and all had assessed risk of bias in the primary literature. The 20 reviews which had followed a reporting guideline inconsistently included a risk-of-bias assessment and were typically assessed to be of lower quality on AMSTAR (with score ranging from 4 to 9) and the 27 reviews that followed neither a formal framework nor reporting guideline were even more variable in quality (with score ranging from 2 to 9). The uptake of frameworks such as OHAT, IRIS and the Navigation Guide is recommended for reviewers interested in meta-analysis of plastic-associated chemical exposure on human health.

FUTURE EVIDENCE SYNTHESIS

This umbrella review reports only on eligible systematic reviews published up until August 2020. A subsequent search until August 2023 identified a further 76 potentially eligible systematic reviews, reflecting an exponential increase in the primary literature and its subsequent quantitative synthesis by systematic review with meta-analysis (Suppl File 1.7). Although the current umbrella review represents findings only up to August 2020, those findings nevertheless demonstrate associations between exposure and a wide range of adverse health outcomes. Of note, 74 of the subsequent systematic reviews covered the same breadth of human health outcomes as in our umbrella review, with only 2 examining a different domain, namely 'immunology'. Inevitably, further synthesis will be required to evaluate this burgeoning literature on the same chemical classes quantitatively, on these and other health outcomes.

In addition, to address the gaps in terms of the chemicals evaluated, we recommend that the focus is shifted to include emerging plastic-associated chemicals of concerns such as substitutes for bisphenols, phthalates and flames retardants [98, 110–112], as well as other classes of plastic-associated chemicals with likely high human exposure risk such as UV-stabilisers (bensophenones, benzotroazoles), antioxidants (e.g., hindered phenol antioxidants, nonylphenols) and heat stabilisers (e.g., organotins) [3].

CONCLUSION

We are exposed to plastic during everyday life via food packaging, construction materials, household goods, and transport as well as via environmental pollution of air, water, land and soil [3]. Our umbrella review summarises available evidence of adverse human health effects of plastic-associated chemicals in consumer products. We find that each chemical group with available meta-analysis or pooled-analysis data is associated with at least one adverse human health impact within the broad categories of birth, child and adult reproductive and endocrine, child neurodevelopment, nutritional, circulatory, respiratory, skin-related disorders and cancer outcomes. We also find significant gaps in the literature, considering there are over 16,000 chemicals used in plastics [5, 21, 22] Our findings have implications for the unknown safety of multiple plastic-associated chemicals which lack evaluation in humans.

Key priority areas without available data include the health effects of micro- and nanoplastics, bisphenol analogues, non-phthalate plasticisers and the alternative halogenated and organophosphate flame retardants that have replaced PBDEs. The critical importance of such post-market surveillance to regulation of chemicals is underscored by the high-volume plastic-associated chemicals evaluated in this umbrella review. Indeed, the findings of this

umbrella review exemplify the principle that safety cannot be assumed at the point of entry of a chemical to market, without process to systematically monitor for and identify post-market toxicity.

ADDITIONAL FILES

The additional files for this article can be found as follows:

- **Supplementary File 1.** Glossary and abbreviations. DOI: https://doi.org/10.5334/aogh.4459.s1
- **Supplementary File 2.** Characteristics of included reviews. DOI: https://doi.org/10.5334/aogh.4459.s2

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AUTHOR CONTRIBUTIONS

EA, CSy, JD and SD conceptualised the work. JD, THB, AW, DP, TM, CSt, CSy and EA completed the appraisal of included studies and extraction of data. EA, CSy, YM, CSt and SD completed the analysis of data. EA, CSy, YM and SD completed initial and ongoing drafts of the manuscript. All authors provided review, feedback and approval of the final draft.

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DATA ACCESSIBILITY

All extracted data from included reviews are available in Suppl File 2. Excel format data are also available upon request.

AUTHOR AFFILIATIONS

Christos Symeonides https://orcid.org/0009-0009-9415-4097
Minderoo Foundation, Perth, Western Australia, Australia; Centre for Community Child Health, Royal Children's Hospital, Parkville, Victoria, Australia

Edoardo Aromataris https://orcid.org/0000-0002-6866-1388
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

Yannick Mulders https://orcid.org/0000-0002-4879-4773
Minderoo Foundation, Perth, Western Australia, Australia

Janine Dizon https://orcid.org/0000-0002-4892-7310
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia; College of Nursing and Health Sciences, Flinders University, Adelaide, South Australia, Australia

Cindy Stern https://orcid.org/0000-0002-0924-5042
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

Timothy Hugh Barker https://orcid.org/0000-0002-6897-814X
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

Ashley Whitehorn https://orcid.org/0000-0002-1255-5279
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

Danielle Pollock https://orcid.org/0000-0002-6604-0609
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

Tania Marin https://orcid.org/0000-0001-8734-7928
JBI, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia; College of Nursing and Health Sciences, Flinders University, Adelaide, South Australia, Australia

Sarah Dunlop https://orcid.org/0000-0002-1306-3962
Minderoo Foundation, Perth, Western Australia, Australia; School of Biological Sciences, The University of Western Australia, Perth, Australia

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UMBRELLA REVIEW: IMPACT OF PLASTIC-ASSOCIATED CHEMICAL EXPOSURE ON HUMAN HEALTH

JBI: Janine Dizon, Timothy Barker, Ashley Whitehorn, Tania Marin, Danielle Pollock, Edoardo Aromataris*

Minderoo Foundation: Christos Symeonides*, Yannick Mulders*, Sarah Dunlop*

***Authors contributed equally to this report**

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PUBLICATIONS ARISING FROM UMBRELLA REVIEW

With the aim of increasing awareness of the health impacts of everyday plastics use and providing recommendations, we have presented the output of the Umbrella Review in different formats with appropriate detail for different purposes and audiences.

As a suite of reports and peer-reviewed scientific publications, the Umbrella Review has unique value in drawing together the high-level quantitative evidence of the impact exposure to commonly studied plastic-associated chemicals on human health outcomes. These are:

1) A peer-reviewed scientific publication:

Symeonides C, Aromataris E, Mulders Y, Dizon J, Stern C, Barker TH, Whitehorn A, Pollock D, Marin T, Dunlop S. An Umbrella Review of Meta-Analyses Evaluating Associations Between Human Health and Exposure to Major Classes of Plastic-Associated Chemicals. Annals of Global Health. 2024; 90 (1): 00, 1 – 52.

2) This Umbrella Review report comprising:
    i. Part 1 - Executive Summary
    ii. Part 2 - Evidence Review Summary
    iii. Part 3 - Evidence Review

3) A peer reviewed methodology paper on statistical errors of analysis in meta-analyses identified during this Umbrella Review.

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PART 1: EXECUTIVE SUMMARY

INTRODUCTION

UMBRELLA REVIEW QUESTION

What is the impact of plastic-associated chemical exposure on human health?

Large-scale plastic production began in the 1950s and has since outpaced any other manufactured material (Geyer et al., 2017). Plastic is the signature material of our age which has transformed our everyday lives via, for example, food packaging, construction materials, household and personal goods, transport and medical applications (Landrigan et al., 2023). Plastic contamination of the environment, including air, water and soil, is ubiquitous, with plastics representing 'a singular uncontrolled experiment on a global scale' (Geyer et al., 2017) that are predicted to exceed planetary boundaries, defined as a 'safe operating space for humanity' (Persson et al., 2022).

During use, and once released into the environment, plastic fragments into smaller and smaller particles called micro- and nanoplastics (World Health Organization (WHO), 2022a). These plastic particles are beginning to be detected in human biospecimens (Kannan and Vimalkumar, 2021; Sripada et al., 2022). In addition, chemicals in plastics leach out of products during use and degradation, reflecting the complex nature of plastic materials (Hahladakis et al., 2018). Indeed, there are thousands of different known plastic-associated chemicals used to manufacture the polymer matrix of plastics, as well as added to the polymer matrix to give properties like flexibility (plasticisers) or fire resistance (flame retardants)(UNEP, 2023; Wagner et al., 2024; Wiesinger et al., 2021), with additional chemicals that are inadvertently included in the manufacture of plastics, or formed and released during the degradation of plastics (Kato and Conte-Junior, 2021). Only a limited number of these chemicals have been looked for in human research or bio-surveillance programs, but of these, there are some common plastic-associated chemicals that have routinely detected in many human studies over several decades (Woodruff et al., 2011) although we are, in fact, exposed to mixtures of multiple chemicals (Wang et al., 2021).

As part of its mission to eliminate the harmful effects of plastic on people and the planet, Minderoo Foundation formed a partnership with the JBI to examine the published evidence for the impacts of plastic exposure on human health. Evidence syntheses, such as pooled analyses and systematic reviews with meta-analysis, review the scientific literature both systematically and quantitatively, and provide a rigorous and transparent evaluation of the published evidence (Curtin University Library Services, 2022).

Here, we undertook an umbrella review to systematically evaluate this synthesised evidence. Umbrella reviews represent one of the highest levels of evidence synthesis currently available and are becoming increasingly influential for translating research into best practice as well as policy (Fusar-Poli and Radua, 2018).

KEY FINDINGS OF UMBRELLA REVIEW

- **There are no systematic reviews with meta-analyses of the health effects of plastic polymers, micro- and nanoplastics.**
- **We are exposed to plastic-associated chemicals from preconception onwards.**
- **Despite a multitude of plastic-associated chemicals in use, only a fraction has been researched more than once, and subsequently meta-analysed, to assess health effects in humans.**
- **Exposure to plastic-associated chemicals is linked to a wide range of adverse health outcomes from before birth (miscarriage), at birth (weight, genital development and appearance), in children (neurodevelopment, obesity, blood pressure, asthma and bronchitis, precocious puberty in girls, i.e. onset before eight years), and in adults**

(endometriosis, sperm concentration and quality, type 2 diabetes and insulin resistance, thyroid function, polycystic ovary syndrome, obesity, cardiovascular disease, hypertension, and cancer).

- **None of the plastic-associated chemicals examined can be considered safe, with multiple harmful health effects linked to each chemical class.**

RECOMMENDATIONS

RECOMMENDATIONS FOR REGULATORS AND POLICY MAKERS

For those plastic-associated chemicals that have been found to be harmful to human health – as identified in this review – we call for their urgent removal from all non-essential applications where they are not already banned, with particular urgency for consumer goods with direct human exposure including food contact materials, clothing, cosmetics and children's toys.

Beyond those chemicals, we also call for:

- The urgent development of global precautionary standards, including under the United Nations Global Plastics Treaty: an international legally binding instrument to end plastic pollution. It has to be recognised that the full range of human health risks associated with plastic-associated chemicals remains unknown. As such, we caution that plastic-associated chemicals belonging to the same class as chemicals with identified harmful effects on human health should be presumed to also carry a risk to human health. These chemicals must be subject to the highest degree of assessment prior to registration or use in the market as well as systematic post-market monitoring and ongoing re-evaluation as below.
- Periodic and ongoing re-evaluation of all plastic-associated chemicals post-market that includes review of available human epidemiological data to take account of long-term, low dose exposure patterns seen for human lifetime environmental exposure, as well as complex human health outcomes such as neurodevelopment or chronic disease, neither of which are possible in in vitro or animal studies.
- Systematic post-market monitoring of exposure and health effects of all plastic-associated chemicals, including large-scale biomonitoring as well as observational health studies, rather than relying on ad hoc investigator-driven research. Such monitoring could, for example, be funded by extended producer responsibility schemes that acknowledge industry responsibility for the introduction of chemicals that require management throughout the life cycle of plastics.
- Mandated disclosure of plastic composition to enable effective management of the risk associated with plastic-associated chemicals throughout the lifecycle of plastics.

RECOMMENDATIONS FOR CHEMICAL PRODUCERS AND PLASTIC MANUFACTURERS

We recommend cessation of the production and use of those plastic-associated chemicals that have been found to be harmful to human health as identified in this review.

We also call for chemical producers and plastic manufacturers to:

- Actively and cooperatively engage in the development and implementation of disclosure schemes that facilitate transparency and traceability of plastic-associated chemicals within plastic products, to enable effective management of chemical loads throughout the lifecycle of a product and to empower brands, consumers, recyclers and other users to make choices based on health risks.
- Pursue more rigorous pre- and post-market evaluation and testing of plastic-associated chemicals, using the examples within this Umbrella Review as case studies to explore a) how

and why pre-market evaluation failed to identify the potential for human health harms that subsequently emerged, b) where those risks could have been identified with improved pre-market evaluation, and c) what post-market health and environmental monitoring would be needed to more quickly and reliably detect harms that go undetected during pre-market evaluation.
- Work with regulators to routinely make available the necessary detail both on chemical composition and a robust, reliable and practical analytical methodology for detecting and quantifying human exposure to all plastic-associated chemicals; these are critical for post-market evaluation of human exposure and identification of any health effects.
- Make routine provision for funding the systematic post-marketing monitoring of exposure and health effects of their plastic-associated chemicals once accepted into the market and produced at volume.

RECOMMENDATIONS FOR PUBLIC HEALTH COMMUNICATION

Given the current relative lack of awareness about the effects of plastic on human health by both the medical profession as well as the public (Kelly et al., 2020; Sunyach et al., 2018; Sutton et al., 2012; Tan et al., 2021; World Health Organization (WHO), 2022b), we recommend that public health authorities:

- Launch public campaigns to raise awareness that plastic pollution is not only a waste issue, but also a health issue.
- Develop evidence-based resources, guided by knowledge translation principles, to better inform public health professionals and the public about how to reduce personal exposure to plastic-associated chemicals.
- Consider requirements for public health warning labels on products and packaging where there is a higher risk of chemical leaching, such that consumers are empowered to make choices based on health risks.

RECOMMENDATIONS FOR RESEARCH

Systematic review & meta-analysis methodology

Given the low to moderate quality of many eligible systematic reviews and common statistical issues that meant we had to exclude multiple reviews and analyses, we recommend:

- Strengthening standards for registration, conduct and reporting of systematic reviews and meta-analyses.
- Ensuring that editorial review includes adherence to conduct and reporting standards prior to acceptance for publication in scientific journals.

Primary research

- Broadening the evidence base by increasing investment in human observational cohort studies, including longitudinal cohorts, thereby expanding the scope of plastic-associated chemical exposures and health outcomes assessed. This approach is essential to counter an absence of identified harm being interpreted as no harm (Leslie and Depledge, 2020).
- Urgently developing methods to evaluate the impact of thousands of other plastic-associated chemicals, individually, as well as mixtures, on human health.
- Urgently prioritising primary research on micro- and nanoplastics in humans by developing accurate and reliable measurement techniques in order to undertake high quality clinical studies.

METHODS

The primary research literature (i.e. individual journal articles) on the impact of plastic exposure on human health is burgeoning. Relatively little is known about the extent to which micro- and nanoplastic particles enter the human body nor about health outcomes in relation to exposure. By contrast, the literature on plastic-associated chemicals is much more extensive and a range of human health outcomes have been assessed (Eales et al., 2022; Lin et al., 2023; Symeonides et al., 2021). However, the primary research literature is typically replete with studies which may not be large enough to individually address these questions or may have different aims or approaches, and there is a need to bring this existing data together in a systematic way for decision makers.

We therefore turned to systematic reviews with meta-analyses to examine the extent and strength of the quantitative evidence (Curtin University Library Services, 2022). Meta-analyses or pooled analyses statistically combine data across multiple individual primary research studies and allow for ready evaluation of the overall evidence for links between a specific exposure, or exposures, and a human health outcome, or outcomes. This approach offers increased confidence about the findings. A considerable number of systematic reviews with meta-analysis have been conducted to date in which a range of plastic-associated chemicals and a number of health domains have been examined. However, to date, no attempt has been made to summarise the systematic review evidence across each of these plastic-associated chemicals and the diverse range of health outcomes investigated. We therefore undertook an umbrella review to 'review the systematic reviews with meta-analyses'.

The current Umbrella Review was undertaken in parallel with a companion systematic evidence map called the Plastic Health Map (Seewoo et al., 2023), which examined primary *in vivo* research on everyday human exposure to plastic. Here, we adopted a similar search strategy (see Part 3 and Appendix 2) as in the Plastic Health Map, focussing on polymers, the backbone of plastic; micro- and nanoplastic particles, due to their widespread occurrence; plasticisers and flame retardants, two additives with high production volumes, and high concentrations in plastic; as well as bisphenol monomers and per- and polyfluorinated alkyl substances, which are common in plastics and have known health concerns. Polymer metabolites, monomers other than bisphenols and plastic additives such as UV, heat and light stabilisers, colourants, lubricants, biocides, antistatic agents, fillers and reinforcers were not included in the search strategies for either review.

Only systematic reviews with meta-analysis that assessed risk of a health outcome with exposure, as measured directly from human biospecimens (i.e. internal measure of exposure), were eligible. Methodological quality of eligible reviews, meta-analyses and pooled analyses was independently assessed by two reviewers with the AMSTAR tool, an 11-item checklist (Shea et al., 2007) that is a reliable and valid tool for quality assessment of systematic reviews and meta-analyses of observational research (Pieper et al., 2014). The original AMSTAR was selected due to more rapid completion and greater inter-rater reliability (Gates et al., 2020). The statistical handling of data was evaluated separately. Analyses were excluded if there were statistical errors.

OVERVIEW OF FINDINGS

POPULATIONS

- In total 939 meta-analyses were extracted from the included 52 eligible systematic reviews with meta-analyses, and meta-analyses and pooled analyses. This encompasses more than 1.5 million individuals; noting that some individuals may have contributed to multiple analyses.
- The first eligible systematic review was published in 2009, and two-thirds between 2017-2020, reflecting increasing research intensity.

- Health outcomes were assessed across the lifespan, i.e. preconception (fertility), in pregnancy, at birth, and in infants, children, adolescents and adults.

STUDY DESIGN

- Ten (16%) of the 62 systematic reviews initially selected were identified as flawed during data extraction and appraisal and therefore excluded (see Appendix 5, table A5.2). The principal concerns were unit of analysis errors leading to invalid measures of precision and increased risk of false positives.
- The quality of the included systematic reviews, meta-analyses and pooled analyses varied, with 12 (23%) rated as low, 34 (65%) moderate and six (11%) high quality using the AMSTAR tool [A MeaSurement Tool to Assess systematic Reviews (Shea et al., 2007)].
- Study designs included in the analyses were cohort, case control and cross-sectional with some longitudinal studies.

TYPES OF PLASTIC-ASSOCIATED CHEMICALS EXAMINED

See GLOSSARY & ABBREVIATIONS as well as Background Information on Included Plastic-associated chemicals (Appendix 1) for details.

- There are no systematic reviews with meta-analysis identified examining the health impacts of plastic polymers, nor micro- or nanoplastics.
- Of the thousands of plastic-associated chemicals to which humans are exposed in everyday life, only a minute fraction has been systematically evaluated for quantitative human health impacts *via* systematic reviews with meta-analysis, meta-analyses and pooled analyses.
- The plastic-associated chemicals that have been evaluated to date are:
    a. **Bisphenol A (BPA)**, a monomer used to make polycarbonate and epoxy resins and as a stabiliser in certain plastics.
    b. **Phthalates (DEHP and other ortho-phthalic diesters),** a common type of plasticiser mostly measured as their metabolites**.**
    c. Two classes of flame retardants, namely **polychlorinated biphenyls (PCBs)** and **polybrominated diethyl ethers (PBDEs).**
    d. A number of **per- and polyfluorinated alkyl substances (PFOA, PFOS and other PFAS)** that have a wide range of applications including repelling water, grease and heat, and are used in the production of fluoropolymers with broad consumer applications such as polytetrafluoroethylene (PTFE, Teflonä). PFAS may also form from surface fluorination of plastic products, a chemical process to make plastic packaging more resilient.
- The majority of exposures to plastic-associated chemicals was measured in urine or blood. Exposure to BPA in the womb has been measured in amniotic fluid. Exposure to flame retardants has also been measured in breast milk and adipose (fat) tissue.

FINDING OF HARM: STATISTICALLY SIGNIFICANT ADVERSE HEALTH EFFECTS OF PLASTIC-ASSOCIATED CHEMICALS

Adverse health effects were identified across the human lifespan from birth through to adulthood. Exposure to the four main classes of plastic-associated chemicals examined is linked to the following adverse health effects (see Part 2: Evidence Review Summary for details):

Prenatal foetal exposure linked to adverse outcomes at birth (for abbreviations, see Glossary):

- Miscarriage (**DnBP, DEHP**); Birthweight (**DEP; PCBs, PBDEs**; **PFOA, PFOS**); Birth length (**PFOA**); Genital structure (ano-genital distance) (**BPA**; **DEHP**)

Prenatal foetal exposure linked with adverse infant health outcomes:

- Bronchitis (**PCBs**)

Prenatal exposure linked to adverse child health outcomes:

- Poorer psychomotor development (**DEHP**); Lower IQ (**PBDEs**); ADHD in girls (**PFOA**); Obesity (**PFOA**); increased BMI (**PFOA**); Asthma (**BBP**); Allergic rhinitis (**PFOA**)

Infant exposure linked with adverse child health outcomes:

- Increased Body Mass Index (BMI) (**PFOA**); Obesity (**PFOA**)

Child exposure linked to adverse child health outcomes:

- Poorer cognitive development (IQ) (**DEHP**); Precocious puberty in girls (**DEHP**); Abnormal timing of breast development (**DEHP**); Higher systolic blood pressure (**DEHP**; Obesity (**BPA**); Allergic rhinitis (**PFOA**)

Exposure linked to adverse health outcomes in children & adults (combined):

- Insulin resistance (**DiBP, BBP, DEHP**); Changes in thyroid function (**PBDEs in highly exposed populations**); Insulin resistance (total phthalates, **DiBP, BBP, DEHP**); Increased waist circumference (**BPA**)

Adult exposure linked to adverse adult health outcomes:

- Endometriosis (**DEHP**; **PCBs**); Lower sperm concentration (**DnBP, BBP**); Sperm DNA measures (**DEP, BBP**); Lower sperm motility (**DEHP**, **DnBP**); Decreased sperm velocity (**DnBP**); Type 2 diabetes (**BPA**; **DiBP**; **PCBs**); Increased insulin resistance (**BPA**, **DiBP, BBP, DEHP**); Increased fasting glucose (**PCBs**); Changes in thyroid function (**PFOS**); Liver disease deaths (**PCB poisoning**)**;** Polycystic ovary syndrome (**BPA**); Obesity (**BPA**; **DEHP**); Increased waist circumference (**BPA**); Overweight (**BPA**); Cardiovascular disease (**BPA**; **PCB 138 & 153**); Cardiovascular disease deaths (**PCB poisoning**); Hypertension (**BPA, dioxin-like PCBs**); All cancer-related deaths for males (**PCB poisoning**); Cancer-related deaths for: lung cancer for males (**PCB poisoning**); Non-Hodgkin's lymphoma (**PCBs**); Breast cancer (**PCB 99, 105, 183 & 187**), liver cancer for females (**PCB poisoning**), and malignant melanoma (**PCB in those with work-related exposure**)

POTENTIALLY PROTECTIVE EFFECTS

In contrast to the breadth of adverse health effects found, there were only two examples of effects in the opposite direction (potentially protective effects):

- For adolescent boys, increased phthalate (**DnBP, DEHP)** exposure is linked to a lower chance of one type of abnormal pubertal timing (pubic hair development)
- For the general population (adults and children), exposure to **PCBs** is linked to lower chance of one subtype of non-Hodgkin's lymphoma (chronic lymphocytic leukaemia); noting that **PCBs** are associated with increased risk of non-Hodgkin's lymphoma as a whole

NONE OF THE CHEMICAL CLASSES OF PLASTIC-ASSOCIATED CHEMICALS EVALUATED CAN BE CONSIDERED SAFE

There were no chemical classes without an adverse finding for at least one health outcome, and indeed all classes – and all commonly studied plastic-associated chemicals within each class – were linked with adverse health outcomes across multiple health domains (Fig 1.1).

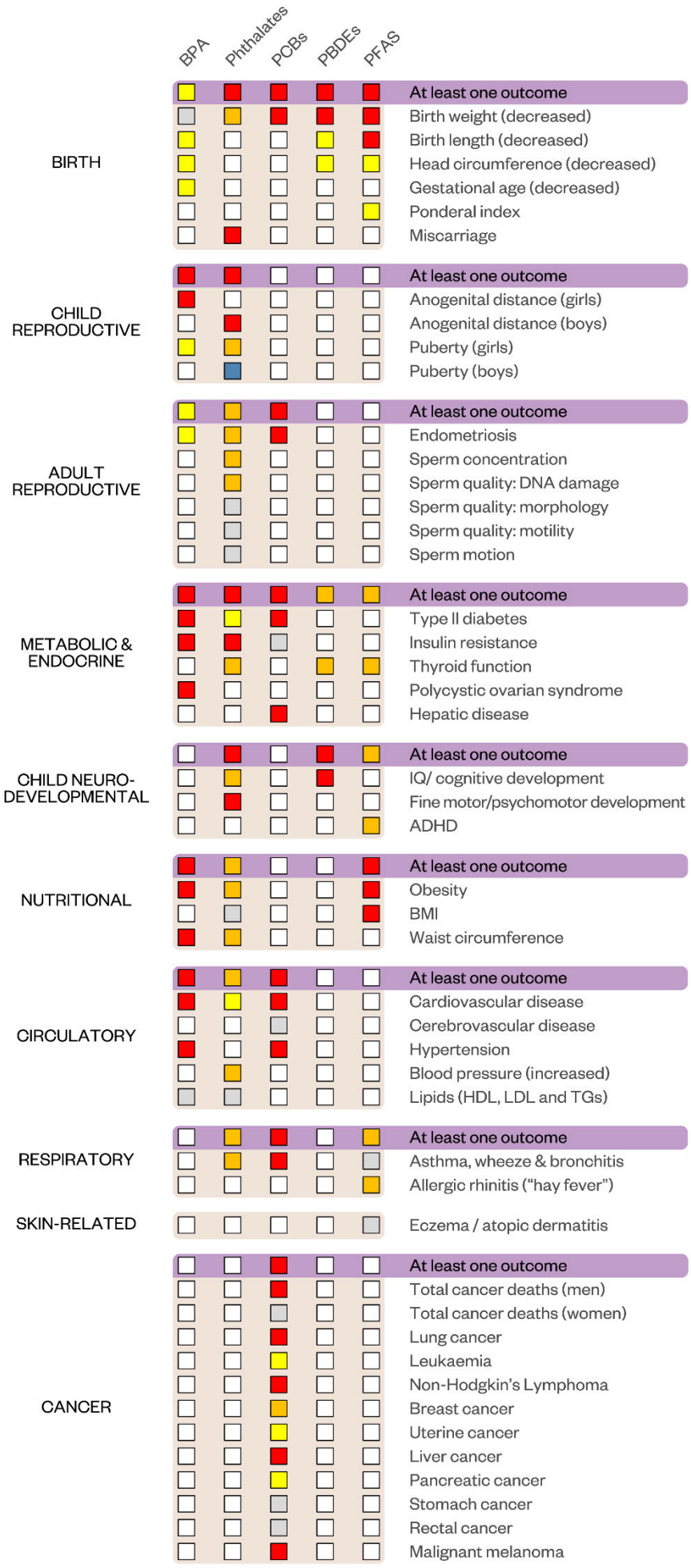


Figure 1.1: Overview of high-level quantitative evidence for the effects of five classes of plastic-associated chemicals on human health. Each square represents a summary of findings from all included meta-analyses that have evaluated the combination of internal exposure to a plastic-associated chemical and a human health outcome according to the following colour code:

RED: 'Consistent and statistically significant evidence of harm.' 95% confidence of association with harmful health effects on meta-analysis. Defined by a statistically significant adverse association between total exposure to a class of chemicals and a health outcome OR a statistically significant adverse association between each chemical evaluated within a class and that health outcome OR a mix of statistically significant adverse associations and non-significant trends towards adverse association for each chemical evaluated within a class (without any trends in the other direction).

ORANGE: 'Strong reason for concern.' Statistically significant evidence of harmful health effects on meta-analysis (95% confidence of association), but with some inconsistency in findings. Defined by a mix of statistically significant adverse associations and non-significant trends in either direction for various chemicals in a class and a health outcome and no statistically significant protective associations.

YELLOW: 'Reason for concern.' Some evidence of harmful health effects on meta-analysis but not meeting statistical significance (95% confidence). Defined by consistent non-significant trends towards adverse associations for various chemicals in a class and health outcomes, but no statistically significant findings.

GRAY: 'Unclear.' No consistent pattern of harmful health effects on meta-analysis but, equally, safety is not established. Defined by no statistically significant adverse associations and no consistent trends towards adverse associations OR non-significant trends towards protective associations but no statistically significant findings OR where there are both statistically significant adverse associations and statistically significant protective associations.

BLUE: 'Reassuring.' Statistically significant evidence against harmful health effects on meta-analysis (95% confidence). Defined by statistically significant protective associations between total exposure to a class of chemicals and health outcomes OR statistically significant protective associations between each chemical evaluated within a class and that health outcome OR a mix of statistically significant protective associations and non-significant protective trends for each chemical evaluated within a class (without any trends in the other direction).

PART 2: EVIDENCE REVIEW SUMMARY

INTRODUCTION

This **Evidence Review Summary** (Part 2) provides an overview of the background and the findings of the Umbrella Review. **Here we summarise health outcomes for each of the plastic-associated chemicals studied.**

UMBRELLA REVIEW QUESTION

What is the impact of plastic-associated chemical exposure on human health?

PLASTIC

Plastic: Plastic comprises a polymer matrix which provides its basic structure, and various "plastic-associated chemicals" (namely, monomers, additives and processing aids) that are used in the production of the polymer or to modify properties of the plastic (Shrivastava, 2018; UNEP, 2023; Wagner et al., 2024; Wiesinger et al., 2021). While there is a relatively limited number of plastic polymers, plastic-associated chemicals are numerous (> 10,500) and include a diverse range of plasticisers, flame retardants, UV, light and heat stabilisers, biocides, fillers, lubricants, slip agents, colourants fillers and reinforcers (Wiesinger et al., 2021). The extraordinary versatility and utility of plastic has made it part of our everyday lives and it is used in transport, construction, agriculture, medical products, electronics, household goods, fabrics, packaging including especially for food and drink, as well as many other single-use products (Landrigan et al., 2023).

Plastic production and waste: The plastic material revolution has been highly successful with more than eight billion metric tonnes (Mt, one tonne being 1,000 kilograms) being been produced since 1950, that is, approximately one tonne for every person on the planet (Geyer et al., 2017). Indeed, production is accelerating with half (3900 Mt) being produced between 2004-2013 (Geyer et al., 2017) and is predicted to increase further in the face of alternative green energy resources replacing fossil fuels (Beyond Plastics, 2021). However, single or short-term use - coupled with low recycling rates of approximately 10% - have resulted in significant waste generation estimated at 5800 Mt in 2015 and predicted to increase to 25,000 Mt by 2050; indeed in 2015, only 30% of all plastic generated was still in use (Geyer et al., 2017).

Plastic pollution of the environment: Plastics' wide utility, coupled with its long-term durability and lack of waste management (Basuhi et al., 2021) has resulted in plastic pollution reaching every corner of the planet from the deep ocean trenches to the Himalayas and Artic (Chiba et al., 2018; Cózar et al., 2017; Napper et al., 2020). In addition to macroplastics, micro- and nanoplastics form as plastic fragments during everyday use and in the environment (Andrady, 2017). Microplastics are also intentionally added to products (Malankowska et al., 2021). Another issue is that additives such as plasticisers and flame retardants are not chemically bonded to the polymer matrix and therefore leach out; some residual monomers are also released from the polymer (Zimmermann et al., 2021). These plastic-associated chemicals have been widely detected in the environment including in the ocean, fresh water, sediments, soil and landfill (Hermabessiere et al., 2017; Metcalfe et al., 2022; Net et al., 2015; Oehlmann et al., 2008).

HUMAN EXPOSURE

Human exposure - plastic particles: With the development of new imaging and spectroscopy measurement techniques, we are beginning to understand the extent to which micro- and nanoplastics enter the human body (Landrigan et al., 2023). Microplastics have been reported to be detected using microscopy and Raman spectroscopy in human lung, colon, placenta, gut and stool (Braun et al., 2021; Ibrahim et al., 2021; Pauly et al., 1998; Ragusa et al., 2021; J. Zhang et al., 2021); they have also been reported to be detected in human blood using mass spectroscopy (particle sizes >700nm)(Leslie et al., 2022). With respect to health impacts, industrial exposure in textile workers is linked to a wide range of lung diseases (Prata, 2018). More recently, microplastics have been linked to cirrhotic liver in liver transplant patients (Horvatits et al., 2022), to cardiovascular disease in patients with asymptomatic carotid artery disease (Marfella et al., 2024) and microplastic load in faeces has been found to be associated with inflammatory bowel disease status (Yan et al., 2022).

Human exposure - plastic-associated chemicals: Because plastic is widely used in every aspect of our lives (Landrigan et al., 2023), humans are exposed to leaching plastic-associated chemicals from multiple sources such as clothing (Tang et al., 2020), food and its packaging (N. Zhang et al., 2020), furniture and electronic products (Chokwe et al., 2020). Intake occurs *via* ingestion, inhalation and/or dermal contact (Luo et al., 2020; Wentao Wu et al., 2020). In contrast to plastic particles, techniques for measuring certain plastic-associated chemicals in human bio-specimens are more established and, consequently, more is known about internal exposure profiles. Plastic-associated chemicals have

been detected in human seminal fluid, follicular fluid, amniotic fluid, cord blood, meconium, breast milk, urine, serum, saliva, sweat and hair (Genuis et al., 2012; Katsikantami et al., 2020; Kim et al., 2021; Kolatorova et al., 2018; Vitku et al., 2015; Y.-J. Zhang et al., 2021).

ASSESSING THE IMPACTS OF PLASTIC EXPOSURE ON HUMAN HEALTH

The primary research literature on the impact of everyday plastic exposure on human health is rapidly increasing (Seewoo et al., 2023). However, although many papers report adverse effects on human health, findings often require confirmation or there may be inconsistent findings and therefore uncertainty about the overall strength of the evidence for harm. Another issue is that, because health effects may not be immediate, studies need to be conducted over time, sometimes decades, to provide answers about long term cumulative exposure or latent effects of early exposure.

It is unethical to deliberately expose humans to potentially toxic plastic particles or plastic-associated chemicals, and therefore health impacts in humans are studied using epidemiological observational studies. These studies evaluate whether differences in exposure to a chemical or group of chemicals are associated with a particular health outcome by measuring the incidental exposure of the individuals in the study. Because that exposure is not directly controlled by the researchers, this introduces an inherent variability, along with differences in study design such as the metabolites that are measured, the biospecimen in which they are measured, the population studied, and timing of measurement. One approach to account for this inherent variability is to undertake observational studies in which large numbers of participants are recruited to increase statistical power.

Another approach is to systematically synthesise the published evidence. This approach provides a rigorous and transparent basis for translating research into best practice as well as policy (Fusar-Poli and Radua, 2018). Systematic reviews statistically combine data across multiple individual primary research studies by meta-analysis and evaluate the overall evidence for links between a specific exposure or exposures and a human health outcome or outcomes, thereby increasing confidence about the findings. By definition, systematic reviews are focused and address health outcomes in specific domains, for example birth outcomes, in relation to exposures to specific plastic substances. Since 2005, the number of systematic reviews with meta-analysis that address plastic exposure and human health has increased, indicating rising interest and concern. To date, no attempt has been made to provide an exhaustive quantitative overview of the available evidence summarising the risks associated with exposure to plastic-associated chemicals across human health conditions and across all populations. Umbrella reviews allow an approach to systematically synthesise the evidence from pooled analyses and systematic reviews, and represent one of the highest levels of evidence synthesis currently available and are increasingly authoritative in informing policy (Fusar-Poli and Radua, 2018).

METHODS

OVERVIEW

Structured searches were undertaken in two databases for systematic reviews on plastic-associated chemicals as well as micro- and nanoplastics and human health outcomes. Two independent researchers assessed the eligibility of, and extracted data from, systematic reviews and the individual meta-analyses within those reviews, with additional checking by two others. All researchers have expertise in systematic reviews and meta-analysis.

ELIGIBILITY

Reviews were eligible if they presented meta-analyses including primary studies that assessed risk of a health outcome with plastic-associated chemical exposure measured in biosamples. Only reviews published in English were eligible for inclusion. Epistemonikos and PubMed were searched to locate eligible reviews with meta-analyses, meta-analyses and pooled analyses. Systematic reviews and pooled analyses indexed prior to August 26th 2020 were included. A list of systematic reviews with meta-analysis published subsequently is provided in Supplementary Data in (Symeonides et al., 2024).

SEARCH TERMS

The full search strategy employed is available in Part 3: Evidence Review (See also Appendix 2)

In brief, for populations, search terms included the entire human lifespan i.e. from *in utero* to adulthood.

For exposures, we focused on those related to the use of plastic products in everyday life. We did not include the broader pipeline of plastic production from fossil fuel extraction through to manufacture of consumer plastic products, nor the management of plastic waste.

We set out to include all polymers and searched for both general references to "plastic" and chemical names of common polymers such as: polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PETE), polyvinyl chloride (PVC), polystyrene (PS), nylon (polyamides) and polycarbonate. Micro- and nanoplastic were also included in the search.

A systematic evidence map of the primary literature conducted in parallel, identified that of all the multiple plastic-associated chemicals that are in use only a fraction has been examined in humans (Seewoo et al., 2023). We included polymers, the main building blocks of plastic; micro- and nanoplastics, due to their environmental ubiquity and therefore potential for human exposure; plasticisers and flame retardants which have high production volumes and are used in high concentrations in plastic products; as well as bisphenols and PFAS, plastic-associated chemicals with known health concerns. Search terms included: functional classes such as plasticiser(s)/plasticizer(s) and flame retardant(s); chemical classes such as bisphenol(s), phthalate(s), terephthalate(s), cyclohexanoate(s), adipate(s), trimellitate(s), dibenzoate(s), polychlorinated biphenyl(s), polybrominated diphenyl ether(s), organophosphate ester(s), and PFAS; as well as terms to capture specific chemicals within these classes by their standard chemical names. Other additives such as UV, heat and light stabilisers, colourants, lubricants, biocides, antistatic agents, fillers and reinforcers were excluded.

DATA EXTRACTION AND ANALYSIS

All retrieved records were screened against the inclusion and exclusion criteria. Methodological quality of the conduct of the included systematic reviews and pooled analyses was assessed using the AMSTAR (A MeaSurement Tool to Assess systematic Reviews; (Shea et al., 2007) appraisal tool. Based on scores, reviews were classified as low (1-4), moderate (5-8) and high quality (9-11), the maximum being 11 (see Appendix 3). Relevant data were extracted and summarised in narrative and tables. Screening, selection, assessment of methodological quality and data extraction were all conducted in duplicate. A third reviewer was consulted to validate data and resolve disagreements in the selection and quality assessment stages. The health outcomes investigated for each plastic-associated chemical exposure have been summarised in narrative that includes clear indication of the effect estimate, 95% confidence limits around each effect estimate, the number of studies included in the meta-analysis and the number of participants included in the analysis where this information was available.

DEFINITIONS

To account for variations in terms and descriptions between the published reviews, we generated standardised definitions to describe certain plastic-associated chemical exposures. This was only required for plasticisers (phthalates) and flame retardants.

Plasticisers

Total phthalates: *composite measure of phthalate exposure which is the total concentration of all phthalate metabolites measured in the individual primary research study.*

ΣDEHP: *composite measure of diethylhexyl phthalate (DEHP) exposure as the molar sum of the individual DEHP metabolites measured in the individual primary research study, such as: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP),*

mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-carboxymethyl-5-hexyl) phthalate (MCMHP).

DEHP metabolites: *an alternative approach to harmonising measures of diethylhexyl phthalate (DEHP) exposure across studies, where a systematic review or meta-analysis selected a single "best" measure of DEHP exposure from the DEHP measures available within each individual primary research study, following a predetermined hierarchy if multiple measures were available within that study (typically selecting findings for ΣDEHP if available, but otherwise substituting this with findings for the most reliable individual DEHP metabolite available within that study)*

Flame retardants

Total PCBs: *composite measure of PCB exposure which is the total concentration of all PCB congeners measured in the individual primary research study.*

Special PCB exposure (poisoning): *the main exposure to PCBs in the study or studies was attributable to PCB poisoning of a geographically-defined population through contaminated food products.*

Special PCB exposure (occupational): *the main exposure to PCBs in the study or studies was attributable to the occupation (work) of the sample population.*

Total PBDEs: *a composite measure of PBDE exposure which is the total concentration of all PBDE congeners measured in the individual primary research study.*

The findings presented in this Evidence Review Summary are organised based on the health outcomes identified during this project. For clarity, outcomes are presented in categories aligned to the International Classification of Diseases 11th revision (ICD-11) (World Health Organization, 2020).

WORDING OF FINDINGS

We developed a wording proforma to convey the findings in a consistent manner that was based on health outcomes and significance of the findings.

Continuous outcomes

Statistically significant findings: *There was a significant increase (or decrease) in (outcome, e.g., birth weight) … OR (outcome, e.g., birth weight) significantly increased or decreased… with higher plastic-associated chemical exposure.*

Absence of statistically significant findings or strong trends in findings: *There was no clear increase or decrease in (outcome)… with higher plastic-associated chemical exposure.*

Findings that were not statistically significant, where describing trends relative to other statistically significant findings: *There was a non-significant trend towards increase (or decrease) in (outcome) … with higher plastic-associated chemical exposure.*

Dichotomous outcomes

Statistically significant findings: *There was significant increased (or decreased) risk of (outcome, e.g., breast cancer) … OR risk of (outcome, e.g., breast cancer) significantly increased (or decreased) … with higher plastic-associated chemical exposure.*

Absence of statistically significant findings or strong trends in findings: *There was no clear increased or decreased risk of (outcome)… with higher plastic-associated chemical exposure.*

Findings that were not statistically significant, (e.g. where describing trend relative to other statistically significant findings): *There was a non-significant trend towards increased (or decreased) risk of (outcome) … with higher plastic-associated chemical exposure.*

STRUCTURE OF THE EVIDENCE REVIEW SUMMARY

The results in this Evidence Review Summary reflect a high-level compilation of the risk estimates and changes in health outcomes with plastic-associated chemical exposure as reported by the eligible meta-analyses and pooled analyses. All results and values are available in the Part 3: Evidence Review and in the peer-reviewed publication arising from the Umbrella Review (Symeonides et al., 2024).

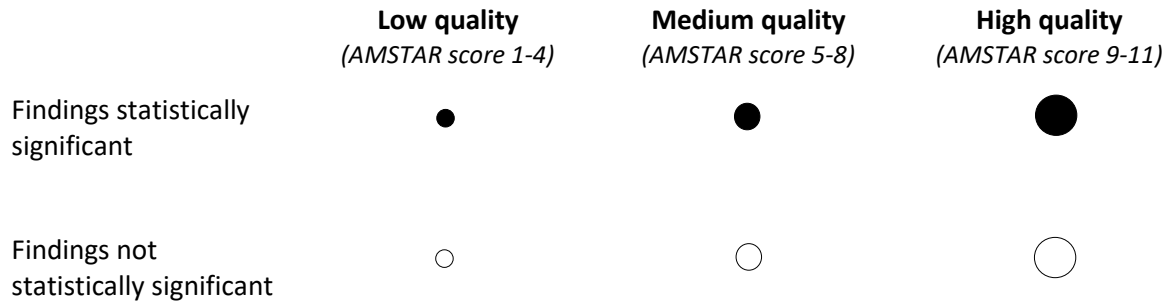
In this Evidence Review Summary, for outcomes measured on a continuous scale, in various diverse measures and units such as birthweight (grams) or anogenital distance (millimetres), the location of the corresponding data point in the figures (2.1-2.10) is a qualitative representation of whether there is a statistically significant increase or decrease in that outcome, and we do not set out to represent the magnitude of that increase or decrease per unit of exposure to the plastic-associated chemical(s). Quantitative effect sizes are provided in the Evidence Review.

For dichotomous (binary) outcomes, including measures such as risk of miscarriage or risk of precocious puberty, the scale presented in the figures (2.1-2.10) represents the magnitude of relative risk estimates (e.g. odds ratio, relative risk) for each outcome, and statistical evidence is represented separately as outlined in the key below.

KEY FOR INTERPRETING QUALITY AND SIGNIFICANCE OF FINDINGS

The key is to assist interpretation of Figures 2.1-2.10. The size of the circles (small, medium, large) represents the quality of individual systematic reviews (low, medium, high), as determined using the AMSTAR tool (Shea et al., 2007). Black and white circles, respectively indicate whether findings were statistically significant (95% confidence) or not. Furthermore, significant findings were written in bold text and asterisked in each figure.

Key



LIMITATIONS

Limitations of this Umbrella Review are detailed in Part 3: Evidence Review, with main issues as follows:

Meta-analyses included observational study designs exclusively (i.e. cohort, case control, cross sectional). This type of research is considered the most appropriate to assess risk of, and association with, adverse health outcomes in humans where controlled experimental exposure would not be ethical, compared to experimental (animal) research designs. Confounding factors, both known or unknown, may also have a direct effect on the health outcome. This can mask adverse health effects, or result in spurious findings where it is the confounding factor that is affecting the health outcome, not the plastic-associated chemical itself.

For example, the risk of developing cardiovascular disease from exposure to plastic-associated chemicals should be interpreted in the light of other risk factors such as family history and lifestyle factors, including diet and exercise. Epidemiological studies consider these factors in their methods and analyses. Thus, the more consistent the findings are, the stronger the association, and the better

that confounding factors have been accounted for within the primary studies, the more likely that an association reflects an underlying causal relationship.

SUMMARY OF FINDINGS

STUDIES IDENTIFIED AND INCLUDED

The findings in this report are based on 52 included systematic reviews (for illustration of study identification and inclusion; see Appendix 4). The first was published in 2009, and two-thirds between 2017-2020, reflecting increasing concern about the impact of plastic exposure on human health. Of note, 10 systematic reviews were excluded due to analysis errors identified during study appraisal and extraction.

PLASTIC-ASSOCIATED CHEMICALS REPORTED

Our search strategy covered a comprehensive range of polymers, plastic-associated chemicals and health outcomes. However, systematic reviews with meta-analysis were only identified for small number of plastic-associated chemicals, and no meta-analyses were identified for micro- or nanoplastics.

Plastic-associated chemicals that were identified by the comprehensive search and reported in this Umbrella Review are:

- Bisphenol A (BPA)
- Phthalates (plasticisers)
- Flame retardants (PCBs and PBDEs)
- Per- and polyfluoralkyl substances (PFAS)

All are high volume industrial chemicals used in a wide range of products and applications. Overall, approximately 25 million Mt (metric tonnes) of additives are produced every year (Ryberg et al., 2018). Chemical release, and therefore pollution, occurs during industrial processing. Moreover, all share the characteristic leaching from products during use and after disposal of plastic in the environment (Seewoo et al., 2023). Further details on each chemical's production volume, when they were discovered or first made, their properties, applications and occurrence in the environment, and therefore the sources for human exposure, as well as how the chemicals are measured in humans are provided in Appendix 1.

Collectively, BPA, phthalates, flame retardants and PFAS, along with other chemicals such as pesticides (e.g. DDT), heavy metals (e.g. lead, cadmium) and anti-bacterials (e.g. triclosan), are considered to be endocrine-disrupting chemicals (Diamanti-Kandarakis et al., 2009; Gore et al., 2014). These chemicals interfere with endocrine systems that regulate growth, behaviour, and reproduction and are linked to a wide range of health impacts.

HEALTH OUTCOMES REPORTED

BIRTH OUTCOMES

Number of systematic reviews: Birth outcomes were reported in 10 systematic reviews and one pooled analysis addressing exposure to BPA (n=2), phthalates (n=2), flame retardants (n=4) and PFAS (n=3).

Quality: Quality appraisal of the reviews and pooled analysis was rated between 3 – 10/11 (low to high quality).

Exposure: Exposures were prenatal and measured in maternal urine samples during pregnancy, amniotic fluid, cord blood or serum, maternal serum, blood or breast milk, or paternal blood.

Health outcomes: Birth outcomes included predominantly anthropometric outcomes of infants (birth weight, birth length, head circumference, gestational age, ponderal index and secondary sex ratio) and mothers (miscarriage).

Populations: These outcomes were measured at birth.

Statistically significant findings were reported for: decreased birth weight with higher exposure to DEP, PCB 153, total PCBs, total PBDEs, PFOA and PFOS (Fig 2.1a), decreased birth length with exposure to PFOA (Fig 2.1b), and an increased risk of miscarriage (spontaneous pregnancy loss) with higher exposure to the phthalates DnBP and DEHP (Fig 2.1f).

Trends: There was a trend for increased risk of miscarriage with higher exposure to each phthalate studied, but this was only found to be statistically significant for DnBP and DEHP (Fig 2.1f).

No statistically significant findings: There was no clear increase or decrease in birth weight with exposure to BPA or with exposure to phthalates other than DEP (Fig 2.1a). There was additionally no clear increase or decrease in birth length with exposure to BPA or total PBDEs (Fig 2.1b). Similarly, there was no clear increase or decrease in ponderal index with PFOA (Fig 2.1c), or gestational age with exposure to BPA (Fig 2.1d). A non-significant trend was found for decreased in head circumference with exposure to each of BPA, total PBDEs and PFOA (Fig 2.1e).

Figure 2.1 – Plastic-associated chemicals and birth outcomes

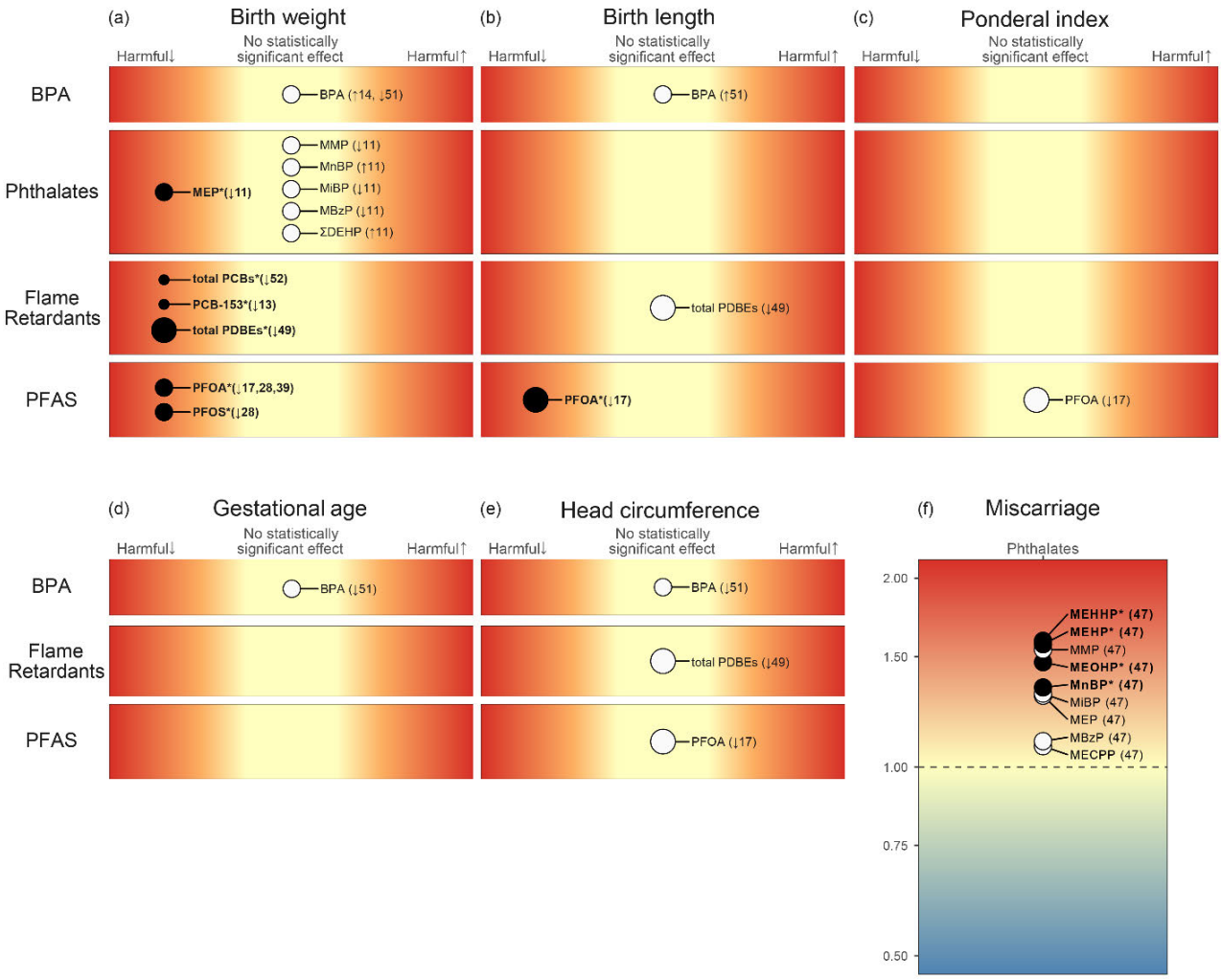


Figure 2.1 – Plastic-associated chemicals and birth outcomes. *Each outcome or set of related outcomes is presented in an individual panel with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included (a) birth weight; (b) birth length; (c) ponderal index; (d) gestational age; (e) head circumference and (f) risk of miscarriage.*
The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome (small circle, low; intermediate circle, moderate; and large circle, high quality respectively). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.
For continuous outcomes (panels a - e), colour in the panel indicates harm for higher exposure to the plastic-associated chemical (red is harmful, yellow is no statistically significant increase or decrease). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to the plastic-associated chemical, an arrow down indicates a decrease) in the systematic review. For dichotomous (risk) outcomes (panel f), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (Odds Ratio, OR; Risk Ratio, RR; Effect Size, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Birth weight (Fig 2.1a)

- Birth weight was investigated in eight systematic reviews and one pooled analysis. Birth weight significantly decreased when infants were prenatally exposed to higher levels of the phthalate DEP (measured as urinary metabolite MEP; AMSTAR score [AS] 5/11; moderate quality), PCB 153 (AS 3/11; low quality), total PCBs (AS 4/11; low quality), total PBDEs (AS 9/11; high quality), PFOA (AS 4-10/11; low-high quality) and PFOS (AS 8/11; moderate

quality). There was no clear increase or decrease in birth weight when exposed to BPA (AS 5-8/11; moderate quality) or with exposure to phthalates other than DEP (AS 5/11; moderate quality).

Birth length (Fig 2.1b)

- Birth length was reported in three systematic reviews investigating BPA, flame retardants and PFAS. Birth length significantly decreased when infants were prenatally exposed to higher PFOA (AS 10/11; high quality). There was no clear increase or decrease in birth length with exposure to BPA (AS 5/11; moderate quality) and total PBDEs (AS 9/11; high quality) respectively.

Ponderal index (weight for length) (Fig 2.1c)

- Ponderal index was reported in one systematic review on PFOA. There was no clear increase or decrease in ponderal index with exposure to PFOA (AS 10/11; high quality).

Gestational age (Fig 2.1d)

- Gestational age was reported in one systematic review investigating BPA. There was no clear increase or decrease in gestational age when infants were prenatally exposed to BPA (AS 5/11; moderate quality).

Head circumference (Fig 2.1e)

- Head circumference was reported in three systematic reviews investigating BPA, flame retardants and PFAS. There was no clear increase or decrease in head circumference when infants were prenatally exposed to BPA (AS 5/11; moderate quality), total PBDEs (AS 9/11; high quality) or PFOA (AS 10/11; high quality).

Miscarriage (spontaneous pregnancy loss) (Fig 2.1f)

- Spontaneous pregnancy loss was reported in one systematic review on phthalates. An increased risk of spontaneous pregnancy loss was found when mothers were exposed to higher levels of the phthalates DnBP and DEHP (measured as urinary metabolites MnBP, MEHP, MEOHP and MEHHP). There was a trend for increased risk of miscarriage with higher exposure to each phthalate studied, but this was not found to be statistically significant for other phthalates other than DnBP and DEHP (AS 7/11; moderate quality).

Secondary sex ratio (not in figure)

- Secondary sex ratio (that is ratio of male to female live births) was investigated in one review of PCBs. There was no increase or decrease found in secondary sex ratio when exposed to higher total PCBs (AS 3/11; low quality).

CHILD REPRODUCTIVE OUTCOMES

Number of systematic reviews: Child reproductive outcomes were reported in five systematic reviews addressing exposure to BPA (n=2) and phthalates (n=3).

Quality: Quality of the systematic reviews was rated between 7-8/11 (moderate quality).

Exposure: Exposures were prenatal and/or postnatal and measured using urine or blood serum samples.

Health outcomes: Child reproductive outcomes reported were predominantly measures of anogenital distance (AGD) and outcomes focused on timing of puberty. Specific AGD measures were anoclitoral and anofourchette distance in girls and predominantly anoscrotal distance in boys. Timing of puberty outcomes included onset of early puberty, precocious puberty and timing of thelarche, pubarche and menarche in girls, and timing of pubarche in boys. Changes in testicular volume were also reported.

Populations: These outcomes were measured at birth, and at puberty.

Statistically significant findings: In girls, a statistically significant decrease in anoclitoral distance was found with higher prenatal BPA exposure (Fig 2.2a). In boys, a significant decrease in AGD was found with higher prenatal DEHP exposure (measured as urinary DEHP metabolites) (Fig 2.2c). Considering puberty-related outcomes, statistically significant findings were found for: increased risk of precocious (early) puberty in girls with higher postnatal DEHP (measured in blood), and increased risk of abnormal timing of thelarche (breast development) in girls with higher postnatal exposure to the phthalate DEHP (measured as urinary metabolites MEHHP and MEOHP) (Fig 2.2e). In boys, postnatal exposure to DnBP and DEHP (measured by urinary MnBP and urinary MEHHP and MEOHP) was associated with a decreased risk of abnormal timing of pubarche (Fig 2.2f).

Trends: There was a trend towards decrease in anofourchette distance was not found to be statistically significant (Fig 2.2b).

No statistically significant findings: There were non-significant trends towards increased risk of precocious (early) puberty in girls with increased postnatal exposure to BPA (Fig 2.2d) and DnBP (measured in blood) (Fig 2.2e). There was no clear increased or decreased risk in abnormal timing of thelarche, pubarche and menarche in girls (Fig 2.2e) or and changes in testicular volume in boys with exposure to other phthalates studied (Fig 2.2f).

Figure 2.2 – Plastic-associated chemicals and child reproductive outcomes

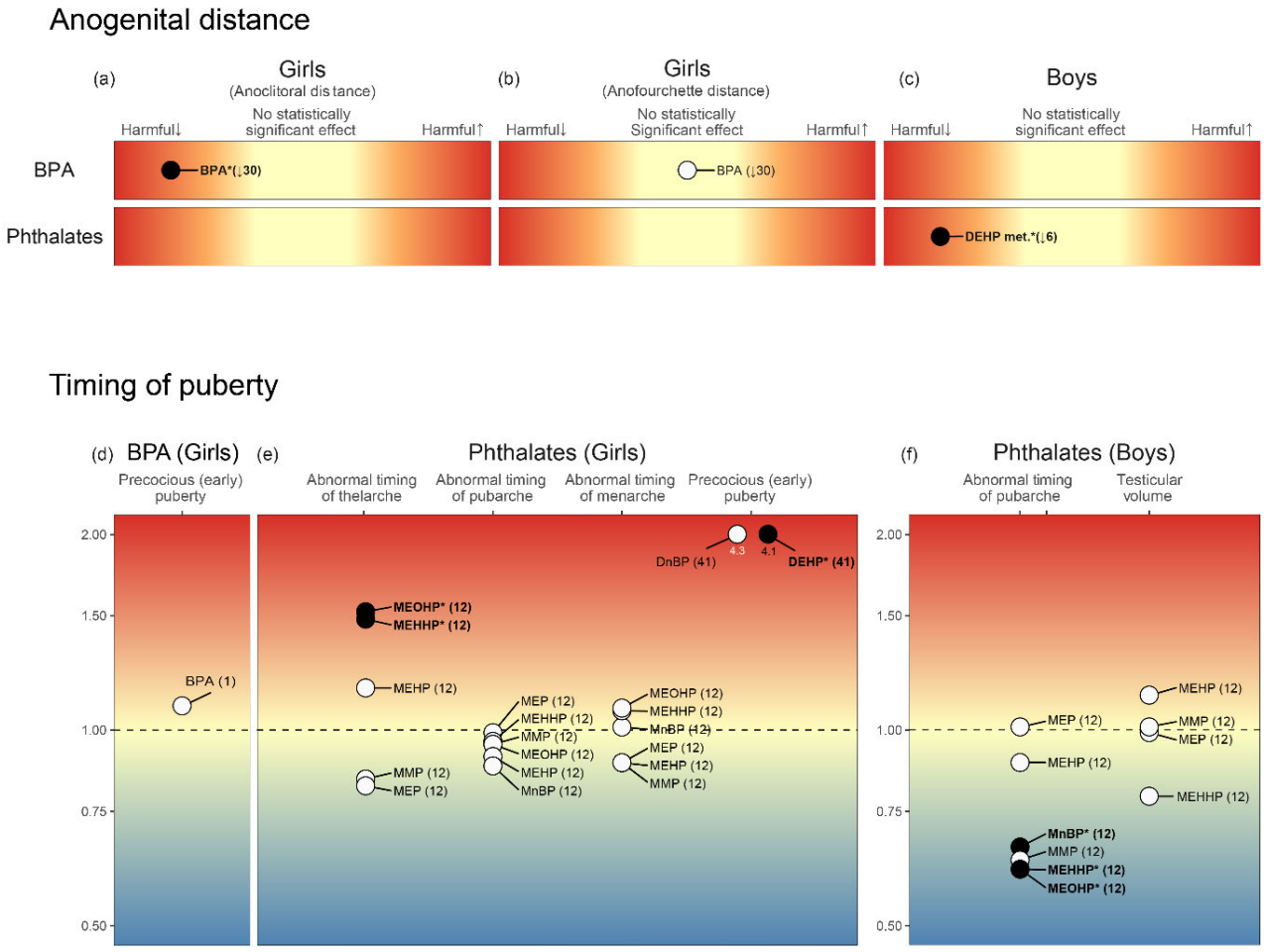


Figure 2.2 – Plastic-associated chemicals and child reproductive outcomes. *Each outcome or set of related outcomes is presented in an individual panel with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included measures of anogenital distance in (a – b) girls; and (c) boys; and markers of timing of puberty in (d – e) girls and (f) boys.*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome. For the outcomes presented in this figure, all reviews were moderate quality (intermediate circle, moderate). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For continuous outcomes (panels a - c), colour in the panel indicates harm for higher exposure to the plastic-associated chemical (red is harmful, yellow is no statistically significant increase or decrease). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to the plastic-associated chemical, an arrow down indicates a decrease) in the systematic review. For dichotomous (risk) outcomes (panel d-f), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Anogenital distance (AGD) (Fig 2.2a-c)

- AGD was reported in two systematic reviews investigating BPA and phthalates respectively. Anoclitoral distance significantly decreased with higher prenatal BPA exposure with a non-significant trend towards decreased anofourchette distance (AS 7/11; moderate quality). AGD (measured predominantly using anoscrotal distance) significantly decreased in boys with higher prenatal exposure to DEHP (measured as sum of urinary DEHP metabolites) (AS 8/11; moderate quality).

Timing of puberty (Fig 2.2d-f)

- Timing of puberty outcomes were investigated with BPA and phthalates in three systematic reviews. Risk of precocious puberty in girls significantly increased with higher postnatal exposure to DEHP (measured as in blood) with a similar but non-significant trend towards increased risk with postnatal DnBP exposure measured in blood (AS 7/11; moderate quality), or with postnatal exposure to BPA (AS 5/11; moderate quality). There was also a significant increase in risk of abnormal timing of thelarche in girls with higher postnatal exposure to the phthalate DEHP (measured as urinary metabolites MEHHP and MEOHP) (AS 7/11; moderate quality). By contrast, risk of abnormal timing of pubarche in boys significantly decreased with postnatal exposure to the phthalates DnBP (measured as urinary metabolite MnBP) and DEHP (measured as urinary metabolites MEHHP and MEOHP) (AS 7/11; moderate quality). There was no clear risk of other timing of puberty outcomes, nor change in testicular volume found with other phthalate metabolites.

ADULT REPRODUCTIVE OUTCOMES

Number of systematic reviews: Adult reproductive outcomes were reported in five systematic reviews addressing exposure to BPA (n=1), phthalates (n=2) and flame retardants (n=2).

Quality: Quality appraisal of the systematic reviews was rated between 3 – 8/11 (low to moderate quality).

Exposure: Exposures were measured in adult urine, or serum, or standardised serum lipid samples, adipose tissue and seminal fluid.

Health outcomes: Outcomes reported included compromised sperm concentration, sperm DNA damage, sperm morphology, sperm motility, sperm motion and semen volume in subfertile males and endometriosis in females.

Populations: These outcomes were measured in adult males (subfertile men) and females.

Statistically significant findings: Statistically significant findings were reported for sperm DNA damage (measured as comet extent and tail distributed moment) with higher exposure to the phthalates DEP and BBP (measured as urinary metabolites MEP and MBzP respectively; Fig 2.3b & 2.3c), decreased straight line and curvilinear velocity (sperm motion) with higher exposure to the phthalate DnBP (measured as urinary metabolite MnBP; Fig 2.3d & 2.3e), increased straight line and curvilinear velocity with higher exposure to the phthalate DEP (measured as urinary metabolite MEP; Fig 2.3d & 2.3e), decreased motility of sperm with higher DnBP and DEHP in seminal fluid (Fig 2.3g), increased risk of a low sperm concentration with higher exposure to the phthalates BBP and DnBP (measured as urinary metabolites MBzP and MnBP; Fig 2.3h), and increased risk of endometriosis with higher exposure to the phthalate DEHP (measured as urinary metabolite MEHHP; Fig 2.3i). A significant increased risk of endometriosis was also found for total PCB exposure (Fig 2.3i).

No statistically significant findings: There was no clear increase or decrease in other sperm DNA damage, motility, morphology or semen volume with other phthalates (Fig 2.3a-h), and no clear increased or decreased risk of endometriosis with BPA exposure.

Figure 2.3 – Phthalate exposure and adult reproductive outcomes

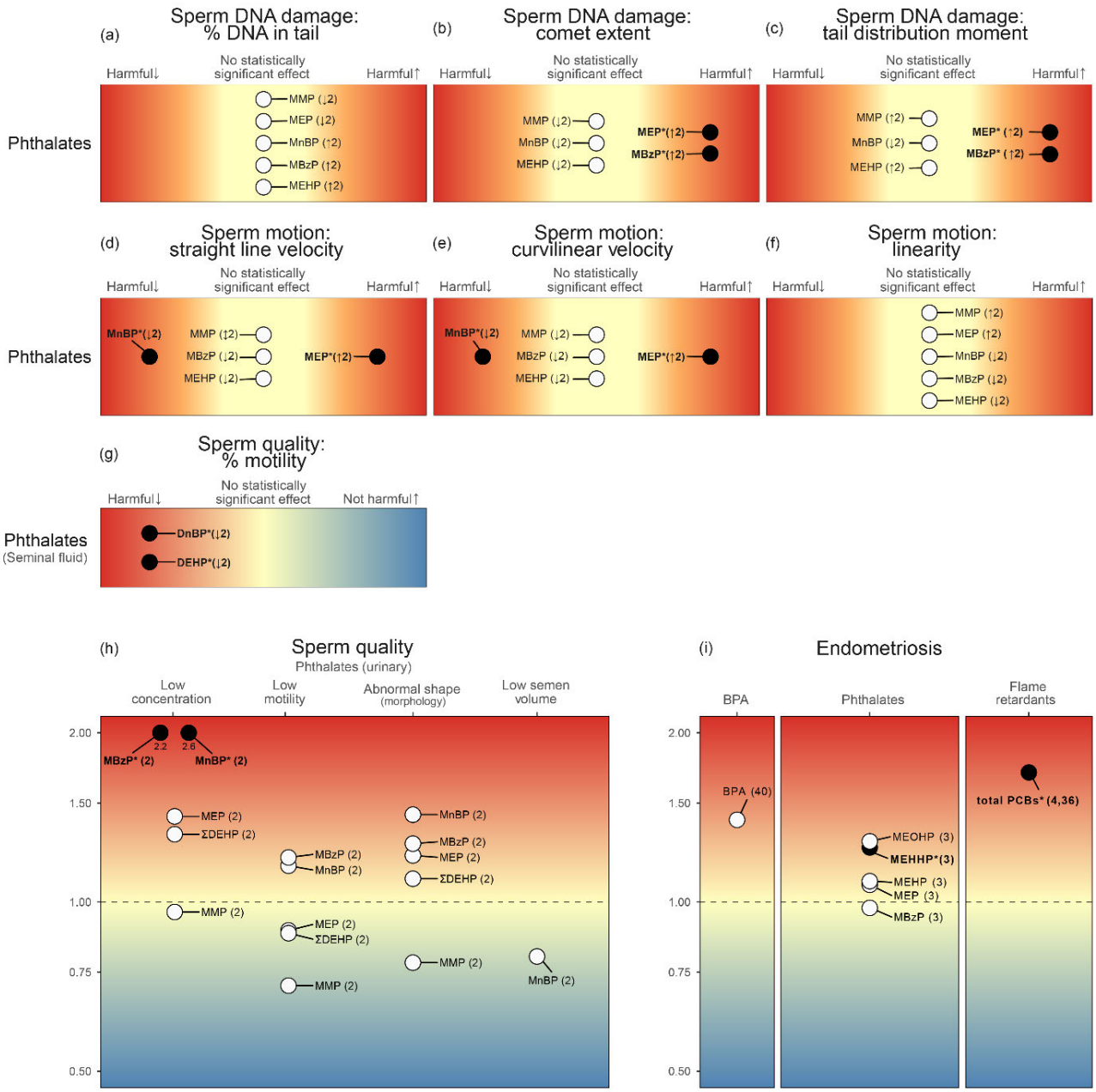


Figure 2.3 – Phthalate exposure and adult reproductive outcomes. *Each outcome or set of related outcomes is presented in an individual panel with phthalates for which evidence is available. Outcomes reported included measures of sperm DNA damage (a – c), sperm motion (d – e) and markers of sperm quality including motility, concentration, shape and semen volume (g – h). Risk of endometriosis in women was also reported (i).*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome. For the outcomes presented in this figure, all reviews were moderate quality (intermediate circle, moderate). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For continuous outcomes (panels a - g), colour in the panel indicates harm for higher exposure to phthalates (red is harmful, yellow is no statistically significant increase or decrease; blue is not harmful/protective). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to phthalates, an arrow down indicates a decrease) in the systematic review. For dichotomous (risk) outcomes (panel h - i), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Sperm DNA damage (Fig 2.3a-c)

Sperm DNA damage was assessed using comet assay parameters % DNA in tail, comet extent and tail distributed moment. Sperm DNA damage was investigated in a review on phthalate exposure in subfertile males.

- Comet extent and tail distributed moment significantly increased with higher exposure to the phthalates DEP and BBP (measured as urinary metabolites MEP and MBzP respectively). There was no clear increase or decrease in comet extent measures or tail distributed moment with other phthalates (AS 6/11; moderate quality).
- There was no clear increase or decrease in sperm % DNA in tail with exposure to phthalates (AS 6/11; moderate quality).

Sperm motion (Fig 2.3d-f)

Sperm motion was measured using straight line velocity, curvilinear velocity and linearity. Sperm motion was investigated in one systematic review on phthalate exposure and subfertile males (AS 6/11; moderate quality).

- Straight line velocity significantly increased with higher exposure to the phthalate DEP (measured as urinary metabolite MEP) but significantly decreased with higher exposure to the phthalate DnBP (measured as urinary metabolite MnBP). There was no clear increase or decrease in straight line velocity with other phthalates (AS 6/11; moderate quality).
- Curvilinear velocity significantly increased with higher exposure to the phthalate DEP (measured as urinary metabolite MEP) but significantly decreased with higher exposure to the phthalate DnBP (measured as urinary metabolite MnBP). There was no clear increase or decrease in curvilinear velocity with other phthalates (AS 6/11; moderate quality).
- There was no clear increase or decrease in linearity with phthalate exposure (AS 6/11; moderate quality).

Low sperm concentration (Fig 2.3h)

- Sperm concentration was investigated in one systematic review on phthalate exposure and subfertile males (reference standard ≥ 20×10^6 *m*L). Risk of low sperm concentration significantly increased with higher exposure to the phthalates BBP and DnBP (measured as urinary metabolites MBzP and MnBP, respectively). No clear increased or decreased risk was found with higher exposure to the phthalates DEP and DEHP (measured as urinary metabolites MEP and sum of DEHP metabolites) and no clear increased or decreased risk was found with exposure to the phthalate DMP (measured as urinary metabolite MMP) (AS 6/11; moderate quality).

Sperm motility (Fig 2.3g & 2.3h)

Sperm motility was investigated in one systematic review on phthalate exposure and subfertile males.

- The percentage of (normal) motile sperm significantly decreased with higher DnBP and DEHP in seminal fluid (AS 6/11; moderate quality).
- There was no clear increased or decreased risk of low sperm motility (reference standard of ≥ 50 % motile) with exposure to the phthalates investigated (DMP, DEP, DnBP, and BBP, DEHP) (measured as urinary metabolites MMP, MEP, MnBP, MBzP and sum of DEHP metabolites) (AS 6/11; moderate quality).

Abnormal sperm morphology (Fig 2.3h)

- Sperm morphology (shape) was investigated in one systematic review on phthalate exposure and subfertile males (reference standard of ≥ 4 % normal morphology). There was no clear increased or decreased risk of having abnormal sperm morphology with exposure to the phthalates DMP, DEP, DnBP, BBP and DEHP (measured respectively as urinary metabolites MMP, MEP, MnBP, MBzP and sum of DEHP metabolites). (AS 6/11; moderate quality).

Low semen volume (Fig 2.3h)

- Semen volume was investigated in one systematic review on phthalate exposure and subfertile males. There was no clear increased or decreased risk of reduced semen volume when exposed to the phthalate DnBP (measured as urinary metabolite MnBP) (AS 6/11; moderate quality).

Endometriosis (Fig 2.3i)

- Endometriosis was investigated in four systematic reviews on BPA, phthalates and flame-retardant exposure in females. Risk of endometriosis was increased with higher exposure to the phthalate DEHP (measured as urinary metabolite MEHHP) (AS 7/11; moderate quality) and total PCBs (AS 3-8/11; low to moderate quality). There were also similar but non-significant trends towards increased risk of endometriosis with exposure to DEHP measured as alternative urinary metabolites MEHP and MEOHP (AS 7/11; moderate quality). There was no clear increased or decreased risk of endometriosis with exposure to BPA (AS 7/11; moderate quality) and the phthalates DEP and BBP (measured as urinary metabolites MEP and MBzP) (AS 7/11; moderate quality).

METABOLIC AND ENDOCRINE OUTCOMES

Number of systematic reviews: Metabolic and endocrine outcomes were reported in eight systematic reviews and two pooled analyses addressing exposure to BPA (n=4), phthalates (n=3), flame retardants (n=4) and PFAS (n=1).

Quality: Quality appraisal of the reviews was rated between 4 – 9/11 (low to high quality).

Exposure: Exposures were measured in infants, children and adults. Samples were urine, blood and serum.

Health outcomes: Outcomes reported included measures of thyroid function (including levels of thyroid stimulating hormone (TSH), free thyroxine (fT4), total thyroxine (TT4), and triiodothyronine (T3)), measures of glucose homeostasis (including type 2 diabetes, fasting glucose levels, 2-hour glucose, insulin resistance (HOMA-IR), fasting insulin, 2-hour insulin), polycystic ovary syndrome (PCOS) and death from liver (hepatic) disease.

Populations: These outcomes were mainly assessed in the general population of children and adults but effects of PCB on death from liver disease were assessed in studies of special high-risk population groups (food contamination and PCB poisoning).

Statistically significant findings: Statistically significant findings were reported for: decreased fT4 with higher exposure to the phthalate DEHP (measured as urinary metabolite MEHHP) (Fig 2.4b), increased fT4 with higher PFOS exposure (Fig 2.4b), increased TT4 with higher total PBDE levels (Fig 2.4c), increased insulin resistance (HOMA-IR) with higher BPA exposure (Fig 2.4d), increased insulin resistance (HOMA-IR) with higher exposure to total phthalates as well as specifically to DiBP, BBP and DEHP (measured respectively as urinary metabolites MiBP, MBzP, and sum of DEHP metabolites) and with higher concentration of the nonspecific phthalate metabolite MCPP (Fig 2.4d), increased fasting glucose with higher total PCB exposure (Fig 2.4e), increased risk of type 2 diabetes with higher exposure to BPA, the phthalate DiBP (measured as urinary metabolite MiBP) and total PCBs (Fig 2.4g), women with PCOS having higher BPA levels than women without PCOS (Fig 2.4h), and increased risk of death from liver disease was found for PCB poisoning (Fig 2.4i).

Trends: There were also similar but non-significant trends towards decreased fT4 with exposure to DEHP measured as alternative urinary metabolites MEHP and MEOHP (Fig 2.4b).

No statistically significant findings: There was no clear increase or decrease in TSH with exposure to the phthalate DEHP (measured as urinary metabolites MEHP, MEHHP, MEOHP), exposure to total PBDEs, or exposure to PFOA, PFOS and PFHxS (Fig 2.4a). Likewise, there was no clear increase or decrease in fT4 with exposure to PFOA and PFHxS (Fig 2.4b), and no clear increase or decrease in TT4

with exposure to DEHP (measured as urinary metabolites MEHP, MEHHP, MEOHP) or exposure to PFOA, PFOS, and PFHxS (Fig 2.4c).

There was no clear increase or decrease in insulin resistance with exposure to the phthalates DMP and DEP (measured as urinary metabolite MMP and MEP), or total PCBs (Fig 2.4d), no clear increase or decrease in fasting glucose with exposure to BPA or total phthalates (Fig 2.4e), no clear increase or decrease in 2-hour glucose with total PCB exposure (Fig 2.4f), and no clear increased or decreased risk of type 2 diabetes with exposure to DEP (measures as urinary metabolite MEP) or total phthalates (Fig 2.4g).

Figure 2.4 – Plastic-associated chemicals and metabolic and endocrine outcomes

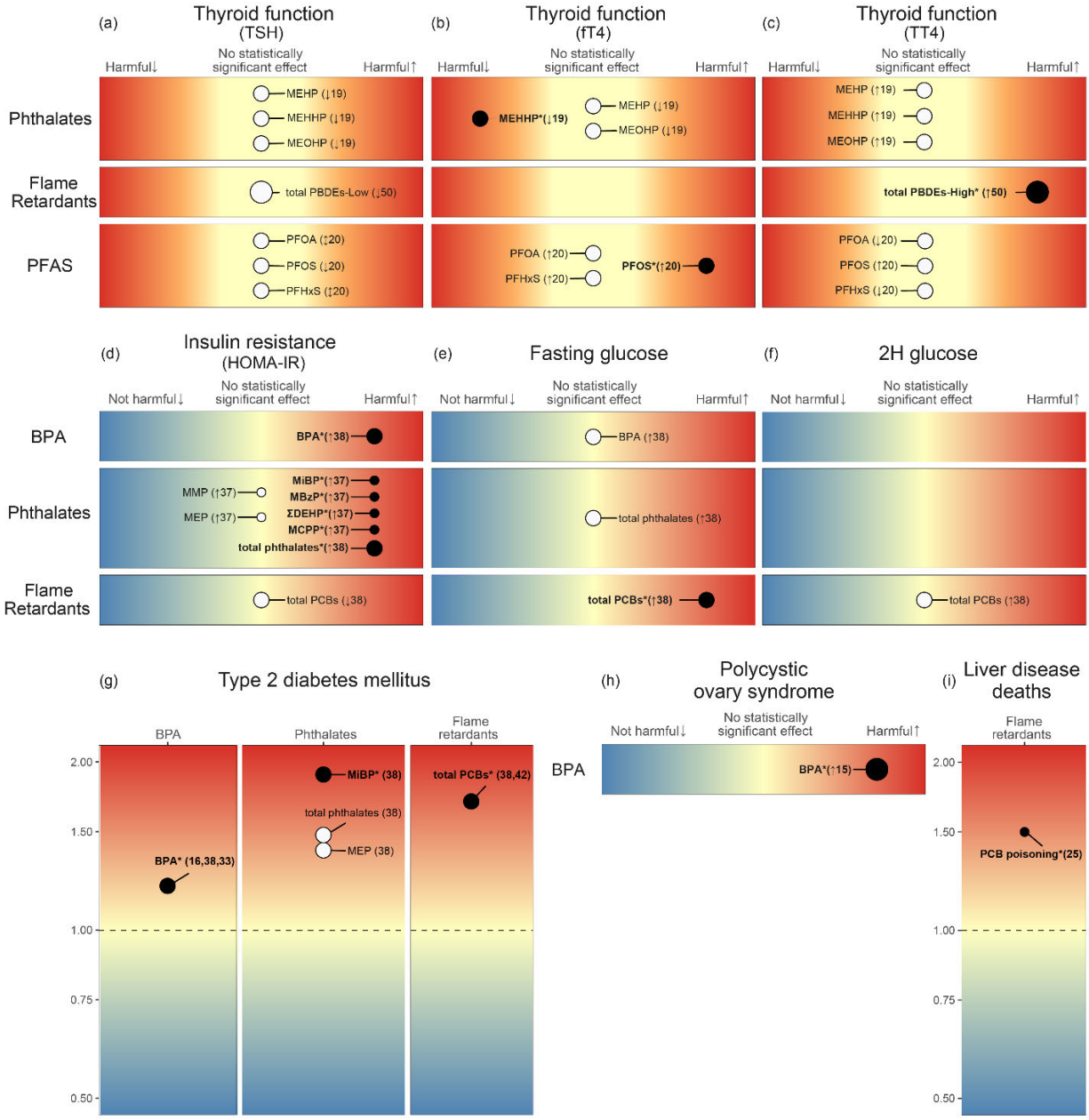


Figure 2.4 – Plastic-associated chemicals and metabolic and endocrine outcomes. *Each outcome or set of related outcomes is presented in an individual panel with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included measures of thyroid function (a – c), blood glucose regulation (d – f) and risk of type 2 diabetes (g). Levels of BPA in women with polycystic ovary syndrome (h), and death attributable to liver disease following PCB poisoning (i) were also reported. Fig. 4(a) PBDEs-Low. Findings for total PBDE exposure and TSH on meta-analysis of the subgroup of lower total PBDE exposure studies (a subgroup meta-analysis of higher total PBDE exposure studies was excluded for methodological issues, see Evidence Review). Fig. 4(b) PBDEs-High. Findings for total PBDE exposure and TT4 on meta-analysis of the subgroup of higher total PBDE exposure studies (a subgroup meta-analysis of lower total PBDE exposure studies was excluded for methodological issues, see Evidence Review)*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome (small circle, low; intermediate circle, moderate; and large circle, high quality respectively). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For continuous outcomes (panels a – f, h), colour in the panel indicates harm for higher exposure to the plastic-associated chemical (red is harmful, yellow is no statistically significant increase or decrease; blue is not harmful/protective). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to the plastic-associated chemical, an arrow down indicates a decrease, and a double-headed arrow indicates no clear direction of effect) in the systematic review. For dichotomous (risk) outcomes (panel g and i), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Thyroid function (Fig 2.4a-c)

- Thyroid function was investigated in three systematic reviews on phthalates, flame retardants and PFAS exposure in adults and children. Thyroid function measures included thyroid stimulating hormone (TSH), free thyroxine (fT4), total thyroxine (TT4), and triiodothyronine (T3). There was no clear increase or decrease in TSH levels with exposure to the plastic-associated chemicals included in these reviews (AS 5-9; moderate to high quality). Free thyroxine (fT4) significantly decreased with higher exposure to the phthalate DEHP measured as urinary metabolite MEHHP, with similar but non-significant trends towards decreased fT4 with exposure to DEHP measured as alternative urinary metabolites MEHP and MEOHP) (AS 5/11; moderate quality), but also non-significant trends towards increased total thyroxine (TT4) for each of these DEHP metabolites (AS 5/11; moderate quality). Conversely, fT4 significantly increased with higher PFOS exposure (AS 7/11; moderate quality), with similar but non-significant trends towards increased fT4 with exposure to the other PFAS chemical studied (AS 7/11; moderate quality). No data were found for changes in fT4 with flame retardant exposures, but TT4 significantly increased with higher exposure to total PBDEs, in an analysis limited to studies of populations with higher PBDE exposure (AS 9/11; high quality; subgroup of higher total PBDE exposure studies; findings for studies of lower total PBDE exposure excluded, details in Part 3: Evidence Review).

Insulin resistance (HOMA-IR) (Fig 2.4d)

- Insulin resistance was measured using HOMA-IR and reported in two systematic reviews investigating BPA, phthalates and flame-retardant exposure on adults. Insulin resistance significantly increased with higher BPA exposure (AS 6/11; moderate quality), higher exposure to phthalates DiBP, BBP and DEHP (measured respectively as urinary metabolites MiBP, MBzP, and sum of DEHP metabolites) and with higher concentration of the nonspecific phthalate metabolite MCPP (AS 4/11; low quality). There was no clear increase or decrease in insulin resistance with exposure to the phthalates DMP and DEP (measured as urinary metabolites MMP and MEP respectively), with total phthalates, or with total PCBs (AS 4-6/11; low to moderate quality).

Fasting glucose (Fig 2.4e)

- Fasting glucose was investigated in one systematic review on BPA, phthalates and flame-retardant exposure in adults. Fasting glucose significantly increased with exposure to total PCBs whilst there was no clear increase or decrease in fasting glucose with BPA or total phthalates (AS 6/11; moderate quality).

2-hour glucose (Fig 2.4f)

- 2-hour glucose was investigated in one systematic review on flame-retardant exposure in adults. There was no clear increase or decrease in the 2-hour glucose test with exposure to total PCBs (AS 6/11; moderate quality).

Fasting insulin (not in figure)

- Fasting insulin was investigated in one systematic review on both BPA and flame-retardant exposure in adults. There was no clear increase or decrease in fasting insulin with exposure to BPA or total PCBs (AS 6/11; moderate quality).

2 hr insulin (not in figure)

- 2 hr insulin was investigated in one systematic review on flame-retardant exposure in adults. There was no clear increase or decrease in 2 hr insulin with exposure to total PCBs (AS 6/11; moderate quality).

Type 2 diabetes (Fig 2.4g)

- Type 2 diabetes (T2D) was reported in three systematic reviews and one pooled analysis investigating BPA, phthalates and flame-retardant exposure in adults. Risk of T2D significantly increased with higher exposure to BPA, the phthalate DiBP (measured as urinary metabolite MiBP) and total PCBs (AS 6-7/11; moderate quality). There were similar but non-significant trends towards increased risk of T2D with higher exposure to the phthalate DEP (measured as urinary metabolite MEP) and total phthalates (AS 6/11; moderate quality).

Polycystic ovary syndrome (PCOS) (Fig 2.4h)

- PCOS was investigated in one systematic review on BPA. Women with PCOS were found to have significantly higher BPA levels than women without PCOS (AS 9/11; high quality).

Hepatic disease death (Fig 2.4i)

- Hepatic disease death was investigated in one pooled analysis on flame retardants on special high-risk populations. The special high-risk populations were population cohorts from Japan (Yu-Sho) and Taiwan (Yu-Cheng) during a PCB poisoning incident. There was no clear increased or decreased risk of hepatic disease death found with special exposure from PCB poisoning (AS 4/11; low quality).

CHILD NEURODEVELOPMENTAL OUTCOMES

Number of systematic reviews: Child neurodevelopmental outcomes were reported in three systematic reviews and one pooled analysis addressing exposure to phthalates (n=2), flame retardants (n=1) and PFAS (n=1).

Quality: Quality of the systematic reviews rated between 3-11/11 (low to high quality).

Exposure: Exposures were prenatal, child, as well as current and measured in maternal urine, plasma or serum, breast milk or cord blood.

Health outcomes: Child neurodevelopmental outcomes included cognitive development and intelligence quotient (IQ), fine motor development, and attention deficit hyperactivity disorder (ADHD). Specific outcome measures of child cognitive development and IQ included: Mental Development Index (MDI) subscale of the Bayley Scales of Infant Development, 2nd edition (BSID-II), Cognitive Development subscale of the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III), General Cognitive Scale (GCS) of the McCarthy Scales of Children's Abilities (MSCA), and Full Scale IQ (FSIQ) of the Wechsler Preschool & Primary Scale of Intelligence (WPPSI) or Wechsler Intelligence Scale for Children (WISC). Fine motor development outcomes were for young children only, measured on the Psychomotor Development Index (PDI) subscale of the Bayley Scales of Infant Development, 2nd edition (BSID-II), and Fine Motor subscale of the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III). ADHD status was determined by symptoms reported on standardised questionnaire measures including the Attention Problems Syndrome Scale of the Child Behaviour Checklist (CBCL-ADHD), the Hyperactivity/Inattention Problems subscale of the Strengths and Difficulties Questionnaire (SDQ-Hyperactivity/Inattention) or based upon ADHD criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Populations: These outcomes were assessed in children.

Statistically significant findings: Significant findings were reported for: decreased children's cognitive development and IQ with higher current exposure to DEHP (measured as urinary DEHP metabolites) and higher prenatal exposure to BDE-47 (Fig 2.5a); decreased preschool children's fine motor development with higher prenatal exposure to DEHP (measured as urinary DEHP metabolites) (Fig 2.5b); and increased risk of ADHD in girls and prenatal PFOA exposure (Fig 2.5c).

No statistically significant findings: There was no clear increase or decrease in the other child neurodevelopmental outcomes with prenatal exposure to phthalates (Fig 2.5a & 2.5b) and no clear increased or decreased risk of ADHD in boys with prenatal exposure to PFAS (Fig 2.5c).

Figure 2.5 – Plastic-associated chemicals and child neurodevelopmental outcomes

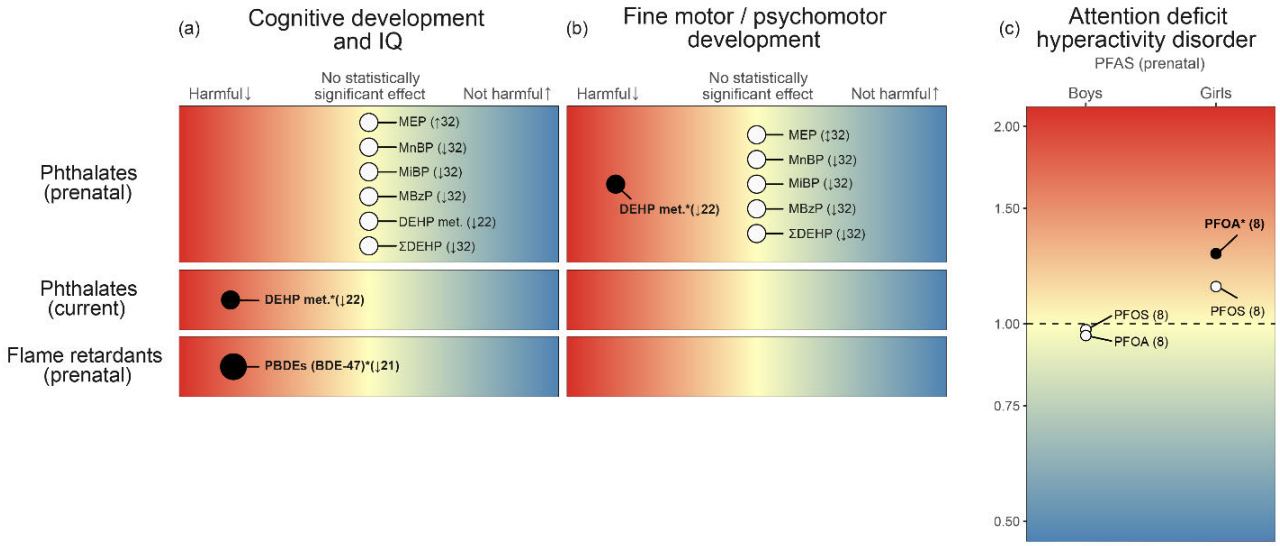


Figure 2.5 – Plastic-associated chemicals and child neurodevelopmental outcomes. *Each outcome is presented in an individual panel with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included child's cognitive development and IQ (a), fine motor/psychomotor development (b) and risk of attention deficit hyperactivity disorder (c).*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome (small circle, low; intermediate circle, moderate; and large circle, high quality respectively). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For continuous outcomes (panels a – b), colour in the panel indicates harm for higher exposure to the plastic-associated chemical (red is harmful, yellow is no statistically significant increase or decrease; blue is not harmful/protective). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to the plastic-associated chemical, an arrow down indicates a decrease, and a double-headed arrow indicates no clear direction of effect) in the systematic review. For dichotomous (risk) outcomes (panel c), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Cognitive development and intelligence quotient (IQ) (Fig 2.5a)

- Cognitive development and IQ were investigated in two systematic reviews investigating phthalates and a third investigating PBDE flame retardants. Cognitive development and IQ significantly decreased among children with current exposure to DEHP (measured as urinary DEHP metabolites) (AS 7/11; moderate quality) and among preschool children with prenatal exposure to PBDE 47 (AS 11/11; high quality). There was no clear increase or decrease in cognitive development among children with prenatal exposure to DEHP (measured as urinary DEHP metabolites) or other phthalates DEP, DnBP, DiBP, BBP (measured as urinary metabolites MEP, MnBP, MiBP and MBzP) (AS 7-8/11; moderate quality).

Fine motor development (Fig 2.5b)

- Fine motor development was reported in two systematic reviews both investigating phthalates. Fine motor development significantly decreased among preschool children with higher prenatal exposure to DEHP (measured as urinary DEHP metabolites) (AS 7/11; moderate quality). There was a similar but non-significant trend towards decreased fine motor development in preschool children with higher prenatal exposure to DEHP measured exclusively as a sum of urinary DEHP metabolites, and most other phthalates evaluated (DnBP, DiBP, BBP measured as urinary metabolites MnBP, MiBP and MBzP) but no clear increase or decrease with DEP (measured as urinary metabolite MEP) (AS 8/11; moderate quality).

Attention deficit hyperactivity disorder (ADHD) (Fig 2.5c)

- ADHD was investigated in one pooled analysis on PFAS. Analysis was based on a validated pharmacokinetic model to generate estimates of exposure at different times of pregnancy and postnatal life. Risk of ADHD in girls significantly increased with higher prenatal exposure to PFOA with a similar but non-significant trend towards increased ADHD in girls for higher postnatal PFOA exposure up to 24 months of age, and a weaker and non-significant trend towards increased ADHD in girls for higher prenatal and postnatal exposure to PFOS. There was no clear increased or decreased risk of ADHD found for prenatal exposure to PFOA or PFOS in boys (AS 3/11; low quality; note, only ADHD at birth is plotted in the figure).

NUTRITIONAL OUTCOMES

Number of systematic reviews: Nutritional outcomes were reported in seven systematic reviews addressing exposure to BPA (n=4), phthalates (n=2), PFAS (n=1).

Quality: Quality appraisal of the systematic reviews was rated between 5–7/11 (moderate quality).

Exposure: Exposures were measured in maternal serum, plasma and cord blood as well as in infants, children and adults using urine samples.

Health outcomes: Outcomes reported were BMI, elevated waist circumference, obesity and overweight.

Populations: These outcomes were reported for the general population of adults and children.

Statistically significant findings: Statistically significant findings were reported for: increased BMI z-score in children and higher prenatal and postnatal PFOA exposure (Fig 2.6a); increased child waist circumference and higher postnatal exposure to phthalate BBP (measured as urinary metabolite MBzP) and DEHP (measured as urinary metabolites MEHP and MEHHP) (Fig 2.6b); increased adult waist circumference with exposure to phthalate DEHP (measured as urinary metabolite MEHP) (Fig 2.6d); increased risk of obesity and overweight, and elevated waist circumference in children and adults with BPA exposure (Fig 2.6e); increased risk of obesity in adults and exposure to phthalate DEHP measured as urinary metabolite MECPP (Fig 2.6f); and increased risk of obesity in children and prenatal or postnatal PFOA exposure (Fig 2.6g).

No statistically significant findings: There was no clear increase or decrease in BMI in adults and children (measured as z-score), or waist circumference in children with exposure to other phthalates (Fig 2.6a-c). There was no clear increased or decreased risk of obesity in adults and children and exposure to DEP (measured as urinary metabolite MEP) or to DEHP when measured as urinary metabolite MEHP (Fig 2.6f).

Figure 2.6 – Plastic-associated chemicals and nutritional outcomes

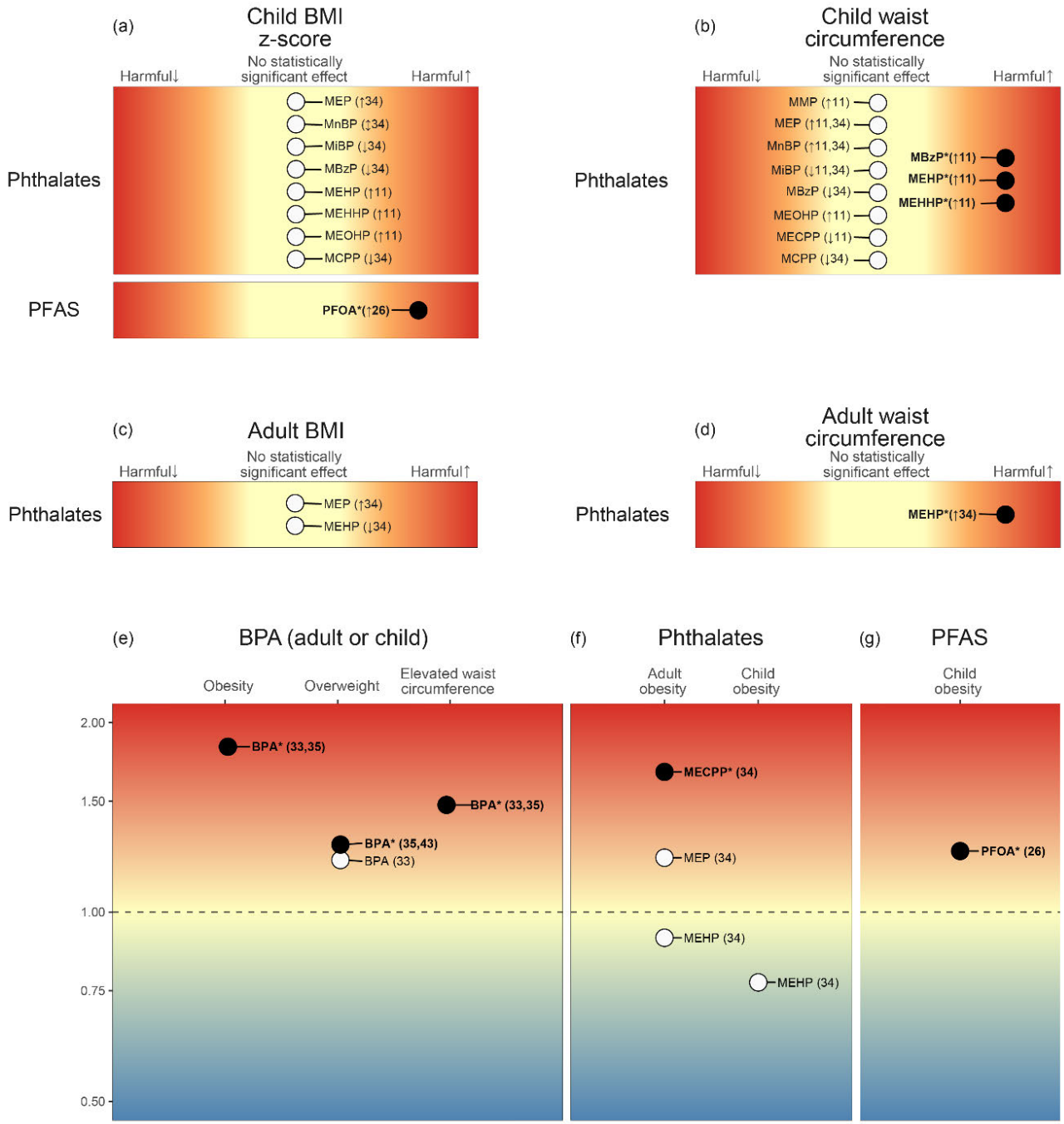


Figure 2.6 – Plastic-associated chemicals and nutritional outcomes. *Each outcome is presented in an individual panel or individual column with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included BMI and waist circumference of both children (a – b) and adults (c – d), as well as measures of obesity and overweight with BPA (e), phthalates (f) and PFAS (g).*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome. For the outcomes presented in this figure, all reviews were moderate quality (intermediate circle, moderate). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For continuous outcomes (panels a – d), colour in the panel indicates harm for higher exposure to the plastic-associated chemical (red is harmful, yellow is no statistically significant increase or decrease). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to the plastic-associated chemical, an arrow down indicates a decrease, and a double-headed arrow indicates no clear direction of effect) in the systematic review. For dichotomous (risk) outcomes (panel e - g), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

BMI (Fig 2.6a & 2.6c)

- BMI was investigated in three systematic reviews including phthalate and PFAS exposure in children and adults. BMI significantly increased in children with higher prenatal or postnatal PFOA exposure (AS 7/11; moderate quality). Child BMI also significantly increased with higher postnatal exposure to phthalates DiBP and DEHP (measured as urinary metabolites MiBP and MEHHP; not in figure), but there was no clear increased or decreased child BMI with DEHP measured as other metabolites, or with other phthalates, and no clear increased or decreased BMI with the phthalates studied where BMI was reported adjusted for age as a z-score (AS 5-6/11; moderate quality). There was no clear increase or decrease in BMI in adults with exposure to the phthalates DEP or DEHP (measured as urinary metabolites MEP and MEHP respectively) (AS 6/11; moderate quality).

Waist circumference (Fig 2.6b, 2.6d & 2.6e)

- Waist circumference was reported in four systematic reviews investigating BPA and phthalate exposure in children and adults. In children, waist circumference significantly increased with higher postnatal exposure to phthalates BBP (measured as urinary metabolite MBzP) in one of 2 reviews, and DEHP measured as urinary metabolites MEHP or MEHHP. However, there was no clear increase or decrease in waist circumference with BBP in the other review to investigate this, with DEHP measured as metabolites MEOHP or MECPP, or with other phthalates (AS 5-6/11; moderate quality). In adults, waist circumference significantly increased with higher exposure to phthalate DEHP (measured as urinary metabolite MEHP) in adults (AS 6/11; moderate quality). Risk of an elevated waist circumference significantly increased in children and adults with higher BPA exposure (AS 7/11; moderate quality).

Obesity (Fig 2.6e)

- Obesity was investigated in five systematic reviews on BPA, phthalate and PFAS exposure in children and adults. Risk of obesity significantly increased in children and adults with higher exposure to BPA (AS 7/11; moderate quality). Risk of obesity significantly increased in adults for higher exposure to the phthalate DEHP measured as urinary metabolites MECPP, however, there was no clear increased or decreased risk found with another DEHP phthalate metabolite (MEHP) and no clear increased or decreased risk with the phthalate DEP (measured as urinary metabolite MEP) (AS 6/11; moderate quality). There was a significant increase in risk of obesity in children with higher pre- or postnatal exposure to PFOA (AS 7/11; moderate quality). There was no clear increased or decreased risk of obesity in children with higher postnatal exposure to the phthalate DEHP (measured as urinary metabolites MEHP) (AS 6/11; moderate quality).

Overweight (Fig 2.6e)

- Association with being overweight was investigated in three systematic reviews on BPA exposure in children and adults. Two systematic reviews found significant increased risk of being overweight with higher BPA exposure (AS 6-7/11; moderate quality) and the third found a similar but non-significant trend for increased risk of being overweight (AS 7/11; moderate quality).

Generalised and abdominal obesity (not in figure)

- Subtypes of obesity were investigated in one systematic review on BPA exposure in children and adults. Risk of both generalised and abdominal obesity significantly increased with higher postnatal exposure to BPA (AS 5/11; moderate quality).

CIRCULATORY OUTCOMES

Number of systematic reviews: Circulatory outcomes were reported in four systematic reviews and two pooled analysis addressing exposure to BPA (n=3), phthalates (n=2) and flame retardants (n=3).

Quality: Quality appraisal of the reviews was rated between 4–7/11 (low to moderate quality).

Exposure: Exposures were measured in children and adults. Samples were urine, blood, plasma, serum, serum lipid or adipose tissue.

Health outcomes: Circulatory outcomes reported were blood pressure, serum lipid levels (including high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides), cardiovascular disease (CVD), cardiovascular disease deaths, cerebrovascular disease deaths, hypertension and hypertension deaths.

Populations: These outcomes were mainly assessed in the general population of children and adults, but effects of PCB exposure were additionally assessed in studies of special exposure populations with PCB poisoning due to food contamination, and one review of phthalate exposure was restricted to children only.

Statistically significant findings: Statistically significant findings were reported for: increased systolic BP in children with higher postnatal exposure to the phthalate DEHP (measured as urinary metabolites MEHHP and MEOHP) (Fig 2.7e); increased risk of cardiovascular disease and hypertension with higher BPA exposure (Fig 2.7f); increased risk of cardiovascular disease with higher PCB 138 and PCB 153 exposure, increased risk of hypertension with higher dioxin-like PCB exposure, and increased risk of cardiovascular disease deaths with special PCB exposure by poisoning (Fig 2.7h).

Trends: There was a non-significant trend towards increased systolic blood pressure with higher exposure to other phthalates DMP and BBP (measured as metabolites MMP and MBzP) and to DEHP measured as metabolite MEHP (Fig 2.7e), and a non-significant trend towards increased risk of cardiovascular disease with higher exposure to a third PCB flame retardant (PCB 180) and total PCBs (Fig 2.7h). There was a trend towards increased risk of cardiovascular disease with exposure to each phthalate evaluated, but no statistically significant findings amongst these (Fig 2.7g).

No statistically significant findings: There was no clear increase or decrease in HDL cholesterol, LDL cholesterol or triglycerides in adults and children with exposure to BPA (Fig 2.7a-c). There was no clear increase or decrease in HDL cholesterol, triglycerides or diastolic blood pressure with exposure to phthalates (Fig 2.7a, 2.7c & 2.7d). There was no clear increased or decreased hypertension with exposure to non-dioxin-like PCBs, and no clear increased or decreased risk in deaths related to cerebrovascular disease or hypertension with special PCB exposure by poisoning (Fig 2.7h).

Figure 2.7 – Plastic-associated chemicals and circulatory outcomes

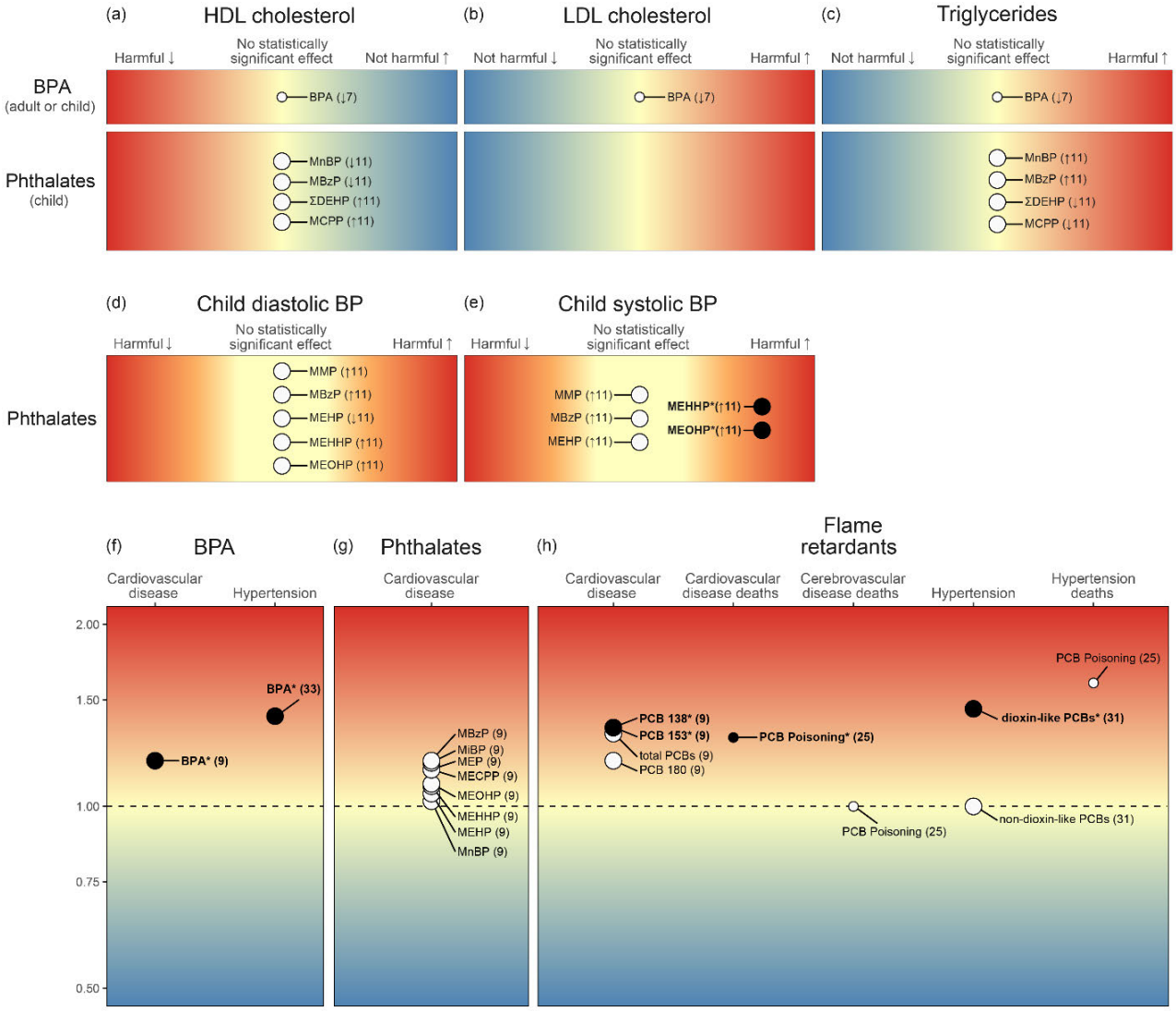


Figure 2.7 – Plastic-associated chemicals and circulatory outcomes. *Each outcome or set of related outcomes is presented in an individual panel or individual column with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included measures of serum lipids (a - c), blood pressure in children (d – e), risk of cardiovascular disease (f – h), risk of hypertension (f and h) as well as risk of death attributable to circulatory related diseases following PCB poisoning (h).*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome (small circle, low; and intermediate circle, moderate quality respectively). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For continuous outcomes (panels a – e), colour in the panel indicates harm for higher exposure to the plastic-associated chemical (red is harmful, yellow is no statistically significant increase or decrease; blue is not harmful/protective). Arrows represent the direction of the effect found (an arrow up indicates an increase in value of the outcome for higher exposure to the plastic-associated chemical, an arrow down indicates a decrease) in the systematic review. For dichotomous (risk) outcomes (panel c), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Serum lipids (Fig 2.7a-c)

- Serum lipids were investigated in a pooled analysis and one systematic review on BPA and phthalate exposure in children (postnatal) and adults. There was no clear increase or decrease in HDL cholesterol, LDL cholesterol or triglycerides with higher BPA exposure in adults and children (AS 4/11; low quality). There was no clear increase or decrease in HDL cholesterol or triglycerides with phthalate exposure in children. A significant increase in HDL cholesterol was found for higher DEHP exposure when measured as the metabolite MEOHP (not in figure), but

no clear increase or decrease with DEHP measured as alternative metabolites MEHP and MEHHP (not in figure), nor total DEHP metabolites (AS 5/11; moderate quality).

Blood pressure (Fig 2.7d & 2.7e)

- Blood pressure was investigated in one systematic review on phthalate exposure in children. Systolic blood pressure significantly increased with higher postnatal exposure to the phthalate DEHP (measured as urinary metabolites MEHHP and MEOHP) with a non-significant trend for increased systolic blood pressure with higher exposure to DEHP when measured as metabolite MEHP instead, and with higher exposure to phthalates DMP and BBP (measured as metabolites MMP and MBzP). There was no clear increase or decrease found in diastolic blood pressure with postnatal exposure to phthalates (AS 5/11; moderate quality).

Hypertension (Fig 2.7f & 2.7h)

- Risk of hypertension (SBP >140mmHg and/or DBP >90mmHg) was investigated in two systematic reviews investigating BPA and flame-retardant exposure in adults. An increase in hypertension was reported with higher exposure to BPA, and with higher exposure to dioxin-like PCBs (group II) and PCB 118, but no clear increase or decrease in risk was seen with non-dioxin-like PCBs and PCB 153 (AS 7/11; moderate quality).

Cardiovascular disease (Fig 2.7f-h)

- Risk of cardiovascular disease was reported in one systematic review investigating BPA, phthalates and flame-retardant exposure in children and adults. There was a significant increase in risk of cardiovascular disease with higher exposure to BPA as well as PCB 138 and 153, and a non-significant trend towards increased risk of cardiovascular disease with higher exposure to a third PCB (PCB 180) as well as total PCBs. There was also a trend towards increased risk of cardiovascular disease with exposure to each phthalate evaluated, but no statistically significant findings with any phthalate (AS 6/11; moderate quality) (Fig 2.7g).

Cardiovascular disease deaths (Fig 2.7h)

- Cerebrovascular disease deaths were investigated in a pooled analysis on flame-retardant exposure in adults with special PCB exposure by poisoning. A significant increase in risk of cardiovascular disease death was found with special PCB exposure by poisoning in adults (AS 4/11; low quality).

Cerebrovascular disease deaths (Fig 2.7h)

- Cerebrovascular disease deaths were investigated in a pooled analysis on flame-retardant exposure in adults with special PCB exposure by poisoning. There was no clear increased or decreased risk of cerebrovascular disease death with special PCB exposure by poisoning in adults (AS 4/11; low quality).

Hypertension deaths (Fig 2.7h)

- Hypertension deaths were investigated in a pooled analysis on flame-retardant exposure in adults with special PCB exposure by poisoning. There was no clear increased or decreased risk of hypertension deaths with special PCB exposure by poisoning in adults (AS 4/11; low quality).

RESPIRATORY OUTCOMES

Number of systematic reviews: Respiratory outcomes were reported in three systematic reviews and one pooled analysis addressing exposure to phthalates (n=2), flame retardants (n=1) and PFAS (n=1).

Quality: Quality appraisal of the reviews was rated between 3–9/11 (low to high quality).

Exposure: Exposure to the plastic-associated chemicals was commonly measured pre- and postnatally using maternal whole blood/ serum/cord plasma or serum/breast milk as well as in children.

Health outcomes: Respiratory outcomes reported were asthma, allergic rhinitis, bronchitis and/or wheeze in the general population and specifically in children including infants (less than 18 months) for flame retardants.

Populations: These outcomes were measured in infants (< 18 months) and adults.

Statistically significant findings: A statistically significant increased risk was reported for: asthma in children with prenatal exposure to phthalate BBP (measured as urinary metabolite MBzP) (Fig 2.8a); bronchitis in infants with prenatal exposure to PCB 153 (Fig 2.8b); and allergic rhinitis in children with prenatal or postnatal exposure to PFOA (Fig 2.8c).

Trends: Although there was a trend towards increased risk of adult asthma with current exposure to each phthalate evaluated, there were no statistically significant findings with any phthalate for adult asthma (Fig 2.8a).

No statistically significant findings: There was no clear increased or decreased risk of asthma in children with pre- or postnatal exposure to phthalates (other than prenatal BBP) (Fig 2.8a), or with pre- or postnatal exposure to PFAS (Fig 2.8c). No clear increased or decreased risk of childhood wheeze was found for prenatal exposure to PCB 153, and no clear increased or decreased risk of asthma or wheeze with prenatal or postnatal exposure to PFAS (Fig 2.8b & 2.8c). There was also no clear increased risk of allergic rhinitis in children with exposure to PFAS other than PFOA (Fig 2.8c).

Figure 2.8 – Plastic-associated chemicals and respiratory outcomes

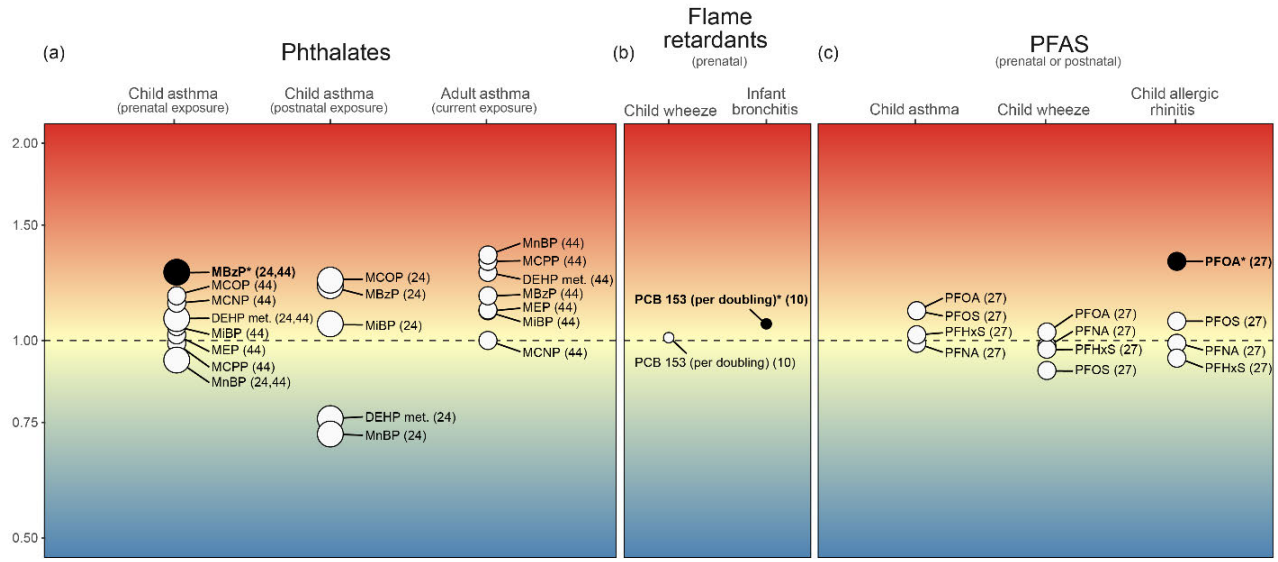


Figure 2.8 – Plastic-associated chemicals and respiratory outcomes. *Each outcome is presented in an individual panel or individual column with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included risk of asthma (a and c), wheeze in children (b - c), as well as risk of infant bronchitis (b) and allergic rhinitis (c).*

The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome (small circle, low; intermediate circle, moderate; and large circle, high quality respectively). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.

For dichotomous (risk) outcomes (panel a - c), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Asthma (Fig 2.8a-c)

- Asthma was investigated in three systematic reviews on phthalates and flame-retardant exposure in children and adults. The risk of asthma in children increased with higher prenatal exposure to the phthalate BBP (measured as urinary metabolite MBzP) and DEHP when measured as urinary metabolite MECPP; with a similar but non-significant trend for increased risk of asthma where prenatal DEHP exposure was measured with other DEHP metabolites (AS 5-9/11; moderate to high quality), or with higher molecular weight phthalates DNP and DDP (measured as urinary metabolites MCOP and MCNP). There was no clear increased or decreased risk of asthma for prenatal exposure to other phthalates (AS 5-9/11; moderate to

high quality). There was a statistically significant increased risk of child asthma with postnatal DEHP exposure measured as urinary metabolite MEHHP (not in figure), but no clear increase or decrease with DEHP measured as alternative metabolites, or other phthalates evaluated (DnBP, DiBP, BBP and DNP) (AS 9/11; high quality). There was a trend towards increased risk of adult asthma with current exposure to each phthalate evaluated, but no statistically significant findings (AS 5/11; moderate quality). Risk of asthma was also evaluated combining studies of child asthma with prenatal or postnatal phthalate exposure, combining studies of adult and child asthma with postnatal phthalate exposure, and restricted to specific sex or geographical regions (not in figure). With respect to PFAS, there was no clear increased or decreased risk of asthma in children with prenatal or postnatal exposure to the PFAS PFNA, PFHxS, PFOA and PFOS (AS 7/11; moderate quality).

Bronchitis and/or wheeze (Fig 2.8b-c)

- Bronchitis and/or wheeze was investigated in one pooled analysis on flame retardants exposure in infants and children, and one systematic review on PFAS exposure in children. Risk of bronchitis in infants significantly increased with higher prenatal exposure to PCB 153, however, there was no clear increased or decreased risk of wheeze in children with prenatal exposure to PCB 153 (AS 3/11; low quality). There was also no clear increased or decreased risk of wheeze in children with prenatal or postnatal exposure to PFAS PFNA, PFHxS, PFOA and PFOS (AS 7/11; moderate quality).

Allergic rhinitis (Fig 2.8c)

- Allergic rhinitis was investigated in one systematic review on PFAS exposure in children. Risk of allergic rhinitis increased with higher prenatal or postnatal exposure to PFOA. There was no clear increased or decreased risk found with exposure to PFHxS, PFNA and PFOS (AS 7/11; moderate quality).

SKIN-RELATED OUTCOMES

Number of systematic reviews: Skin-related outcomes were reported in one systematic review addressing exposure to PFAS.

Quality: Quality appraisal of the review was 7/11 (moderate quality), although there were potential issues with classification of outcomes that are not captured by AMSTAR rating.

Exposure: Exposure to PFAS was measured using maternal or cord serum, blood plasma or fat.

Health outcomes: Skin-related outcomes reported were childhood atopic dermatitis and eczema. The systematic review made distinction between these two closely related terms, and individual studies reviewed were meta-analysed separately depending on whether the outcome of the study was eczema or atopic dermatitis. A combined analysis was not provided to evaluate combined effect.

Populations: These outcomes were measured in children.

Statistically significant findings: Significant findings were found for increased risk of atopic dermatitis with higher prenatal exposure to PFOS, and decreased risk of eczema with higher prenatal exposure to PFNA.

No statistically significant findings: There was no clear increased or decreased risk of atopic dermatitis or eczema in children and prenatal exposure to other PFAS in the review (Fig 2.9).

Figure 2.9 – Plastic-associated chemicals and skin-related outcomes

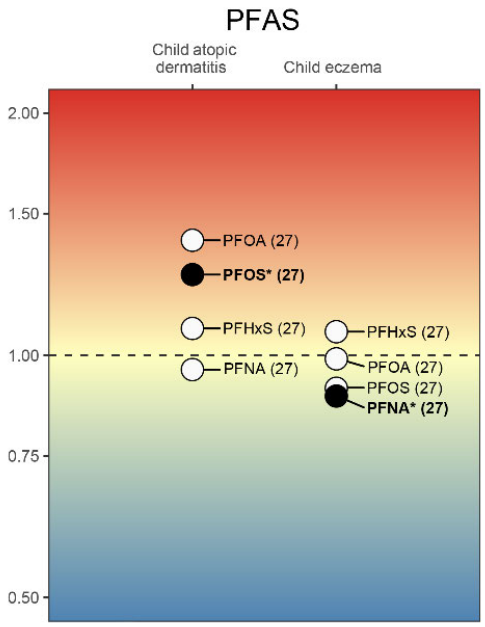


Figure 2.9 – Plastic-associated chemicals and skin-related outcomes. *Each outcome is presented in an individual panel or individual column with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included risk of atopic dermatitis and eczema in children.*
The circles represent findings of a systematic review described in this report. The systematic review informing these outcomes was assessed to be of moderate 'quality' (AMSTAR tool). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.
For this dichotomous (risk) outcome, colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Atopic dermatitis (Fig 2.9)

- Risk of atopic dermatitis in children significantly increased with higher prenatal exposure to PFOS. However, it should be noted that there was no combined analysis including studies of eczema alongside those of atopic dermatitis, and there was trend towards decreased risk of eczema with higher prenatal exposure to PFOS. There was no clear increased or decreased risk of atopic dermatitis found with prenatal exposure to PFNA, PFHxS or PFOA (AS 7/11; moderate quality).

Eczema (Fig 2.9)

- Risk of eczema in children significantly decreased with prenatal exposure to PFNA. However, it should be noted that there was no combined analysis including studies of atopic dermatitis alongside those of eczema, and there was only a weak trend towards decreased risk of atopic dermatitis with higher prenatal exposure to PFNA. There was no clear increased or decreased risk of eczema found with prenatal exposure to PFOS, PFOA or PFHxS (AS 7/11; moderate quality).

CANCER OUTCOMES

Number of systematic reviews: Cancer outcomes were reported in six systematic reviews and one pooled analysis, each addressing exposure to flame retardants, specifically PCBs.

Quality: Quality appraisal of the reviews and pooled analysis was rated between 2–8/11 (low to high quality).

Exposure: Exposure to PCBs included environmental exposure in the general population as well as special exposure groups due to occupation or by poisoning from contaminated food. Special PCB exposure by occupation included occupations such as telecommunication workers, electrical workers, and transformer and capacitor workers. These workers are exposed to PCB containing materials in electric cables or as a flame retardant di-electric fluid inside electrical transformers. Special PCB exposure by poisoning was from cohorts of the population exposed to contaminated rice oil in Japan and Taiwan. Samples were blood, serum or plasma or not specified but with reference to blood levels of the affected population, or adipose tissue.

Health outcomes: Outcomes reported were breast cancer, non-Hodgkin's lymphoma (including subtypes) and cancer-related mortality across different types of cancer.

Populations: These outcomes were measured in adults.

Statistically significant findings: Statistically significant increase in risk was reported for breast cancer and higher exposure to PCB congeners 99, 105, 183 and 187 (Fig 2.10a); non-Hodgkin's lymphoma and higher exposure to total PCBs (Fig 2.10b); all cancer-related deaths in males, death with liver cancer in females, and death with lung cancer in males and females combined following special PCB exposure by PCB poisoning (Fig 2.10c); and death with malignant melanoma and special PCB exposure by occupation.

No statistically significant findings: There was no clear increased or decreased risk of breast cancer for exposure to other specific PCB congeners or total PCB exposure (Fig 2.10a), and no clear increased or decreased risk of non-Hodgkin's lymphoma for specific PCBs congeners studied. There was no clear increased or decreased risk of death with the other cancers studied following special PCB exposure by PCB poisoning, or death with non-Hodgkin's lymphoma with special PCB exposure by occupation (Fig 2.10c & 10d).

Mixed findings across systematic reviews: Of two reviews that evaluated PCB 153 exposure, one found a statistically significant increased risk of non-Hodgkin's lymphoma, and the second found a non-significant trend towards increased non-Hodgkin's lymphoma.

Figure 2.10 – Plastic-associated chemicals and cancer outcomes

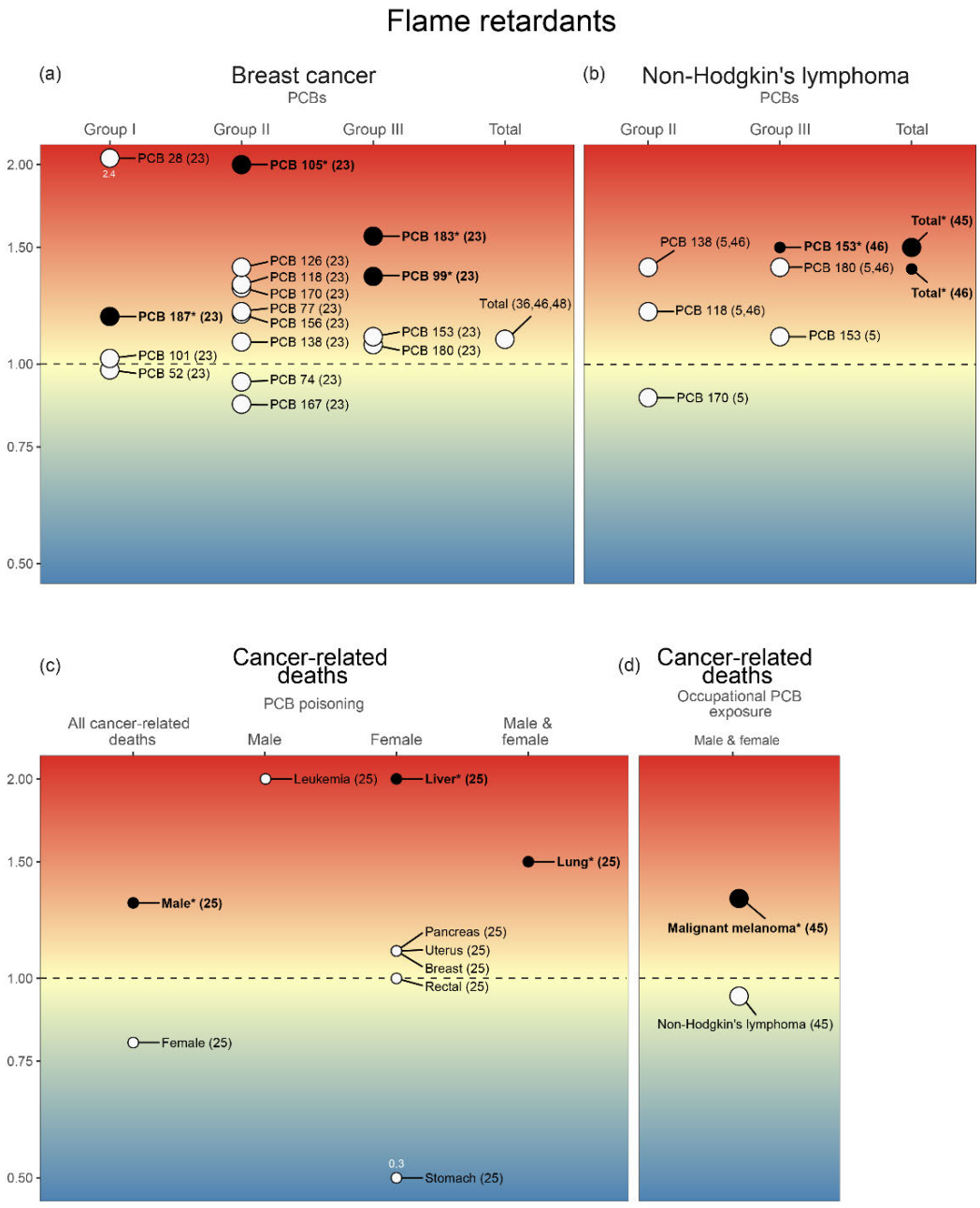


Figure 2.10 – Plastic-associated chemicals and cancer outcomes. *Each outcome is presented in an individual panel or individual column with the plastic-associated chemical(s) for which evidence is available. Outcomes reported included risk of breast cancer (a), non-Hodgkin's lymphoma (b), and cancer-related deaths following exposure to PCBs (c – d).*
The circles represent findings of systematic reviews described in this report. The size of the circles represents the 'quality' score (AMSTAR tool) of the systematic review(s) informing the outcome (small circle, low; and intermediate circle, moderate quality respectively). Shading of circles indicates statistical significance (black filled circles are statistically significant and white circles are not statistically significant). Statistical significance of a finding is additionally indicated with an asterisk and bold text in the corresponding label. Numbers are reference numbers of the systematic reviews informing the outcome.
For dichotomous (risk) outcomes (panel a - d), colour in the panel indicates harm or not (red is harmful, blue is not harmful/protective). The scale is an approximation of the estimated change in risk for that outcome (OR, RR, ES), where a value below 1 indicates a reduced risk and values above 1 indicate an increased risk.

Breast cancer (Fig 2.10a)

- Breast cancer was investigated in four systematic reviews on PCBs. There was no clear increased risk of breast cancer found with total PCBs (AS 2-8/11; low to moderate quality).

One review (AS 8/11; moderate quality) investigated specific PCB congeners (PCB congeners 28, 52, 74, 77, 99, 101, 105, 118, 126, 138, 153, 156, 167, 170, 180, 183, 187). In this review, an increased risk of breast cancer was found with higher PCB 99, 105, 187 and 183 exposure, but no clear increased or decreased risk with other congeners.

Non-Hodgkin's lymphoma (Fig 2.10b)

- Non-Hodgkin's lymphoma was investigated in three systematic reviews on PCB exposure and children and adults. Two systematic reviews found a significant increase in risk of non-Hodgkin's lymphoma with exposure to higher total PCBs (AS 2-5/11; low to moderate quality). Two systematic reviews (AS 2-6/11; low to moderate quality) investigated specific PCB congeners (PCB congeners 118, 138, 153, 180, 170). One of these two reviews found a significant increase in risk of non-Hodgkin's lymphoma with higher exposure to PCB 153 (AS 2/11; low quality) and the second a non-significant trend towards increased non-Hodgkin's lymphoma (AS 6/11; moderate quality). No clear increased or decreased risk was found with other congeners (AS 2-5/11; low to moderate quality).
- For subtypes of non-Hodgkin's lymphoma, there was a significant decrease in the risk of chronic lymphocytic leukaemia with higher exposure to total PCBs and no clear increase or decrease in risk of diffuse large B-cell lymphoma and follicular lymphoma (AS 6/11; moderate quality; not in figure). The findings for specific subtypes of non-Hodgkin's lymphoma should be interpreted in the context of an increased risk for all subtypes combined, as found in the other reviews above (AS 2-5/11; low to moderate quality).

Cancer deaths (Fig 2.10c-d)

Cancer-related deaths were investigated in one systematic review of high-risk PCB exposure groups and one pooled analysis on special PCB exposure by poisoning. Cancer-related deaths were reported as all cancer-related deaths and cancer death by type.

All cancer-related deaths (Fig 2.10d)

- All cancer-related deaths were investigated in one pooled analysis on special PCB exposure by poisoning. There was a significant increase in risk of all cancer-related deaths following special PCB exposure by poisoning in males, but no clear increased or decreased risk for females (AS 4/11; low quality).

Cancer-related deaths by type of cancer (Fig 2.10d)

- Cancer-related deaths were additionally evaluated considering the type of cancer in one pooled analysis of cancer-related death following special PCB exposure by poisoning, and one systematic review considering high-risk PCB exposure groups based on occupation. An increased risk of death with liver cancer in females, and death with lung cancer in males and females combined, was found following special PCB exposure by PCB poisoning (AS 4/11; low quality). There was no clear increased or decreased risk of death with the other cancers following special PCB exposure by PCB poisoning, which included pooled analyses of breast, uterus, pancreatic, stomach and rectal cancer in females, and leukaemia in males (AS 4/11; low quality). A significant increase in risk of death with malignant melanoma was found with PCB exposure in systematic review of special risk groups by occupation (AS 5/11; moderate quality). There was no increased risk of deaths with non-Hodgkin's lymphoma with PCB exposure in these occupational risk groups (AS 5/11; moderate quality).

PART 3: EVIDENCE REVIEW

INTRODUCTION

This **Evidence Review (Part 3)** provides details for the methods, results, limitations as well as summaries of the evidence. **Here, data are presented by plastic-associated chemical for each of the health outcomes studied.**

UMBRELLA REVIEW QUESTION

What is the impact of plastic-associated chemical exposure on human health?

METHODS

PROSPERO registration number: CRD42020204893

A priori inclusion criteria were provided by the Minderoo Foundation and are outlined below. The remainder of this section articulates the methods for developing and undertaking the overview of the evidence, including searching, study selection, assessment of methodological quality, and data extraction, summary/synthesis, and presentation.

INCLUSION CRITERIA

Reviews assessing the exposure to plastic and plastic-associated additives/chemicals (independent variable) and the relationship with health outcome (dependent variable).

Types of participants

Humans across the lifespan (infants, children, adults and elderly).

Types of exposure

Exposure to plastic-associated chemicals focused on plastic products used in everyday activities and plastic-associated chemicals as environmental pollutants to which humans are exposed.

Exposure to the following plastics and plastic-associated chemicals that are in everyday use were included:

Plastic polymers (Groh et al., 2019)

- Polyethylene terephthalate (PETE)
- High-density polyethylene (HDPE)
- Low-density polyethylene (LDPE)
- Polyvinyl chloride (PVC)
- Polypropylene (PP)
- Polystyrene (PS) or styrofoam
- Others (Teflon, poly carbonate, poly lactide etc.)

Plastic additives and plastic-associated chemicals (Hahladakis et al., 2018; Thompson et al., 2009)

- Bisphenols
- Plasticisers with a focus on phthalates
- Flame retardants with a focus on brominated and chlorinated types
- Per- and Polyfluoroalkyl substances (PFAS)

Exposure to endocrine-disrupting chemicals including the above were also considered as exposures of interest in this Evidence Review.

Exposure exclusion criteria at screening stage

Studies reporting on the following or using the following methods were beyond the scope of the review and excluded:

- Indirect measure of exposure such as surveys, questionnaires, dust measures and nature of occupation;
- Fossil fuel extraction and plastic manufacturing;
- Plastics used in medical, surgical or dental devices or procedures such as implants, prostheses etc.;
- Other plastic additives such as antimicrobials, antioxidants, antistatics, fillers, foaming agents, lubricants, slip agents and UV stabilisers.

Types of outcomes

Any health outcome was considered. For inclusion, a quantified risk estimate (odds ratios or relative risk for dichotomous data and beta coefficient, correlation coefficient or mean difference for continuous data, derived from pooled analysis of multiple included studies) must have been available. Health outcomes are interrelated sets of attributes and can refer to a variety of manifestations such as health status, death, injury or disease. The International Classification of Diseases 11th revision (ICD-11) (World Health Organization, 2020) was used as guide for the health outcomes.

Types of studies

Systematic reviews and syntheses with pooled data/meta-analysis(es) were included. Systematic reviews provide a comprehensive, unbiased synthesis of many relevant studies on a specific question in a single document using rigorous and transparent methods (Aromataris et al., 2020). Systematic reviews generally consist of:

- Research question and/or objective
- Sources searched, with a reproducible search strategy (naming of databases, naming of search platforms/engines, search date and complete search strategy)
- Inclusion and exclusion criteria
- Selection (screening) methods
- Critical appraisal of the evidence
- Data analysis and presentation

Pooled analyses are quantitative, formal, epidemiological study designs which are not full systematic reviews but report on meta-analysis of cohort(s) of the population. Literature searching, screening and appraisal are generally not part of the methods of this type of synthesis. Data from cohorts of the populations examined served as the source of information. In most cases, pooled data from multiple cohorts under consideration represent a more readily comparable sample and analysis of a population, derived using similar methods, and therefore were included in this Evidence Review.

Exclusion criteria at appraisal and data extraction stage

Reviews with findings limited to only overall combined estimates from included studies where data were used repeatedly in the analyses (multiple counting) were excluded. Data from such analyses were considered invalid as it ignored the assumption of independence of data and introduced a unit of analysis error. This practice artificially increased the sample size of analyses, skewed the weight attributable to studies in the analyses and narrowed confidence limits around effect estimates.

> Note: if reviews had findings of individual chemical exposures or subgroups where data from included studies were only used once in the analyses, these were included and extracted and used in this report; only the overall summary data were excluded.

Limits

No date limits were applied. Only reviews/analyses published in English were included in this Evidence Review.

SEARCH STRATEGY

Information source

Epistemonikos (https://www.epistemonikos.org), a large source of scientific evidence and systematic reviews in health-decision-making, was the principal information source searched for this Evidence Review. It reportedly indexes over 90% of systematic reviews published in the literature (Bravo-Soto et al., 2020) as it regularly trawls the following databases and sources that index health related literature for published systematic reviews:

- Cochrane Database of Systematic Reviews (CDSR)
- CINAHL (The Cumulative Index to Nursing and Allied Health Literature)
- Database of Abstracts of Reviews of Effects (DARE)
- EMBASE
- EPPI-Centre Evidence Library
- JBI Database of Systematic Reviews and Implementation Reports/JBI Evidence Synthesis
- LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud)
- PsycINFO
- PubMed
- PubMed (via NLM)
- The Campbell Collaboration online library

Epistemonikos was searched using a combination of broad and specific search terms relating to *plastics, plastic polymers, plasticisers, flame retardants and stabilisers*. Broad terms such as bisphenols, plasticisers, flame retardants, per- and polyfluoroalkyl substances and endocrine-disrupting chemicals are commonly used. Specific search terms are the chemical names and the keyword search strings or other related keywords such as 4,4'-isopropylidenediphenol for bisphenol and di(2-ethylhexyl) phthalate for phthalates or plasticiser. Broader terms were used as they yield more sensitive and specific results in Epistemonikos (Lake et al., 2019). However, to ensure that reviews with the specific plastic type and additives/chemicals in the titles and abstracts were not missed, the specific search terms were also applied in combination with the broad terms using the Bolean term 'OR'. The initial scan of the search results yielded a number of records on plastic surgery and therefore, 'NOT surgery' was applied to improve the specificity and sensitivity of the search (Appendix 2). Searches were conducted until the 26th August 2020.

PubMed was also searched to validate the sensitivity and specificity of the Epistemonikos search and ensure a comprehensive capture of the evidence base related to the review topic. Search terms were applied in PubMed (Appendix 2) until the 30th September 2020.

STUDY SELECTION

All identified citations from Epistemonikos were collated and uploaded into EndNote with the duplicates removed. Titles and abstracts of all records returned from the search were screened considering the Evidence Review inclusion criteria. The screening procedures derived from the inclusion criteria and indicated below were applied.

Similarly, all identified citations retrieved from the subsequent search of PubMed were collated and uploaded into EndNote and the duplicates from the Epistemonikos search removed. Titles and abstracts of all the remaining records were also screened against the inclusion criteria above.

Screening studies

PLASTIC TYPES	YES	NO

Does the review or synthesis with meta-analysis assess any of the following plastics? Plastic polymers • Polyethylene terephthalate (PETE) • High-density polyethylene (HDPE) • Low-density polyethylene (LDPE) • Polyvinyl chloride (PVC) • Polypropylene (PP) • Polystyrene (PS) or styrofoam • Others (Teflon, poly carbonate, polylactide etc.) Plastic additives & plastic-associated chemicals • Plasticisers (phthalates) • Flame retardants (brominated and chlorinated) • Bisphenols • Per- and Polyfluoroalkyl Substances (PFAS) Endocrine-disrupting chemicals which included any of the plastic additives or plastic-associated chemicals above. *If NO, EXCLUDE.*		
HEALTH OUTCOME CRITERIA Does the review or the synthesis report a pooled analysis/meta-analysis with risk estimates/effects of any health outcome for humans? (RR/OR/beta coefficients, standardised mean difference and confidence intervals). *If NO, EXCLUDE.*	YES	NO

Full text of potentially relevant reviews and syntheses were retrieved and reviewed. Two reviewers conducted the screening process and where necessary, inclusion was determined by discussion between reviewers. Following the search of Epistemonikos, systematic reviews with no clear indication of meta-analysis in the titles and abstracts were included in the full text review to ensure that no systematic reviews with meta-analysis were missed. However, no additional reviews were found to be eligible.

The same screening procedures were applied to the results of the PubMed search, except for the retrieval and full text review of systematic reviews with no clear indication of conduct of meta-analysis in the titles and abstracts. As mentioned, the full text assessment of these potentially eligible systematic reviews conducted in Epistemonikos revealed no additional reviews.

CRITICAL APPRAISAL

Eligible systematic reviews and syntheses were appraised using the AMSTAR tool. AMSTAR has 11 questions answerable with a Yes, No, Can't answer or Not applicable (Shea et al., 2007) (Appendix 3). Scores may range between 0-11. A high score indicates low risk of bias in the conduct of the systematic review and adds to the certainty in the results presented. AMSTAR was selected over other available appraisal tools as it needs less time to complete and results in better agreement between reviewers (Gates et al., 2020). Critical appraisal of included reviews and syntheses was conducted independently by two reviewers from the JBI Project Team (JD, TB, AW, TM, DP). A third reviewer (EA) was consulted to resolve any disagreement. A pilot appraisal activity was undertaken on a subset of included reviews prior to appraising all included reviews and syntheses to ensure the reliability of the process between

members of the review team. Discussions to address reliability issues were undertaken. These discussions relate to the following AMSTAR questions:

Q3 - Was a comprehensive literature search performed?

Q3 was assigned a YES, if there were at least two databases searched and one supplementary search strategy used (i.e., reference checking, contacting experts in the field of study, grey literature search).

Q9 - Were the methods used to combine the findings of studies appropriate?

Q9 was assigned a YES if methods to combine overall findings or composite measures and/or subgroup findings were valid. Two categories of meta-analyses were possible- (1) main or overall meta-analysis for each group of plastic-associated chemicals (i.e., bisphenols, phthalates, flame retardants, PFAS) and (2) meta-analysis of specific chemicals within a group of plastic-associated chemicals (i.e., bisphenol A (BPA), specific phthalate metabolites MMP, MEP, MBzP etc. for phthalates, or polychlorinated biphenyl (PCB) congeners like PCB 118, 170). If only one of these analyses is valid, methods were considered partially correct and therefore Q9 was assigned a CAN'T ANSWER.

Q11 – Was the conflict of interest included?

Q11 was assigned a YES, if authors declared no conflict of interest in their review but not for individual studies included. The declaration of conflict of interest from the primary studies is not required in the PRISMA reporting guide. However, as AMSTAR Q11 noted, the team included the following statement in the appraisal: *authors declared no conflict of interest in their review, but no declarations from the authors of the primary studies included were also noted.*

To summarise the appraisal findings, an arbitrary categorisation system was set for this Evidence Review. AMSTAR scores of 9-11 were considered high quality, 5-8 moderate quality and less than 5 low quality. These arbitrary categorisation scores were used as the basis for describing the methodological quality of the evidence informing the relationship between the risk of plastic-associated chemical exposure and specific health outcomes investigated.

DATA EXTRACTION

Descriptive details as well as available exposure and outcome data were extracted independently by two reviewers from the JBI Project Team (JD, TB, AW, TM, DP) and verified by CS from Minderoo. Data were extracted into a table of study characteristics (Appendices 6-9), and included: author, year, conflict of interest declaration, last search, study types, number of studies included (in the review and in the meta-analyses), critical appraisal tool used and findings, participants (characteristics and total number), plastic exposure (type, route, measure and time), health outcome (outcome measures, main findings, subgroup findings) and authors' conclusions. Note that for conflict of interest (COI), *No COIs declared* referred to 'authors declared no conflict of interest', whilst *No COIs reported* referred to 'no COI declaration was found in the reviews'.

For reviews and pooled analyses reporting a combination of, or multiple individual, plastic-associated chemical exposures, relevant data were extracted for the specific plastic or plastic-associated chemical. Therefore, some reviews and syntheses appear in multiple sections of this Evidence Review.

For reviews and pooled analyses reporting only combined analyses for the overall estimate of effect (and other composite exposure findings) and which used data from the same studies repeatedly, findings were not extracted. This approach falsely increased the sample size and constrained confidence limits. Where available, results of analysis of individual chemical exposures have been extracted instead. Where the same studies appear within an analysis of individual chemical exposure, data from the studies were extracted only if they are mutually exclusive subgroups (e.g. boys and girls).

STRUCTURE OF PART 3 – EVIDENCE REVIEW

The data in this Evidence Review have been organised by reported plastic or plastic-associated chemical exposure for ease of navigation and interpretation:

- Bisphenols
- Plasticisers
- Flame retardants
- Per- and Polyfluoroalkyl Substances

These plastic additives/chemicals were defined and described in detail in terms of their use in plastic products to which humans are currently, or have been exposed to, and how they were measured, including the units of measurement. Each section presents a descriptive summary of the reviews and pooled analyses that were identified and included, and the presentation of the results of the critical appraisal of the reviews.

For Bisphenols and Per- and Polyfluoroalkyl Substances, the terms and descriptions of the plastic-associated chemicals were straightforward. However, for plasticisers and flame retardants, there were variations in terms and descriptions used in the reviews. For clarity, a standardised set of terms and definitions was used in this review.

Plasticisers

Total phthalates: *composite measure of phthalate exposure which is the total concentration of all phthalate metabolites measured in the individual primary research study.*

ΣDEHP: *composite measure of diethylhexyl phthalate (DEHP) exposure as the molar sum of the individual DEHP metabolites measured in the individual primary research study, such as: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-carboxymethyl-5-hexyl) phthalate (MCMHP).*

DEHP metabolites: *an alternative approach to harmonising measures of diethylhexyl phthalate (DEHP) exposure across studies, where a systematic review or meta-analysis selected a single "best" measure of DEHP exposure from the DEHP measures available within each individual primary research study, following a predetermined hierarchy if multiple measures were available within that study (typically selecting findings for ΣDEHP if available, but otherwise substituting this with findings for the most reliable individual DEHP metabolite available within that study).*

Flame retardants

Total PCBs: *composite measure of PCB exposure which is the total concentration of all PCB congeners measured in the individual primary research study*.

Special PCB exposure (poisoning): *the main exposure to PCBs in this study or studies was attributable to PCB poisoning of a geographically-defined population through contaminated food products.*

Special PCB exposure (occupational): *the main exposure to PCBs in this study or studies was attributable to the occupation (work) of the sample population.*

Total PBDEs: *a composite measure of PBDE exposure which is the total concentration of all PBDE congeners measured in the individual primary research study.*

The health outcomes for each plastic or plastic additive/chemical exposure categories were organised based on the International Classification of Diseases 11th revision (ICD-11) (World Health Organization,

2020). The following is a list of the health outcomes categories limited to those outcomes that were reported in the included reviews:

- Birth outcomes
- Child reproductive
- Adult reproductive
- Metabolic and endocrine
- Child neurodevelopment
- Nutritional
- Circulatory
- Respiratory
- Skin-related
- Cancer

The Evidence Review included any health outcome investigated by the reviews of plastic-associated chemical exposure. The health outcomes investigated for each plastic additive/chemical exposure have been summarised in narrative that includes clear indication of the effect size, 95% confidence limits around each effect estimate, the number of studies included in the meta-analysis and the number of participants included in the analysis where this information was available. This Evidence Review included subgroup findings relating to types of plastic additives/chemicals, exposure levels, age, sex, outcome parameters, location, study designs and risk of bias of included studies.

For rapid reference, summary tables have been presented in each section for each identified outcome. Results from each review are listed in the summary table. Where more than one review informed a specific outcome, a range of the lower and upper values has been provided in bold (i.e. lowest to highest effect estimate and confidence limits, studies and participants). When fixed and random effects were reported, both were extracted and included in the tables; however, random effects findings were preferred in writing the body of the text. Regarding dibutyl phthalate and its metabolite monobutyl phthalate, the reviews have used two abbreviations interchangeably – DBP or DnBP for dibutyl phthalate and MBP or MnBP for monobutyl phthalate. For consistency, DnBP and MnBP were the preferred abbreviations used in this Evidence Review. Significant findings were indicated with an asterisk after the effect size.

RESULTS

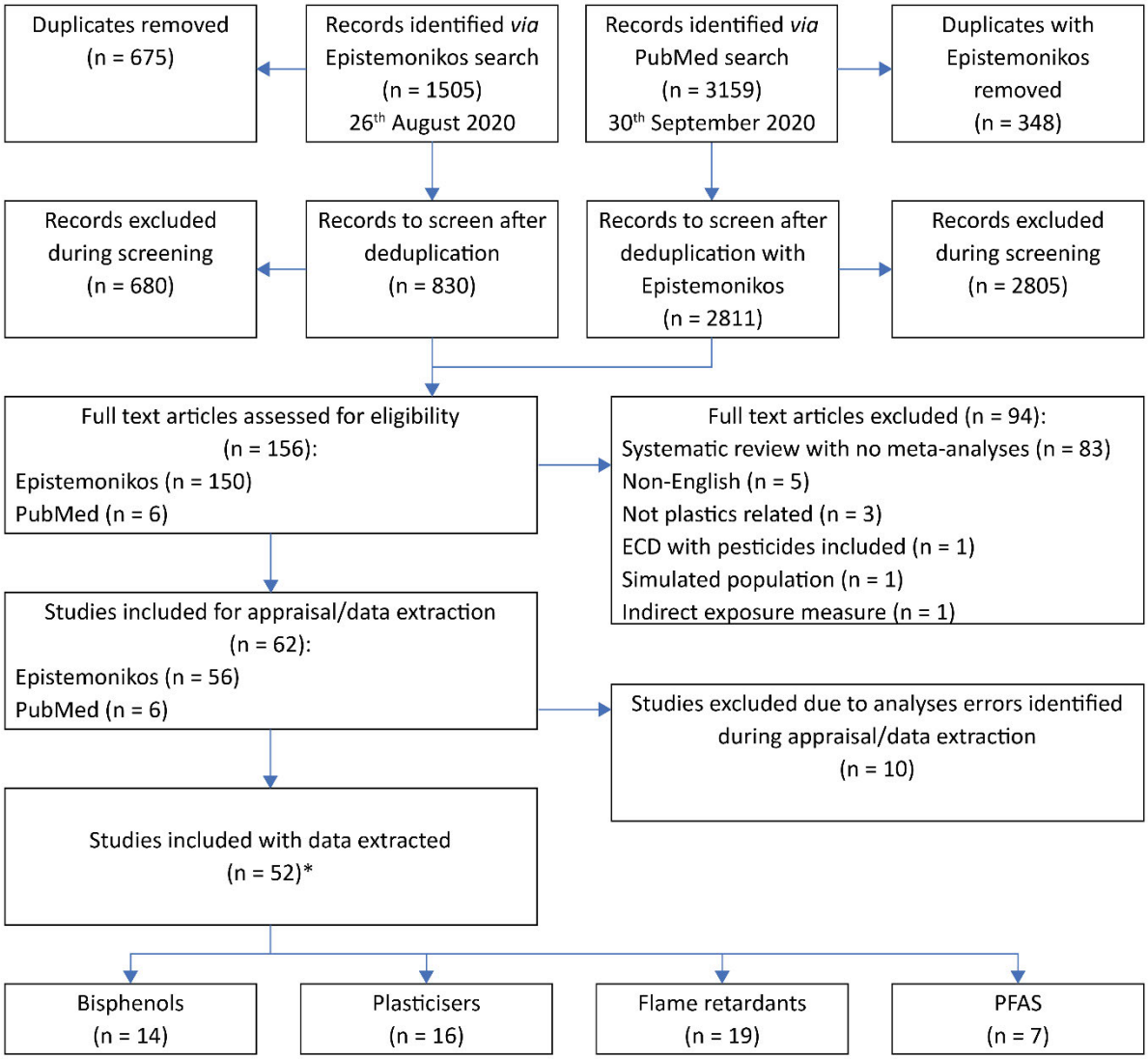
The search of Epistemonikos yielded 1505 records and the search of PubMed yielded 3159 records.

Epistemonikos search: Duplicates were removed from the 1505 records leaving 830 titles and abstracts for screening. A total of 150 reviews were identified as potentially relevant and were retrieved as full texts for screening and assessment of eligibility. Of the 150 reviews, 56 reviews with meta-analyses and pooled analyses were included. Reasons for exclusion of the remaining 94 reviews are provided in Appendix 5.

PubMed search: Duplicates with the Epistemonikos search were removed from the 3159 records leaving 2811 titles and abstracts for screening against the inclusion criteria. An additional six reviews were identified. Of note, three of these reviews are recently published in 2020, and not initially found in Epistemonikos (in August search) but are now indexed in Epistemonikos (as of October 2020).

Ninety-four reviews were excluded following retrieval and full text assessment (Appendix table A5.1). Reasons for exclusion of reviews and syntheses retrieved in full text were (1) included only pesticides and other chemicals not directly plastic-associated, (3) no meta-analysis conducted, (4) non-English, (5) used a simulated population for modelling and (6) indirect measure of exposure. Ten reviews were excluded during the process of appraisal and data extraction for unit of analysis errors encountered (Appendix table A5.2). Reviews and syntheses at this stage were excluded due to multiple use of the same participant data in the analyses.

In total, 52 systematic reviews with meta-analyses, and meta-analyses and pooled analyses, were finally included (Fig 3.1), containing 939 separate meta-analyses.



*A subset of reviews reported on multiple exposures and hence are included as informing multiple exposures/sections

Figure 3.1: Flow diagram illustrating the results of Epistemonikos and PubMed searching, citation screening, and assessment and inclusion of full text studies.

LIMITATIONS

The following limitations of the evidence base and overview processes should be acknowledged in the consideration and interpretation the findings presented in the next section of this report.

- Of all the possible plastics and plastic-associated chemicals humans are exposed to in everyday living, this Evidence Review only found reviews investigating BPA, phthalates (some reviews were restricted to specific/single phthalates only) and polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). Reviews assessing the impact on human health outcomes of other bisphenols, plasticisers, flame retardants and plastic polymers were not identified.
- The studies included in the reviews were all observational study designs including prospective cohort, case-control studies and cross-sectional studies. Considering the nature of the research question, this is entirely appropriate. However, as a result, no claims can be made

regarding causal relationships between plastic-associated chemical exposure and health outcomes. This is due to the likely and unknown influence of confounding factors that may also directly influence the outcome. However, the more consistent the findings are, the greater confidence in the association observed. Similarly, the better that confounding factors have been accounted for within the primary studies included within the review, the more likely that an association reflects an underlying causal relationship.

- The approach used in this review was to select outcomes for which data had been meta-analysed. This approach to include only meta-analyses instantly omitted a large number of reviews and their included studies that were either too heterogenous to combine statistically, or where only one study was available to inform the outcome. Meta-analysis has some distinct advantages when considering an evidence base: it can increase the statistical power of the analysis; increase the generalisability of the results and overall; and increase the confidence in the results where marked heterogeneity is absent (be it methodological, clinical or statistical). However, considering meta-analyses in this regard also has some disadvantages that must be acknowledged. Where only a small number of studies are included, with a small number of participants, it is questionable whether meta-analysis offers any advantage in certainty or greater confidence in the results. Similarly, where only a small number of studies are included, and there is a study or two that have a disproportionate sample size, these studies can 'override' the results of the meta-analysis (small/large study effects). This can be exacerbated or mitigated by the choice of statistical model used. Ideally a sensitivity analysis employing multiple models would be used to assess these effects; however, this was only conducted in a small subset of the included reviews.
- Interpretation of the size of effect is outcome dependent. Whilst the Evidence Review reported on statistical significance based on the findings of the included reviews and pooled syntheses, some clinical interpretation will depend on baseline risk of the outcome. For example, what may be a relevant or noticeable health risk with a 15% increase for one outcome, may be negligible for another. Similarly, for continuous measures (ß coefficient), although statistically significant changes have been reported, interpretation of the size of the change per unit increase in exposure depends on the outcome and what is being measured. Clinical expertise in the outcomes and their measures is required to fully interpret the extent of risk the results represent. These issues highlight the difference between statistical significance and clinical significance. Statistical significance depends on the size of an effect and adequate sampling to achieve it; it does not imply that the effect size is meaningful for people and their health and wellbeing – the same is true for lack of statistical significance, that is, the finding may be clinically significant.
- This Evidence Review only considered reviews and syntheses of primary studies with meta-analyses presented in other systematic reviews or pooled syntheses. This type of research can be referred to by various terms, including overview or review of reviews (meta-analyses). A key consideration when synthesising data using overview methods is independence of data, or issues that arise from 'double or even multiple counting' of data where the reviewers are deliberately searching for and including multiple reviews that address the same topic, that in turn will likely include the same primary studies. However, it is unclear to what extent the same primary data have informed the same outcome in this report. While it is a limitation that must be acknowledged, the presentation of the results where there are multiple reviews informing an outcome in this report, that is with a simple range of effect estimates, is less susceptible to this issue than other forms of synthesis. It is also important to note, that across the range of 65 outcomes and outcome measures reported in this Evidence Review, only 14 were addressed by more than one meta-analysis.
- Measurement of the exposure was varied across all included studies in the reviews. Most meta-analyses assessed association or risk of adverse health outcome with exposure to

plastic-associated chemicals by assessment of the relative odds of the outcome between low and high exposure (in some cases logistic regression analysis (dichotomous/binary dependent variable)) was performed, or by meta-analyses of beta coefficients (linear regression analyses; natural units or standardised) from the primary studies. Only a very small number of the reviews included in this Evidence Review provided any detail pertinent to the level of exposure (generally measured in blood and/or urine) that these categories actually represented (in units).

- The AMSTAR tool was used to assess the quality of all included reviews including the pooled analyses. It should be noted that methods of pooled analyses do not essentially include a comprehensive and systematic search and screening of the literature and therefore would not fulfil these criteria and other systematic review specific criteria. Therefore, they score low in the quality appraisal with use of this tool. However, as noted in the methods, the data from cohorts of the populations in the pooled analyses usually represent a larger sample of the population than primary studies in systematic reviews and therefore were included in this Evidence Review. In this Evidence Review, a low scoring pooled analysis is different from a low scoring review with meta-analysis.
- The assessment of the methods used, and quality of the primary studies in the reviews were beyond the scope of this Evidence Review. However, in some instances where there was unclear reporting in the included review, some primary studies were retrieved to verify the subgroups of the sample used in the reviews (e.g., boys and girls) and to verify the exposure measure and description of the plastic-associated chemicals investigated.

SUMMARY OF THE EVIDENCE

BISPHENOLS (BISPHENOL A)

There were 13 systematic reviews, including 120 meta-analyses (Bigambo et al., 2020; Fu et al., 2020; C.-Y. Hu et al., 2018; Y. Hu et al., 2018; Hwang et al., 2018; K. Y. Kim et al., 2019; Nelson et al., 2020; Rancière et al., 2015; Ribeiro et al., 2020; Song et al., 2016; Wen et al., 2019; Wentao Wu et al., 2020; Zhong et al., 2020) and one pooled analysis (Dunder et al., 2019) that informed outcomes related to bisphenols. All analyses were for Bisphenol A (BPA) exposure. No other eligible reviews of human health effects for any other bisphenol chemicals used as alternatives to BPA in plastics were identified. Outcomes for which statistical meta-analyses were available were grouped into categories based on ICD-11 (World Health Organization, 2020):

- Birth: birth weight, birth length, head circumference, gestational age
- Child reproductive: anogenital distance, onset of puberty (early puberty)
- Adult reproductive:
    - Women's reproductive health – endometriosis
- Endocrine: polycystic ovary syndrome (PCOS), type 2 diabetes, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR): fasting insulin, fasting glucose
- Nutritional: obesity (generalised and abdominal), overweight, elevated waist circumference
- Circulatory: cardiovascular disease, hypertension, serum lipids

Abbreviations

BPA	Bisphenol A	**LDL**	Low-density lipoprotein
BMI	Body Mass Index	**HDL**	High-density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance	**ApoB**	Apolipoprotein B
ICD	International Classification of Diseases	**TG**	Triglycerides
PCOS	Polycystic ovary syndrome	**TC**	Total cholesterol

Exposure description and measures

Bisphenol A (BPA) is a chemical used extensively in the production of plastics and resins and found mostly in food and beverage packaging material and plastic containers (Bigambo et al., 2020; Wentao Wu et al., 2020). Most common routes of exposure are oral and dermal (Wentao Wu et al., 2020); however, specific routes and times of exposure cannot be accurately determined and therefore are not reported in most reviews. An exception is when reporting birth outcomes where exposure is via the pregnant mother and when children exposed to BPA were subsequently followed up postnatally. BPA levels were commonly measured in ng/mL, µg/L or mmol/L, in urine and serum samples in the general population, in fat/lipid (ng/g fat), and also in follicular fluid for ovarian syndrome outcomes and in amniotic fluid for birth specific outcomes. In some reviews, BPA measures were unspecified. For additional details on BPA, see Appendix 1.

BPA exposure levels were usually not reported in detail except for three reviews. Rancière et al. (2015) compared and reported extreme categories of urinary BPA levels (the highest vs. the lowest). The highest urinary BPA concentration was a mean (SE) of 5.0 (0.3) ng/mL in boys and 4.6 (0.3) ng/mL in girls in a surveillance data in children. The lowest was a median (interquartile range, IQR) of 0.60 (0.20 – 1.37) ng/mL in Chinese school children. Nelson et al. (2020) reported the BPA concentration in the studies included in their meta-analysis. The BPA median concentration range was 0.82 - 0.99 µg/L in two studies and 1.26 µg/g Cr (adjusted for creatinine) in one study. Song et al. (2016) compared the highest (>1.43 to >4.20 ng/mL) versus lowest ($\leq$0.47 to $\leq$1.36 ng/mL) exposure categories.

Overall findings

Overall, BPA exposure was not associated with any change in birth outcomes including birth weight, birth length, head circumference and gestational age. BPA exposure was associated with a decreased anoclitoral distance in female infants, but no association was found with anofourchette distance and precocious puberty in girls. BPA was not associated with risk of endometriosis in women. However, women with polycystic ovary syndrome (PCOS) were found to have significantly higher BPA levels than women without PCOS.

In adults, BPA exposure was associated with increased risk of type 2 diabetes, overweight, elevated waist circumference, but not fasting insulin and fasting glucose levels. Higher BPA exposure among adults was found to be associated with increased insulin resistance.

In the general population of adults and children, BPA exposure was associated with increased risk of obesity (including generalised and abdominal obesity), elevated waist circumference, cardiovascular disease and hypertension, but not with any of the serum lipids. No associations were found for overweight and elevated waist circumference in children.

Table 3.1: Summary of health outcomes related to bisphenol A (BPA) exposure

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
Birth outcomes						
BIRTH WEIGHT (BPA) - 2 reviews						
Infants; Prenatal exposure	Hu et al. 2018a (8/11)	Main analysis	ES 4.42g (95% CI = -8.83 to 17.67g)	8	2876	
		Subanalyses				
		first trimester	ES 44.41g (95% CI = -113.45 to 202.67g)	2	395	
		second trimester	ES 37.89g (95% CI = -209.68 to 285.46g)	2	292	
		third trimester	ES 34.38g (95% CI = -16.69 to 85.49g)	3	1512	
		Adjusted confounders group	ES 4.42g (95% CI = -8.83 to 17.67g)	8	2876	
		Unadjusted confounders group	ES 31.42g (95% CI = -19.14 to 81.98g)	3	1543	crude group
	Zhong et al. 2020 (5/11)	Main analysis	β -0.049g (95% CI = -0.199 to 0.101g)	9	4636	
BIRTH LENGTH (BPA) - 1 review						
Infants; Prenatal exposure	Zhong et al. 2020 (5/11)	Main analysis	β 0.058cm (95% CI = -0.072 to 0.188cm)	9	4636	
HEAD CIRCUMFERENCE (BPA) - 1 review						
Infants; Prenatal exposure	Zhong et al. 2020 (5/11)	Main analysis	β -0.004cm (95% CI = -0.119 to 0.111cm)	9	4636	
GESTATIONAL AGE (BPA) - 1 review						
Infants; Prenatal exposure	Zhong et al. 2020 (5/11)	Main analysis	β -0.032weeks (95% CI = -0.163 to 0.1weeks)	9	4636	
Child reproductive health outcomes						
ANOGENITAL DISTANCE (BPA) - 1 review						
Female infants; Prenatal exposure	Nelson et al. 2020 (7/11)	Anoclitoral distance	β -1.374 (95% CI = -2.475 to -0.274) *	3	1760	
		Anofourchette distance	β -1.069 (95% CI = -3.648 to 1.511)	3	1760	
PRECOCIOUS PUBERTY (BPA) - 1 review						
Girls; Postnatal exposure	Bigambo et al. 2020 (5/11)	Main analysis	ES 1.09 (95% CI = 0.88 to 1.35)	8	3498	
Adult reproductive health outcomes (women)						
ENDOMETRIOSIS (BPA) - 1 review						
women	Wen et al. 2019 (7/11)	Main analysis	OR 1.4 (95% CI = 0.94 to 2.08)	4	1130	
		Subanalyses				
		Hospital sample	OR 1.29 (95% CI = 0.72 to 2.31)	2	unsp.	
		Population sample	OR 1.61 (95% CI = 1.03 to 2.52) *	2	unsp.	
		Caucasian	OR 1.23 (95% CI = 0.82 to 1.84)	3	unsp.	
		Case-control studies	OR 1.72 (95% CI = 1.4 to 2.12) *	2	unsp.	
		Cohort studies	OR 1.19 (95% CI = 0.7 to 2.04)	2	unsp.	
Metabolic and endocrine outcomes						
PCOS (POLYCYSTIC OVARY SYNDROME) (BPA) - 1 review						
women	Hu et al. 2018b (9/11)	Main analysis	SMD 2.437 (95% CI = 1.265 to 3.609) *	11	933	
		Serum samples	SMD 2.515 (95% CI = 1.241 to 3.789) *	10	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Subanalyses of serum samples				
		Asian	SMD 3.209 (95% CI = 1.276 to 5.142) *	6	unsp.	
		Caucasian	SMD 1.511 (95% CI = -0.165 to 3.187)	4	unsp.	
		>19 years	SMD 2.311 (95% CI = 1.009 to 3.612) *	9	unsp.	
		BMI >25	SMD 1.56 (95% CI = -0.433 to 3.553)	4	unsp.	
		BMI <25	SMD 2.793 (95% CI = 1.027 to 4.559) *	5	unsp.	
		Sample >50	SMD 4.73 (95% CI = 4.267 to 5.193) *	3	unsp.	
		Sample <50	SMD 1.389 (95% CI = 0.685 to 2.093) *	7	unsp.	
		ELISA method	SMD 1.957 (95% CI = 0.716 to 3.198) *	8	unsp.	
		HPLC method	SMD 4.642 (95% CI = 3.9 to 5.383) *	2	unsp.	
		PCOS to control ratio >1	SMD 3.19 (95% CI = 1.302 to 5.078) *	6	unsp.	
		PCOS to control ratio <1	SMD 1.396 (95% CI = 0.455 to 2.338) *	4	unsp.	
		HOMA- IR >2.5	SMD 1.726 (95% CI = -0.69 to 4.143)	3	unsp.	
		HOMA-IR levels unknown	SMD 3.209 (95% CI = 1.276 to 5.142) *	6	unsp.	
		LH/FSH <1.5	SMD 0.726 (95% CI = 0.411 to 1.04) *	2	unsp.	
		LH/FSH levels unknown	SMD 2.694 (95% CI = 1.062 to 4.326) *	7	unsp.	
		High study quality	SMD 1.944 (95% CI = 0.48 to 3.407) *	6	unsp.	>7 Newcastle-Ottawa Scale
		Medium study quality	SMD 3.424 (95% CI = 1.718 to 5.129) *	4	unsp.	4-7 Newcastle-Ottawa Scale
TYPE 2 DIABETES (BPA) - 3 reviews		**Range of effects:**	**OR 1.20 to 1.47 (95% CI = 1.09 to 1.80) ***	**3 to 16**	**9291 to 41320**	
Adult (general population)	Hwang et al. 2018 (6/11)	Fixed effects	OR 1.28 (95% CI = 1.14 to 1.44) *	16	41320	
		Sensitivity analysis				
		Random effects	OR 1.2 (95% CI = 1.09 to 1.31) *	13	38059	after exclusion of serum BPA levels and high heterogeneity
		Specimen type				
		Urine samples	OR 1.01 (95% CI = 1 to 1.02)	14	38298	
		Serum samples	OR 1.59 (95% CI = 1.06 to 2.38) *	2	3022	
	Ranciere et al. 2015 (7/11)	High vs low exposure	OR 1.47 (95% CI = 1.21 to 1.8) *	3	9291	
	Song et al. 2016 (6/11)	High vs low exposure	RR 1.45 (95% CI = 1.13 to 1.897) *	4	10541	
		Dose-response analysis	RR 1.09 (95% CI = 1.03 to 1.15) *	5	unsp.	
INSULIN RESISTANCE (HOMA-IR) (BPA) - 1 review						
Adult (general population)	Song et al. 2016 (6/11)	Main analysis	WMD 0.8 (95% CI = 0.36 to 1.25) *	4	6520	
FASTING INSULIN (BPA) - 1 review						
Adult (general population)	Song et al. 2016 (6/11)	Main analysis	WMD 0.15 (95% CI = -0.12 to 0.41)	4	9854	
FASTING GLUCOSE (BPA) - 1 review						
Adult (general population)	Song et al. 2016 (6/11)	Main analysis	WMD 0.97mg/dL (95% CI = -0.19 to 2.14mg/dL)	4	9854	
Child neurodevelopmental outcomes – no data						
Nutritional outcomes						
OBESITY (BPA) - 2 reviews		**Range of effects:**	**OR 1.57 to 1.67 (CI 95% = 1.35 to 1.98) ***	**3 to 5**	**10727 to 12749**	
Children and adults;	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.67 (95% CI = 1.41 to 1.98) *	3	10727	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
postnatal exposure (measured in urine)	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.57 (95% CI = 1.35 to 1.83) *	5	12749	
OBESITY (BPA) - 1 review						
Children; postnatal exposure (measured in urine)	Kim et al. 2019a (6/11)	High vs low urinary exposure	OR 1.57 (95% CI = 1.097 to 2.234) *	7	9602	
		Relatively high exposed group	OR 1.58 (95% CI = 1.077 to 2.315) *	6	9522	excluding a small pilot study
		Obese vs normal weight children	SMD 0.166 (95% CI = -0.121 to 0.453)	8	2092	
		Obese vs normal weight children	SMD 0.044 (95% CI = -0.088 to 0.176)	6	1962	excluding pilot studies
OBESITY (BPA) - 2 reviews		**Range of effects:**	**OR 1.50 to 1.60 (CI 95% = 1.27 to 1.93) ***	**2 to 4**	**7357 to 9379**	
Adults	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.6 (95% CI = 1.32 to 1.93) *	2	7357	
	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.5 (95% CI = 1.27 to 1.77) *	4	9379	
GENERALISED OBESITY (BPA) - 1 review						
Children and adults; postnatal exposure (measured in urine)	Wu et al. 2020a (5/11)	random effects	OR 1.831 (95% CI = 1.589 to 2.12) *	8	25779	
		Dose-response analysis	OR 1.16 (95% CI = 1.14 to 1.19) *	unsp.	unsp.	
ABDOMINAL OBESITY (BPA) - 1 review						
Children and adults; postnatal exposure (measured in urine)	Wu et al. 2020a (5/11)	Main analysis	OR 1.43 (95% CI = 1.27 to 1.62) *	7	21629	
		Dose-response analysis	OR 1.12 (95% CI = 1.09 to 1.14) *	unsp.	unsp.	
(GENERALISED) OVERWEIGHT (BPA) - 3 reviews		**Range of effects:**	**OR 1.21 to 1.32 (CI 95% = 0.98 to 1.72)**	**5 to 6**	**11339 to 18404**	
Children and adults; postnatal exposure (measured in urine)	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.21 (95% CI = 0.98 to 1.5)	5	unsp.	
	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.32 (95% CI = 1.01 to 1.72) *	5	11339	
	Wu et al. 2020a (5/11)	Main analysis	OR 1.24 (95% CI = 1.02 to 1.51) *	6	18404	
		Dose-response analysis	OR 1.058 (95% CI = 1.034 to 1.084) *	unsp.	unsp.	
(GENERALISED) OVERWEIGHT (BPA) - 2 reviews		**Range of effects:**	**OR 1.24 to 1.67 (95% CI = 0.82 to 3.38)**	**3**	**5202**	
Children; postnatal exposure	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.24 (95% CI = 0.88 to 1.75)	3	unsp.	
	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.67 (95% CI = 0.82 to 3.38)	3	5202	
(GENERALISED) OVERWEIGHT (BPA) - 2 reviews		**Range of effects:**	**OR 1.25 (95% CI = 1.01 to 1.56) ***	**2**	**6137**	
Adults	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.25 (95% CI = 1.01 to 1.56) *	2	6137	
	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.25 (95% CI = 1.01 to 1.56) *	2	6137	
ELEVATED WAIST CIRCUMFERENCE (BPA) - 2 reviews		**Range of effects:**	**OR 1.48 to 1.49 (CI 95% = 1.25 to 1.76) ***	**4 to 6**	**11757 to 14604**	
Children and adults; postnatal exposure (measured in urine)	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.48 (95% CI = 1.25 to 1.76) *	4	11757	
	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.49 (95% CI = 1.29 to 1.72) *	6	14604	
ELEVATED WAIST CIRCUMFERENCE (BPA) - 1 review						
Children; postnatal exposure	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.62 (95% CI = 0.97 to 2.72)	2	4696	
ELEVATED WAIST CIRCUMFERENCE (BPA) - 2 reviews		**Range of effects:**	**OR 1.50 to 1.52 (95% CI = 1.21 to 1.90) ***	**3 to 4**	**6777 to 8387**	
Adults	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.52 (95% CI = 1.21 to 1.9) *	3	8387	
	Ribeiro et al. 2020 (7/11)	Main analysis	OR 1.5 (95% CI = 1.27 to 1.78) *	4	6777	
			Circulatory outcomes			
CARDIOVASCULAR DISEASE (BPA) - 1 review						

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
General population (measured in urine and serum)	Fu et al. 2020 (6/11)	Main analysis	OR 1.19 (95% CI = 1.03 to 1.37) *	10	23953	
HYPERTENSION (BPA) - 1 review						
children and adults; General population (measured in urine)	Ranciere et al. 2015 (7/11)	Main analysis	OR 1.41 (95% CI = 1.12 to 1.79) *	2	unsp.	SBP > 140mmHg and/or DBP >90mmHg
SERUM LIPIDS (BPA) - 1 pooled analysis						
Children and adults; postnatal exposure (measured in urine)	Dunder et al. 2019 (4/11) [p]	LDL-C	β -0.02 (95% CI = -0.05 to 0.01)	6	15593	
		HDL-C	β -0.01 (95% CI = -0.02 to 0)	6	15593	
		TC	β -0.02 (95% CI = -0.04 to 0)	6	15593	
		TG	β -0.01 (95% CI = -0.03 to 0.01)	6	15593	
		ApoB	β -0.89 (95% CI = -1.843 to 0.06)	6	15593	
Children; postnatal exposure	Dunder et al. 2019 (4/11) [p]	*LDL-C*				
		standard adjusted	β -0.005 (95% CI = -0.05 to 0.05)	6	4604	
		Fully adjusted	β 0.003 (95% CI = -0.05 to 0.05)	6	4604	
		HDL-C				
		standard adjusted	β -0.01 (95% CI = -0.02 to 0.002)	6	4604	
		Fully adjusted	β -0.01 (95% CI = -0.02 to 0.002)	6	4604	
		TC				
		standard adjusted	β 0.008 (95% CI = -0.03 to 0.05)	6	4604	
		Fully adjusted	β 0.01 (95% CI = -0.03 to 0.05)	6	4604	
		TG				
		standard adjusted	β 0.01 (95% CI = -0.02 to 0.05)	6	4604	
		Fully adjusted	β 0.01 (95% CI = -0.02 to 0.05)	6	4604	
		ApoB				
		standard adjusted	β -0.48 (95% CI = -2.1 to 1.2)	6	4604	
		Fully adjusted	β -0.54 (95% CI = -2.3 to 1.2)	6	4604	
		Boys				
		LDL-C	β -0.03 (95% CI = -0.09 to 0.04)	6	unsp.	
		HDL-C	β -0.01 (95% CI = -0.03 to 0.003)	6	unsp.	
		TC	β 0.02 (95% CI = -0.04 to 0.07)	6	unsp.	
		TG	β 0.04 (95% CI = -0.003 to 0.09)	6	unsp.	
		ApoB	β -0.72 (95% CI = -2.8 to 1.4)	6	unsp.	
		Girls				
		LDL-C	β 0.04 (95% CI = -0.04 to 0.11)	6	unsp.	
		HDL-C	β -0.01 (95% CI = -0.03 to 0.007)	6	unsp.	
		TC	β -0.02 (95% CI = -0.08 to 0.04)	6	unsp.	
		TG	β -0.02 (95% CI = -0.07 to 0.03)	6	unsp.	
		ApoB	β -0.18 (95% CI = -2.9 to 2.6)	6	unsp.	
Adults	Dunder et al. 2019 (4/11) [p]	*LDL-C*				
		standard adjusted	β -0.005 (95% CI = -0.05 to 0.05)	6	10989	
		Fully adjusted	β -0.02 (95% CI = -0.05 to 0.01)	6	10989	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		HDL-C				
		standard adjusted	β -0.012 (95% CI = -0.02 to 0.001)	6	10989	
		Fully adjusted	β -0.006 (95% CI = -0.01 to 0.003)	6	10989	
		TC				
		standard adjusted	β -0.02 (95% CI = -0.04 to 0.4)	6	10989	
		Fully adjusted	β -0.02 (95% CI = -0.01 to 0.003)	6	10989	
		TG				
		standard adjusted	β -0.02 (95% CI = -0.04 to 0.004)	6	10989	
		Fully adjusted	β -0.02 (95% CI = -0.03 to 2e-04)	6	10989	
		ApoB				
		standard adjusted	β -0.89 (95% CI = -1.8 to 0.06)	6	10989	
		Fully adjusted	β -0.91 (95% CI = -1.82 to -0.02) *	6	10989	
		Males				
		LDL-C	β -0.02 (95% CI = -0.07 to 0.02)	6	unsp.	
		HDL-C	β -0.008 (95% CI = -0.02 to 0.004)	6	unsp.	
		TC	β -0.02 (95% CI = -0.05 to 0.01)	6	unsp.	
		TG	β -0.01 (95% CI = -0.04 to 0.02)	6	unsp.	
		ApoB	β -0.66 (95% CI = -1.9 to 0.6)	6	unsp.	
		Females				
		LDL-C	β -0.01 (95% CI = -0.05 to 0.03)	6	unsp.	
		HDL-C	β -0.01 (95% CI = -0.03 to 2e-04)	6	unsp.	
		TC	β -0.02 (95% CI = -0.05 to 0.02)	6	unsp.	
		TG	β -0.01 (95% CI = -0.04 to 0.01)	6	unsp.	
		ApoB	β -0.98 (95% CI = -2.3 to 0.4)	6	unsp.	
Respiratory outcomes - No data						
Skin-related outcomes - No data						
Cancer outcomes - No data						

Table legend:

*p Indicates a pooled analysis, * indicates significant effect.*

Studies or participants unspecified (unsp.) indicates no data available from the reviews

Descriptive summary of BPA reviews and pooled analyses

To facilitate rapid reference, included reviews and pooled analysis are presented in this section in alphabetical order. This section includes details of exposures investigated, number and type of studies and total sample size, number of meta-analyses presented and various outcomes reported (Full details are available in Appendix 6). AMSTAR scores are provided for reference.

Bigambo et al. (2020) - *Association between phenols exposure and earlier puberty in children: A systematic review and meta-analysis. No COIs declared, AMSTAR Score: 6/11*.

Bigambo et al. (2020) explored the associations between BPA, 2,5- Dichlorophenol, and benzophenone-3 among young females. The review included nine studies – four cohort, three case control, and two cross-sectional with a total of 4,737 participants. All studies were included in the meta-analyses, 8 studies informed outcomes assessed with exposure to BPA. The Newcastle-Ottawa Scale was used to assess the quality of all included studies. Quality scores ranged from moderate to high. Exposure to the phenolic chemicals was assessed during childhood, except for one study that assessed exposure during in utero and peri-pubertal periods, measured in urine samples using either high-performance liquid chromatography (HPLC), HPLC-tandem mass spectrometry (HPLC-MS/MS), isotope dilution-LC-MS/MS, or µg/L. Outcomes reported were risk of earlier puberty (precocious puberty, earlier puberty, idiopathic central precocious puberty, premature thelarche, earlier menarche, and earlier pubarche) measured using ORs and HRs combined as an overall effect size. For BPA exposure across populations, no associations were found; however, the authors concluded significant positive association with earlier puberty outcomes (not reported separately). It is unclear in the analysis provided for BPA if the studies by Durmaz et al. (2018, 2014) are the same population (case-control studies with Turkish girls). Caution should be applied in interpreting the findings related to other types of phenolic chemicals since in subgroup analysis in some individual studies have shown a positive relationship between BPA, Triclosan and Benzophenone-3 exposures and the risk of earlier puberty in children.

Dunder et al. (2019) - *Urinary bisphenol A and serum lipids: a meta-analysis of six NHAMES examination cycles (2003-2014). No COIs declared, AMSTAR Score: 4/11.*

Dunder et al. (2019) undertook meta-analysis of continuous cross-sectional surveillance data (NHANES cohort) in this pooled study, exploring the association between BPA and serum lipids and cholesterol among children (≤ 17 years; n=4,604) and adults (≥ 18 years; n=10,989) – 15,593 total participants. Exposure route and time were not reported. Levels of BPA were measured in urinary samples in mmol/L; outcomes reported were low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and Apo lipoprotein B (ApoB); associations were reported using beta coefficients. For BPA across populations, the authors concluded no significant positive association with any cholesterol. When grouped by age, still no association was found between BPA exposure and any cholesterol. Evidence suggested no association between urinary BPA levels and five different lipids - LDL-C, HDL-C, TC, TG or ApoB - in children or adults.

Fu et al. (2020) - *The association between environmental endocrine disruptors and cardiovascular disease: A systematic review and meta-analysis. No COI declared, AMSTAR Score: 4/11*.

Fu et al. (2020) explored the association between polychlorinated biphenyl (PCBs), any phthalate compound, BPA and the risk of cardiovascular disease among a general population in whom environmental exposure to endocrine disrupters could be determined. The review and meta-analyses included a total of 29 studies – (cross-sectional studies (n=17), retrospective cohort (n=7), prospective cohort (n=4), case control (n=1)), with a total of 41,854 participants. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. The quality scores of studies ranged from 7 to 9 (all considered to be of high quality).

For exposure to BPA there was a significant positive association with risk of cardiovascular disease (no subgroup analysis conducted).

For exposure to any phthalate, there was a significant positive association with risk of cardiovascular disease. When grouped based on phthalate compound, there was no association between exposure to MEP, MiBP, MBzP, MEHP, MEHHP, MEOHP or MEP.

PCB exposure was via an unspecified route, the measure and timing of this exposure was also unspecified by the authors. The only outcome reported was the risk of cardiovascular disease. For PCB exposure across populations, the authors concluded significant positive association with risk of cardiovascular disease. When grouped according to PCB subtype, exposure to PCB 138 and PCB 153 were found to be positively associated with an increased risk of cardiovascular disease. There were no associations found for PCB 180 and total PCBs.

It should be noted that the combined analyses for BPA were valid, however, for phthalates and PCBs, the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead.

The authors suggest that exposure to environmental endocrine disruptors is a risk factor for CVD. PCBs, BPA, and other endocrine disruptors (such as pesticides) have a great impact on the development and progression of CVD. Except PCB180 and total PCBs, PCB138, PCB153, were all CVD risk factors. However, the findings from the invalid combined analyses should be interpreted with caution.

Hu et al. (2018) – *The association between prenatal bisphenol A exposure and birth weight: a meta-analysis. No COI declared, AMSTAR Score: 8/11.*

Hu et al. (2018) explored the association between prenatal bisphenol A (BPA) exposure and birth weight among infants. The review included 14 studies – including case control (n=2) and cohort (n=12), with a total of 6,208 participants. Eight studies were used in meta-analysis with 2,876 participants. The Office of Health Assessment (OHAT) critical appraisal tool was used to assess the quality of all the included studies. Quality scores of 14 studies ranged from medium to high quality. BPA exposure was via maternal/prenatal exposure before or at the time of delivery, measured in ng/ml or µg/g from maternal urine, maternal blood or amniotic fluid, or cord blood and the time period was not reported. The outcome reported was birthweight or low birthweight. For prenatal BPA exposure, the authors concluded no significant association with birthweight. When grouped by exposure trimester, prenatal BPA exposure was similarly found to be not associated with changes in birthweight in any of the 3 trimesters.

Hu et al. (2018)- *The association between the environmental endocrine disruptor bisphenol A and polycystic ovary syndrome: a systematic review and meta-analysis. No COI declared, AMSTAR score: 9/11.*

Hu et al. (2018) explored the association between BPA and polycystic ovary syndrome (PCOS) among women. The review included nine cross-sectional studies with a total of 933 participants. Eight studies were included in the meta-analysis with 760 participants (pairs matched by age and BMI). The Newcastle-Ottawa Scale was used to assess the quality of all included studies. Quality scores ranged from medium to high. Exposure route and time were not reported. Levels of BPA were measured in serum in ng/mL; outcome reported was PCOS. For BPA across populations, the authors concluded a significant positive association with PCOS. When grouped by BMI and race, BPA exposure was found to be significantly associated with having a higher BMI and Caucasians are more likely to be exposed. Serum BPA levels in women with PCOS were significantly higher than healthy (matched) controls. BPA may be involved in pathogenesis of PCOS as an environmental endocrine disruptor.

Hwang et al. (2018) - *Bisphenol A exposure and type 2 diabetes mellitus risk: a meta-analysis. No COI declared, AMSTAR score: 6/11.*

Hwang et al. (2018) explored the association between BPA and risk of T2D among the general population. The review and meta-analyses included 16 studies – 12 cross sectional, three case control and one cohort with a total of 41,320 participants. The Downs and Black checklist (Downs and Black, 1998) was used to assess the quality of all included studies. Quality scores ranged from 13 to 18. Exposure was measured in urine or serum (only two studies) in ng/mL; exposure route and time were not reported. Fixed and random meta-analyses conducted and sensitivity analyses considering serum measures and high heterogeneity. For BPA exposure across populations, the authors concluded that BPA exposure measured via urine or serum is positively associated with T2D risk (random effects analysis only).

Kim et al. (2019) - *The association between Bisphenol A exposure and obesity in children - A systematic review with meta-analysis. No COI declared, AMSTAR score: 6/11.*

Kim et al. (2019) explored the association between BPA and obesity among children aged 14 months to 19 years. The review included 13 studies – cross sectional (n=8), cohort (n=3) and case control (n=2) with a total of 11,303 participants. All studies were used in the meta-analysis. The Newcastle-Ottawa Scale was used to assess the quality of all included studies. Quality scores ranged from six (one study) to nine (seven studies). The exposure of BPA was postnatal and levels measured in urine samples in µg/L. Outcome reported was obesity (BMI or body weight). BPA levels were reported as highest level versus lowest level (reference); however, no descriptions were provided. Authors concluded a significant increase in obesity with increased BPA exposure.

Nelson et al. (2020) - *In utero exposure to persistent and non-persistent endocrine-disrupting chemicals and anogenital distance. A systematic review of epidemiological studies. No COI declared, AMSTAR Score: 7/11.*

Nelson et al. (2020) explored the association between exposure to environmental anti-androgenic chemicals in utero and anogenital distance (AGD) outcomes among newborn babies up to 12 months. The review included a total of 16 studies – prospective cohorts (n=13), cross-sectional studies (n=2) and a retrospective study (n=1). Three studies were included in the meta-analysis 1,760 participants. The Newcastle-Ottawa Scale was used to assess the quality of all the included studies. Quality scores of all the included studies ranged from 5-15/15; three high-quality cohort studies used in the meta-analysis ranged from 14-15/15. The review considered endocrine-disrupting chemicals which included the following: organochlorides (OCs), polybrominated diphenyl ethers (PBDEs), dioxins and dioxin like, perfluoroalkyl substances, BPA. Meta-analysis was only possible for BPA, though high statistical heterogeneity was observed. BPA levels were measured in the urine of pregnant mothers in their first trimester of pregnancy in µg/L. The median concentration range 0.82-0.99µg/L in two studies and 1.26 µg/g Cr (adjusted for creatinine) in one study. Significant summary estimate for the change in anogenital distance anoclitoral and non-significant estimate for the change in anogenital distance anofourchette in newborn babies, in % change per log10 increase in maternal urinary BPA concentrations were reported.

Rancière et al. (2015) - *Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. No COI declared, AMSTAR Score: 7/11.*

Rancière et al. (2015) explored the association between bisphenol A and 8 outcomes (diabetes, prediabetes, hyperglycaemia, overweight, obesity, elevated waist circumference, cardiovascular disease, hypertension) in adults or children (only diabetes in adults, in an attempt to limit the analysis to type 2). Prediabetes, hyperglycaemia and cardiovascular disease had no pooled estimates provided. The review included 33 studies- (cross sectional (n=28) and prospective longitudinal (n=5), with a total of (n= 69,486) participants. The review used a scoring system based on the Office of Health Assessment and Translation (OHAT) guidelines to assess the quality of the included studies. Quality scores of the individual studies

were not presented in the review. Bisphenol A exposure was non-specific, measured as urinary BPA and in amniotic fluid (µg/L). BPA levels were reported as the highest vs. the lowest. Highest levels found a mean (SE) of 5.0 (0.3) ng/mL in boys and 4.6 (0.3) ng/mL in girls. Lowest: a median (interquartile range, IQR) of 0.60 (0.20–1.37) ng/mL. Exposure time was not specific. Exposure in children was postnatal. For BPA exposure in the general population, the authors concluded significant positive associations with prevalent diabetes. However, in subgroup analyses increased BPA exposure was shown to be associated with being overweight adults, but not children. Exposure to BPA was positively associated with obesity, waist circumference for pooled population (adults and children) and in subanalysis where the populations were separated. However, in subanalysis an increased waist circumference with BPA exposure was only seen in adults, not in children. BPA exposure was positively associated with hypertension in general population. Authors concluded that elevated levels of uBPA found in the general population is associated with increased prevalence of diabetes, general and abdominal obesity and hypertension. However, the authors noted that additional prospective data are needed to ascertain the nature of the relationship between BPA exposure and cardiometabolic disorders.

Ribeiro et al. (2020) - *Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis. No COI declared, AMSTAR Score: 9/11.*

Ribeiro et al. (2020) explored the association between exposure to organochlorines; brominated compounds; BPA and obesity-related outcomes among the general population with age limiters between 6 and 74 years. The review and meta-analysis included nine cross-sectional studies, with a total of 23,214 participants. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. The authors stated that 65% of the studies appraised had a low or medium risk of bias. Organochlorine exposure was via an unspecified route, measured in the urine (metric not specified). The exposure in children were postnatal. Reported outcomes include prevalence of obesity and elevated waist circumference. The authors concluded significant positive associations between exposure to 2,5 DCP and the prevalence of obesity, but no association was found for 2,4 DCP. There was no association between exposure to brominated compounds and waist circumference, but when grouped according to brominated compound subtype there was a positive association between exposure to PBB-153, and no association with exposure to PBDE 47. With BPA exposure there was an increase in the prevalence of an elevated waist circumference, being overweight and obesity. When grouped according to age there was a positive association for adults for all of these outcomes, however, for children this association was only maintained for obesity.

Song et al. (2016) - *Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. No COI declared, AMSTAR Score: 6/11.*

Song et al. (2016) explored the association between endocrine-disrupting chemical exposure and risk of type 2 diabetes and diabetes-related metabolic traits. The review included a total of 49 studies- including cross sectional (n=41) and cohort (n=8), with a total of 55,774 participants. Thirty-two studies were included in the meta-analysis for polychlorinated biphenyls (PCBs; n=21), phthalates (n=7) and bisphenol A (BPA; n=4). Critical appraisal was not undertaken. Exposure routes were not reported but were measured in serum or urine as pg/ml, pg/g or ng/g lipid. The outcome reported was type 2 diabetes and it was analysed using a risk ratio as highest versus lowest exposure categories (no further details of the categories reported). For exposure to PCBs and BPA across populations, the authors concluded a significant positive association with type 2 diabetes risk. No association was found for phthalate exposure and type 2 diabetes risk.

Wen et al. (2019) - *The risk of endometriosis after exposure to endocrine-disrupting chemicals: a meta-analysis of 30 epidemiology studies. No COI declared, AMSTAR Score: 7/11.*

Wen et al. (2019) explored the association between endocrine-disrupting chemical (BPA, PCBs, OCPs and PAEs) exposure and endometriosis in women. The review included 30 studies

– including case control (n=21), cohort (n=8) and cross sectional, with a total of 7,127 participants. All studies were included in the meta-analysis. A modified Newcastle-Ottawa Scale (NOS) for case-control and cohort studies and the Agency for Healthcare Research and Quality (AHRQ) checklist for cross-sectional studies were used to assess the quality of the included studies. The quality of all included studies was acceptable with score range 5-8 (moderate quality). Endocrine-disrupting chemical exposure route was not reported, but the exposure was measured in µg/L, ng/mL, ng/g, pg/g, ppb or ng/g fat from urine, serum or fat and the time period was not reported. The outcome reported was risk endometriosis and it was analysed with categories of endocrine-disrupting chemical exposure (medium or high, no other information reported). For endocrine-disrupting chemical exposure across populations, the authors concluded a significant increase in endometriosis with exposure. Overall analyses for BPA was appropriate, howeverfor phthalates and PCBs, it was unclear how summary (overall) values had been included for analyses, therefore only BPA findings were extracted and reported in this review. BPA (urinary) was not found to increase the risk of endometriosis.

Wu et al. (2020) - *Bisphenol A and the risk of obesity a systematic review with meta-analysis of the epidemiological evidence – No COI declared, AMSTAR Score: 5/11.*

Wu et al. (2020) explored the association between BPA and obesity among the population aged 6-79 years. The review included 10 studies - cross sectional (n=9), and cohort (n=1), with a total of 27,993 participants. All studies were used in the meta-analysis. The Newcastle-Ottawa Scale was used to assess the quality of all the included studies. Quality scores of all the 10 studies ranged from 6-8/9 with a median score of seven. BPA exposure was not specified but authors noted that BPA is ubiquitous in the surroundings. Exposure in children was postnatal. BPA levels were measured in urine samples in ng/mL or µg/L. BPA levels were reported as highest level versus lowest level however, no descriptions were provided. Exposure time was not reported. Outcomes reported were obesity (this was a general measure of all of the other measures of obesity provided; analyses counted data from the same participants multiple times, hence this data has not been extracted for this review), subtypes of obesity (abdominal obesity, generalised obesity) and generalised overweight. Random and fixed effects have been analysed and reported, with the former preferentially extracted in this review. However, no descriptions were provided regarding the differences in these outcomes. For BPA exposure across populations, the authors concluded significant positive association with indices of generalised and abdominal obesity. When grouped by age, BPA exposure was found to be significantly associated with obesity (abdominal obesity, generalised obesity) and overweight in children and adults. However, authors noted that a causal association between BPA and obesity cannot be established due to the cross-sectional nature of the evidence base of the review.

Zhong et al. (2020)- *Association of prenatal exposure to phenols and parabens with birth size: A systematic review and meta-analysis. No COI declared, AMSTAR Score: 5/11.*

Zhong et al. (2020) explored the association between maternal exposure to phenols and parabens, including BPA and birth outcome measures in pregnant women. The review included 21 studies – including case control (n=1) and cohort (n=20), with a total of 11,497 participants. The maximum number of studies used in the meta-analyses for BPA exposure was 9 with 2,876 participants for birthweight. No critical appraisal was undertaken. BPA exposure was via maternal/prenatal exposure (urine); however, the measured units and exposure measures were not reported. For prenatal BPA exposure, the authors concluded no significant association with birthweight, birth length, head circumference and gestational age.

Critical appraisal of included BPA reviews and pooled analysis

The methodological quality of the 13 systematic reviews with meta-analyses and one pooled analysis included are presented in the following table.

Table 3.2: Critical appraisal of bisphenol A (BPA) reviews and pooled analysis

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Bigambo et al. (2020)	N	CA	Y	N	N	Y	Y	CA	CA	Y	Y	**5**	No reference to a priori design or protocol (Q1). It is unclear if selection was in duplicate, extraction was not (Q2). Unclear whether duplicate study selection and data extraction (Q2). Search of 3 databases performed and keyword terms provided (unlikely eligible studies indexed in Cochrane) (Q3), grey literature was not sought (Q4). No list of excluded studies was provided(Q5); Characteristics of included studies were included and critical appraisal undertaken and results reported (Q7). despite the methods indicating sensitivity analyses on the basis of quality, none were provided nor informed the final conclusions (Q8). Statistical analyses appear appropriate; however, it is unclear if the studies by Durmaz 2014, 2018 are the same population (Q9). Less than 10 studies so publication bias was not assessed (Q10). no conflicts were declared by review authors (Q11).
Dunder et al. (2019) *	Y	N	N	N	N	Y	N	N	Y	N	Y	**4**	This was not a systematic review but rather a pooled analysis of CDC National Health and Nutrition Examination Survey (NHANES) continuous cross-sectional surveillance data; therefore, no systematic methods relating to searching, screening, extraction and appraisal of the evidence were undertaken. Required data was accessed from relevant time periods from NHANES study. All required details of study cohort are provided (Q6). Authors declared no competing interests, funders were identified (Q11).
Fu et al. (2020)	N	CA	Y	N	N	Y	Y	Y	CA	Y	Y	**6**	No *a priori* protocol (Q1). Study selection done in duplicate; however, not clear if extraction was done in duplicate or if any strategy was undertaken to check the data extraction (Q2); no grey literature search undertaken (Q4); no list of excluded studies available (Q5); table and narrative appear to be presented with relevant details. NB. an exclusion criterion in this study was to exclude those for which an OR could not be calculated (~33 studies) - this is acceptable practice for conduct of a meta-analysis, however, the SR is likely at risk of bias - evidence has been omitted on this basis (Q6); Combined analyses for BPA were valid, however, for phthalates and PCBs, the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead (Q9). Conflict of interest in the individual review was discussed but not for all included articles (Q11).
Hu et al. (2018)	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	**8**	Overall the quality of the review was good with the main limitations being lack of an 'a priori' protocol. Potentially eligible records were screened in duplicate. The search was comprehensive with the exception of grey literature which authors did not search. Database searching was performed independently and in duplicate. Reasons for exclusion if ineligible studies were provided and the studies identified. OHAT guidelines used for quality appraisal, however, there was little or no consideration of quality aspects in analysis or formulation of conclusions (Q8). Statistical analyses appear appropriate and publication bias was assessed. Authors declared no conflicts of interest for the review but not the individual included studies (Q11).

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Hu et al. (2018)	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	**9**	No a priori protocol or design referred to (Q1). Both selection and extraction performed in duplicate (Q2). Seven databases (incl. Chinese) were searched in duplicate and search strategies provided (Q3 and Q4). Excluded studies not listed (Q5). Study characteristics and quality using Newcastle-Ottawa Scale (NOS) were reported (Q6, Q7). Quality was assessed with meta-regression and statistical analyses appear appropriate (Q8, Q9). Publication bias assessed statistically (Q10). COI not reported for primary studies (Q11).
Hwang et al. (2018)	N	CA	Y	N	N	Y	Y	N	Y	Y	Y	**6**	No a priori design or protocol referred to (Q1). Two major databases were searched with keywords and MESH terms (Q3). Extraction was performed in duplicate; however, it is unclear if study selection was also. Grey literature was not searched for nor was publication status considered as an inclusion criterion (Q4). The numbers of excluded studies and reasons were recorded, yet they were not identifiable (Q5). Characteristics were assessed and quality assessed using Downs and Black tool and reported (Q6; Q7). Quality scores were provided, however, not considered in the analysis, nor mentioned (beyond study design) in the conclusions (Q8). Statistical analyses appeared all appropriate (fixed and random), dose-response meta-analysis also performed (Q9). Publication bias was assessed statistically (Q10). Review authors declared no competing interests (Q11).
Kim et al. (2019)	N	CA	Y	N	N	Y	Y	N	Y	Y	Y	**6**	No a priori design nor protocol referred to (Q1). Three databases searched (unclear why Cochrane considering it doesn't index observational studies) with keywords only, no MESH terms (Q3) were used in the search strategy (not provided) and grey literature was not considered (Q4). Selection was completed independently and in duplicate, it is unclear if extraction was also (Q2). No list of excluded studies provided (Q5). Characteristics of included studies were provided and quality appraisal using Newcastle-Ottawa Scale (NOS) conducted and reported (Q7). Statistical analysis was appropriate (Q9), publication bias was assessed. COI not reported for primary studies but was declared by review authors (Q11).
Nelson et al. (2020)	N	Y	Y	N	N	Y	Y	Y	Y	N	Y	**7**	There was no a priori design nor protocol Q1). Study selection and extraction was performed in duplicate (Q2). Three databases were searched and strategies provided, though no grey literature and supplementary search conducted (Q3, Q4). Details of excluded studies were not provided (Q5) though characteristics of included studies were (Q6). The Newcastle-Ottawa Scale (NOS) was used to assess study quality and results were reported (Q7), they were not considered in meta-analysis, though were in the formulation of conclusions (Q8). Statistical analysis appeared appropriate (Q9). Publication bias was not mentioned nor considered (Q10). Authors declared no conflict of interest in their review, but not for individual studies included (Q11).
Rancière et al. (2015)	N	CA	Y	N	Y	Y	Y	Y	Y	N	Y	**7**	No reference to an a priori protocol provided (Q1). Selection was completed in duplicate, extraction does not appear to have been (Q2). Two databases were searched with keywords and MESH terms (Q3); grey literature searching was not included (Q4). Details of included and excluded studies were provided (Q5, Q6). OHAT guidelines were used for quality assessment and results reported and rudimentary commentary made re impact (Q7, Q8). Statistical analyses appear appropriate; cohorts were tracked and recorded to ensure no duplication of data in analyses; sensitivity analysis removed Ahmadkhaniha study as it led to highly significant heterogeneity ($p<10-5$ and $I2 = 94$ %; diabetes outcome) (Q9). Publication bias was not considered (Q10). review authors declared no conflicts (Q11).
Ribeiro et al. (2020)	N	Y	Y	N	N	Y	Y	Y	CA	Y	Y	**7**	No a priori protocol (Q1). No grey literature search undertaken (Q4); no list of excluded studies provided (Q5); the authors assessed the statistical, clinical and methodological heterogeneity; though not included in analyses, discussion and conclusion raise issues of bias and confounding that are reflected in the conclusions (Q8). Combined analyses for the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; only relevant analysis of individual chemical exposures have been extracted (Q9); conflict of interest in the individual review was discussed but not for all included articles(Q11).

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Song et al. (2016)	Y	Y	CA	N	N	Y	N	N	Y	Y	Y	**6**	Search was undertaken only in MEDLINE as written in the published paper; however, in the PROSPERO version, both MEDLINE and Embase and reference list were searched (Q3); No search of grey literature (Q4); no list of excluded studies (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8). Note: Multiple subgroups within a study (Sun et al.) were included within an analysis of individual chemical exposures (BPA, phthalates and PCBs) and these data have been extracted and included, assuming these are different sub populations; (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Wen et al. (2020)	N	N	Y	Y	N	Y	Y	Y	CA	Y	Y	**7**	No a priori protocol (Q1). Selection and extraction was not performed in duplicate (Q2). Database searching was ok, however, grey literature was not considered (Q3, Q4). No list of excluded studies was provided (Q5) combined analyses for BPA was appropriate but not for PCBs, and DEHP metabolites as individual participants were included on multiple occasions in the same analysis; therefore, only the relevant and appropriate data were extracted and used (Q9); conflict of interest in the individual review was discussed but not for all included articles(Q11).
Wu et al. (2020)	N	CA	Y	N	N	Y	Y	N	CA	Y	Y	**5**	No indication of a priori design or protocol (Q1). Study screening was performed by one reviewer with no further validation or checks undertaken by any of the other reviewers, data extraction was completed in duplicate (Q2). three databases were searched in duplicate with keywords only, and reference lists of included articles (Q3), grey literature was not considered (Q4). Details of excluded studies were not provided (Q5). Characteristics of studies and their quality using the Newcastle-Ottawa Scale (NOS) were reported (Q6, Q7), however, not considered in analysis nor conclusions (Q8). For overall analyses of obesity, analyses of males and females and children and adults, analyses counted the same studies and participants multiple times. Statistical analysis appears appropriate with dose-response analysis performed and also statistical assessment of publication bias (Q10). No conflicts were declared by review authors (Q11).
Zhong et al. (2020)	N	CA	Y	N	N	Y	N	N	Y	Y	Y	**5**	Authors did not report an 'a priori' design or a list of excluded studies (Q1, Q5). Data was extracted by two people, however, authors do not mention how many people completed study selection (Q2). Four databases were searched, however, not for grey literature (Q4) and there was no reported critical appraisal of the included papers (Q7). Statistical analyses appear appropriate. Authors declared no conflicts of interest in their review, but not for individual studies included (Q11).

*Legend: Y = Yes, N = No, CA = Can't Answer

BPA and birth outcomes

Two reviews explored the association between prenatal BPA exposure and birth outcomes in pregnant women and their infants (C.-Y. Hu et al., 2018; Zhong et al., 2020). The outcomes included were birth weight, birth length, head circumference and gestational age. Reviews had a mix of case-control and cohort studies. Both reviews had pooled findings for birth weight and one review had pooled findings for birth length, head circumference and gestational age (Zhong et al., 2020). Hu et al. (2018) reported subgroup findings for birthweight based on the trimesters of pregnancy.

Quality of the reviews informing birth outcomes was moderate, with scores on the AMSTAR tool ranging from 5 to 8/11. Neither of the two included reviews indicated there was an *a priori* protocol available to guide the conduct of the review. Neither review searched for grey literature. Zhong et al. (2020) did not provide a list of excluded studies nor appear to assess the quality of included studies in the review.

Overall, there is no evidence of risk of birth outcomes relating to birth weight, birth length, head circumference and gestational age in infants, when their mothers have been exposed to BPA.

Birth weight

Two reviews reported birth weight outcomes (C.-Y. Hu et al., 2018; Zhong et al., 2020). Prenatal BPA exposure was not associated with birth weight in the two reviews: Zhong et al. (2020) (β -0.049g, 95%CI: -0.199 to 0.101; 9 studies, 4,636 participants) and Hu et al. (2018) (ES 4.42g, 95%CI: -8.83 to 17.67; 8 studies, 2876 participants).

Hu et al. (2018) reported subgroup findings on trimesters of pregnancy and found no association with BPA and birth weight - first trimester and birth weight in infants (ES 44.41g, 95%CI: -113.45 to 202.67; 2 studies, 395 participants); second trimester and birth weight in infants (ES 37.89g, 95%CI: -209.68 to 285.46; 2 studies, 292 participants); third trimester and birth weight in infants (ES 34.39g, 95%CI: -16.69 to 85.49; 3 studies, 1,512 participants). Hu et al. (2018) also reported subgroup findings based on adjustments for potential confounders and found no association with BPA and birth weight - adjusted confounders group (ES 4.42g, 95% CI: −8.83 to 17.67; 8 studies, 2,876 participants) and unadjusted confounders (crude) group (ES 31.42, 95%CI −19.14 to 81.98; 3 studies, 1,543 participants).

Birth length

Zhong et al. (2020) reported no association between prenatal BPA exposure and birth length (β 0.058cm, 95%CI: -0.072 to 0.188; 9 studies, 4,636 participants).

Head circumference

Zhong et al. (2020) reported no association between prenatal BPA exposure and head circumference (β -0.004cm, 95%CI: -0.119 to 0.111; 9 studies, 4,636 participants).

Gestational age

Zhong et al. (2020) reported no association between prenatal BPA exposure and gestational age (β -0.032 weeks, 95%CI -0.163 to 0.10; 9 studies, 4,636 participants).

BPA and child reproductive health outcomes

Two reviews explored the association between BPA exposure and child reproductive health outcomes (Bigambo et al., 2020; Nelson et al., 2020), including anogenital distance (anoclitoral and anofourchette) in newborn babies (Nelson et al., 2020) and precocious puberty in girls (Bigambo et al., 2020). The reviews included cohort, case-control and cross-sectional studies.

The included reviews were assessed to be of moderate quality using the AMSTAR tool (6-7/11) with some methodological deficits identified. Neither appeared to have an *a priori* protocol. It was unclear whether duplicate study selection and data extraction occurred in the review by Bigambo et al. (2020), this was completed by Nelson et al. (2020); however, no list of excluded studies was provided in either review. Quality assessment was completed and reported in both reviews.

BPA exposure was associated with changes in anoclitoral distance in newborn female infants, but not for anofourchette distance. There was no evidence of risk of precocious puberty occurring in girls when exposed to BPA.

Anogenital distance (AGD)

One review reported on anogenital distance outcomes in newborn children (Nelson et al., 2020). BPA exposure (maternal urinary) was associated with a change in anoclitoral (AGD_{AC}) (β −1.374, 95% CI: −2.475 to −0.274; 3 studies, 1,760 participants, % change per log10 change in BPA) however, not anofourchette (AGD_{AF}) distance (β −1.069, 95% CI: −3.648 to 1.511; 3 studies, 1,760 participants).

Precocious puberty

The review by Bigambo et al. (2020) reported BPA exposure was not associated with the risk of precocious puberty in girls (ES 1.09, 95%CI: 0.88 to 1.35; 8 studies, 3,498 participants).

BPA and adult reproductive health outcomes

One review explored the association between BPA exposure and endometriosis (Wen et al., 2019). Cohort, case-control and cross-sectional studies were included in this review.

Wen et al. (2019) was assessed to be of moderate quality, scoring 7/11 on the AMSTAR tool. The review did not have an *a priori* protocol in its design, did not search grey literature, nor provided a list of excluded studies.

BPA exposure was not associated with an increased risk of endometriosis.

Endometriosis

Urinary BPA exposure was not associated with endometriosis (Wen et al., 2019) (OR 1.4, 95%CI: 0.94 to 2.08; 4 studies, 1,130 participants).

Sample of the population

Wen et al. (2019) found that BPA exposure was associated with increased risk of endometriosis in women in the population (OR 1.61, 95%CI: 1.03 to 2.52; 2 studies, participants unspecified) but not in women in the hospitals (OR 1.29, 95%CI: 0.72 to 2.31; 2 studies, participants unspecified). No association was found between BPA exposure and risk of endometriosis in Caucasian women (OR 1.23, 95%CI: 0.82 to 1.84; 3 studies, participants unspecified).

Studies

Wen et al. (2019) found that BPA exposure was associated with increased risk of endometriosis in case-control studies (OR 1.72, 95%CI: 1.40 to 2.12; 2 studies, participants unspecified), but not in cohort studies (OR 1.19, 95%CI 0.70 to 2.04; 2 studies, participants unspecified).

BPA and endocrine outcomes

Four reviews explored the association between BPA exposure (urine and serum measures) and endocrine outcomes (Y. Hu et al., 2018; Hwang et al., 2018; Rancière et al., 2015; Song et al., 2016). The outcomes included were type 2 diabetes, insulin resistance (Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)), fasting insulin, fasting glucose and polycystic ovary syndrome (PCOS). Most reviews included cross-sectional, case-control and cohort studies, the review by Hu et al. (2018), investigating PCOS, included only case-control studies. One review reported on children and adults (adults only for diabetes) (Rancière et al., 2015), one review only included women for PCOS (Y. Hu et al., 2018). whilst the two other reviews did not report the population of interest (Hwang et al., 2018; Song et al., 2016). Three reviews had pooled findings for type 2 diabetes. One review presented pooled findings for HOMA-IR and fasting glucose (Song et al., 2016).

Quality of the four reviews informing metabolic outcomes was moderate to high, with scores on the AMSTAR tool 6-9/11. Included reviews did not indicate there was an *a priori* protocol available to guide the conduct of the review, except that by Song et al. (2016). No included review searched for grey literature, though the search employed by Hu et al. (2018) was extensive and included multiple Chinese sources. Song et al. (2016) did not provide a list of excluded studies and there was no evidence that included studies were appraised for quality of conduct.

Women with polycystic ovary syndrome (PCOS) were found to have significantly higher BPA levels than women without PCOS. There is evidence of a low risk of type 2 diabetes and an associated risk of insulin resistance when exposed to BPA. BPA exposure is not associated with higher fasting glucose.

Polycystic ovary syndrome (PCOS)

Hu et al. (2018) investigated the association of BPA exposure on PCOS. BPA exposure was measured using blood serum levels and follicular fluid. Women with PCOS were found to have significantly higher BPA levels than women without PCOS (SMD 2.437, 95%CI: 1.265 to 3.609, 11 studies, 933 participants).

Subgroup findings

Hu et al. (2018) reported subgroup findings based on serum samples. Women with PCOS were found to have higher BPA levels when serum samples were used in the analysis (SMD 2.515, 95%CI: 1.241 to 3.789; 10 studies, participants unspecified). In subgroups analysed using serum samples, women with PCOS were found to have higher BPA levels in studies in Asia (SMD 3.209, 95%CI: 1.276 to 5.142; 6 studies, participants unspecified); in sample population older than 19 years of age (SMD 2.311, 95%CI: 1.009 to 3.612; 9 studies, participants unspecified); amongst those with BMI <25 (SMD 2.793, 95%CI: 1.027 to 4.559; 5 studies, participants unspecified); in sample population >50 (SMD 4.730, 95%CI: 4.267 to 5.193; 3 studies, participants unspecified) and <50 (SMD 1.389, 95%CI: 0.685 to 2.093; 7 studies, participants unspecified); PCOS control ratio >1 (SMD 3.190, 95%CI: 1.302 to 5.078; 6 studies, participants unspecified) and <1 (SMD 1.396, 95%CI: 0.455 to 2.338; 4 studies, participants unspecified); those assessed using the enzyme-linked immunosorbent assay (ELISA) method (SMD 1.957, 95%CI: 0.716 to 3.198; 8 studies, participants unspecified) and the high-performance liquid chromatography (HPLC) method (SMD 4.642, 95%CI: 3.900 to 5.383; 2 studies, participants unspecified); those with unknown HOMA-IR levels (SMD 3.209, 95%CI: 1.276 to 5.142; 6 studies, participants unspecified); those with <1.5 LH/FSH levels (SMD 0.726, 95%CI: 0.411 to 1.040; 2 studies, participants unspecified) and unknown LH/FSH levels (SMD 2.694, 95%CI: 1.062 to 4.326; 7 studies, participants unspecified); and whether studies were high (SMD 1.944, 95%CI: 0.480 to 3.407; 6 studies, participants unspecified) or medium quality (SMD 3.424, 95%CI: 1.718 to 5.129; 4 studies, participants unspecified). No difference was noted in BPA levels of women with no PCOS and Caucasian women with PCOS (SMD 1.511, 95%CI: -0.165 to 3.187; 4 studies, participants unspecified), those with BMI levels of >25 (SMD 1.560, 95%CI: -0.433 to 3.553; 4 studies, participants unspecified) and those with HOMA – IR >2.5 (SMD 1.726, 95%CI: -0.690 to 4.143; 3 studies, participants unspecified).

Type 2 diabetes

Three reviews explored the association between BPA exposure and type 2 diabetes (Hwang et al., 2018; Rancière et al., 2015; Song et al., 2016). BPA exposure was consistently found to be significantly associated with type 2 diabetes in the general population: Hwang et al. (2018) (OR 1.28; 95% CI: 1.14 to 1.44; 16 studies, 41,320 participants), Rancière et al. (2015) (urinary exposure only) (OR 1.47, 95%CI: 1.21 to 1.80, 3 studies, 9291 participants; lowest to highest exposure) and Song et al. (2016) (urinary exposure only) (RR 1.45, 95%CI 1.13 to 1.87; 4 studies, 10,541 participants). One review reported sensitivity analysis of urine BPA concentrations (Hwang et al., 2018) (i.e. two studies with serum measures and one study with high heterogeneity excluded) (OR 1.20, 95% CI: 1.09 to 1.31, 13 studies; 38,059 participants; random effects). Another review compared the highest (>1.43 to >4.20

ng/mL) versus lowest (≤0.47 to ≤1.36 ng/mL) exposure ranges and reported a dose response RR of 1.09 per 1ng/mL increase (95%CI 1.03 to 1.15) (Song et al., 2016).

One review reported subgroup findings based on sample type and found that BPA exposure was associated with type 2 diabetes either using urine samples (OR 1.01, 95%CI: 1.00 to 1.02; 14 studies, 38,298 participants) or serum samples (OR 1.59, 95%CI: 1.06 to 2.38; 2 studies, 3,022 participants) (Hwang et al., 2018).

Insulin resistance (HOMA-IR)

Song et al. (2016) explored the association between BPA exposure and insulin resistance measured using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Higher BPA exposure was found to be associated with increased insulin resistance (WMD 0.80, 95%CI: 0.36 to 1.25; 4 studies, participants unspecified).

Fasting insulin

Song et al. (2016) explored the association between BPA exposure and fasting insulin. BPA exposure was not associated with higher fasting insulin (WMD 0.15, 95%CI; -0.12 to 0.41; 4 studies, 9,854 participants).

Fasting glucose

Song et al. (2016) explored the association between BPA exposure and fasting glucose. BPA exposure was not associated with higher fasting blood glucose (WMD 0.97mg/dL, 95%CI: -0.19 to 2.14; 4 studies, 9,854 participants).

BPA and nutritional outcomes (obesity and anthropometrics)

Four reviews explored the association between BPA and nutritional outcomes relating to obesity and overweight (K. Y. Kim et al., 2019; Rancière et al., 2015; Ribeiro et al., 2020; Wentao Wu et al., 2020). The outcomes included were obesity, generalised obesity, abdominal obesity, overweight, high BMI and elevated waist circumference. Reviews had a mix of study designs which were cross-sectional, case-control and cohort studies. Three of these reviews had pooled findings across populations (children and adults) (Rancière et al., 2015; Ribeiro et al., 2020; Wentao Wu et al., 2020), which contributed 12 meta-analyses, with subgroup findings for age and sex. One review included children only, contributed to four meta-analyses (K. Y. Kim et al., 2019). Of note, in subgroup findings relating to children, BPA exposure is postnatal.

Quality of the reviews informing nutritional outcomes was generally moderate, with scores on the AMSTAR tool ranging from 5 to 7/11. None of the included reviews indicated there was an *a priori* protocol available to guide the conduct of the review and 4-5/6 had issues with the search ranging from non-inclusion of grey literature to keyword only search and no indication of MESH terms, and similarly, did not provide a list of excluded studies. Few reviews considered study quality in analyses or when stating conclusions. Statistical analyses were appropriate across reviews. Wu et al. (2020) conducted a combined analysis for the overall summary for obesity for male and female and also child and adult subgroups that were considered invalid as data from studies were used repeatedly in the analyses (multiple counting of same participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted and reported in this review. Where available, results of subgroup analyses were extracted and reported instead. Wu et al. (2020) also performed analyses with both random and fixed effects; random effects have been preferentially reported.

Overall, BPA exposure was associated with a risk of obesity in the general population and in subgroups of children and adults. There is a higher risk of having generalised obesity than abdominal obesity in the general population. BPA exposure had inconsistent findings for overweight in the general population. Adults were at risk for overweight but not children. There is a low risk of elevated waist circumference in the general population and in subgroup of adults but no associated in children.

Obesity

The reviews did not provide definition of obesity and cut-offs used. However, as the World Health Organization (WHO) provides a standard definition of obesity, it would be assumed that reviews have used the standard definition and cut-off. Obesity is defined by the WHO as having a body mass index (BMI) of equal to or greater than 30 (WHO, 2020).

Overall findings in children and adults combined

Three reviews reported obesity outcomes in children and adults combined (Rancière et al., 2015; Ribeiro et al., 2020; Wentao Wu et al., 2020). However, the data provided by Wu et al. (2020) for this outcome has not been reported due to multiple counting of participants and issues of independence of data. Urinary BPA exposure was found to be significantly associated with obesity by Rancière et al. (2015) (OR 1.67, 95% CI: 1.41 to 1.98, 3 studies, 10,727 participants) and Ribeiro et al. (2020) (OR 1.57, 95%CI: 1.35 to 1.83, 5 studies, 12,749 participants)

Children

One review reported obesity outcomes specific to children (K. Y. Kim et al., 2019). Urinary BPA exposure was postnatal and exposure was found to be significantly associated with obesity (high versus low urinary exposure) (OR 1.566, 95%CI: 1.097 to 2.234, 7 studies, 9,602 participants) (K. Y. Kim et al., 2019). Kim et al. (2019) conducted an analysis of relatively high exposed group and found an association between urinary BPA exposure and obesity (OR 1.58, 95%CI: 1.077 to 2.315; 6 studies; 9,522 participants). Kim et al. (2019) conducted an analysis of urinary BPA exposure across obese and normal weight groups of children; the obese group showed no significant difference in the exposed BPA concentration compared to the normal group (SMD 0.166, 95%CI: -0.121 to 0.453, 8 studies, 2092 participants). Similar findings were reported when pilot studies were excluded (SMD 0.044, 95%CI: -0.088 to 0.176; 6 studies, 1,962 participants).

Adults

Two reviews reported obesity outcomes specific to adults (Rancière et al., 2015; Ribeiro et al., 2020). Urinary BPA exposure was consistently found to be significantly associated with obesity by both reviews: Rancière et al. (2015) (OR 1.60, 95% CI: 1.32 to 1.93, 2 studies, 7,357 participants) and Ribeiro et al. (2020) (OR 1.50, 95%CI: 1.27 to 1.77, 4 studies, 9,379 participants).

Generalised obesity

Generalised obesity was reported by one review (Wentao Wu et al., 2020). However, no definition and measures were provided. In the body of the literature, generalised obesity refers to a more disperse distribution of fat as opposed to a more central one which is abdominal obesity.

One review reported generalised obesity outcomes in children and adults combined (Wentao Wu et al., 2020). BPA exposure was found to be associated with generalised obesity (OR 1.83, 95% CI: 1.58 to 2.12; 8 studies, 25,779 participants; random effects). Dose-response analysis revealed that a 1-ng/mL increase in BPA increased generalised obesity by 16% (OR 1.16, 95% CI: 1.14 to 1.19, p-value (linear trend) <.001). There was evidence of non-linear association was found between BPA and generalised obesity risk.

Abdominal obesity

Abdominal obesity relates to the central distribution of fat. Abdominal obesity was reported by one review (Wentao Wu et al., 2020). Again, no definition and measures were provided.

One review reported risk of developing abdominal obesity across all population with exposure to urinary BPA OR 1.43 (95% CI: 1.27-1.62, 7 studies, 21,629 participants) (Wentao Wu et al., 2020). Dose-response analysis revealed that a 1-ng/mL increase in BPA increased abdominal obesity by 12% (OR 1.12, 95% CI: 1.09-1.14, p-value (linear trend) <.001). No evidence of non-linear association was found between BPA and abdominal obesity risk.

Overweight

The reviews did not provide any definition of overweight. However, as the WHO provides a standard definition of overweight, it would be assumed that reviews have used the standard definition and cut-off. Overweight is defined by the (WHO) as having a BMI greater than or equal to 25 (WHO, 2020).

Overall findings in children and adults combined

Three reviews reported overweight outcomes in children and adults combined (Rancière et al., 2015; Ribeiro et al., 2020; Wentao Wu et al., 2020). Two reviews found that urinary BPA exposure was significantly associated with overweight (Ribeiro et al., 2020; Wentao Wu et al., 2020). Ribeiro 2020 reported an OR 1.32, 95%CI 1.01 to 1.72, 5 studies, 11,339 participants. Wu et al. (2020) reported an OR 1.24, 95% CI: 1.02 to 1.51, 6 studies, 18,404 participants. One review found no association between urinary BPA exposure and overweight (OR 1.21, 95%CI; 0.98 to 1.50; 5 studies, participants unspecified) (Rancière et al., 2015). Dose-response analysis revealed that a 1-ng/mL increase in BPA increased generalised overweight by 5.8% (OR 1.058, 95% CI: 1.034 to 1.084, p-value (linear trend) <.001). No evidence of non-linear association was found between BPA and generalised overweight risk.

Children

Two reviews reported no association between urinary BPA exposure and overweight in children (Rancière et al., 2015; Ribeiro et al., 2020). Rancière et al. (2015) reported an OR 1.24, 95% CI: 0.88 to 1.75; 3 studies, participants unspecified. Ribeiro et al. (2020) reported an OR 1.67, 95%CI: 0.82 to 3.38; 3 studies, 5,202 participants.

Adults

Two reviews reported overweight outcomes in adults (Rancière et al., 2015; Ribeiro et al., 2020). Both reviews found an association between urinary BPA and risk of overweight (OR 1.25, 95%CI 1.01 to 1.56; 2 studies, 6,137 participants) (Rancière et al., 2015; Ribeiro et al., 2020).

Elevated waist circumference

The reviews did not provide definitions and cut-offs used to report elevated waist circumference. In the body of the literature, elevated waist circumference is considered as follows: women (increased risk ≥80cm, greatly increased ≥88cm) and men (increased risk ≥94cm, greatly increased ≥102cm).

Two reviews reported elevated waist circumference outcomes in children and adults combined (Rancière et al., 2015; Ribeiro et al., 2020). BPA exposure was consistently found to be significantly associated with elevated waist circumference – Rancière et al. (2015) (OR 1.48, 95%CI: 1.25 to 1.76; 4 studies, 11,757 participants), Ribeiro et al. (2020) (OR 1.49, 95%CI: 1.29 to 1.72; 6 studies, 10,005 participants).

Children

One review reported elevated waist circumference outcomes in children (Ribeiro et al., 2020). Urinary BPA exposure was not associated with elevated waist circumference (OR 1.62, 95%CI 0.97 to 2.72, 2 studies, 4,696 participants) (Ribeiro et al., 2020).

Adults

Two reviews reported elevated waist circumference in adults (Rancière et al., 2015; Ribeiro et al., 2020). Urinary BPA exposure was consistently found to be associated with elevated waist circumference – Rancière et al. (2015) (OR 1.52, 95%CI 1.21 to 1.90, 3 studies, 8,387 participants) and Ribeiro et al. (2020) (OR 1.50, 95%CI 1.27 to 1.78; 4 studies, 6,777 participants).

BPA and circulatory outcomes

Two reviews and one pooled analysis explored the association between BPA exposure and circulatory outcomes (Dunder et al., 2019; Fu et al., 2020; Rancière et al., 2015). The outcomes included were cardiovascular disease, prevalent hypertension and serum lipids.

Quality of the two reviews informing circulatory outcomes was low to moderate, with scores of 6/11 (Fu et al., 2020) and 7/11 (Rancière et al., 2015) with the AMSTAR tool. As Dunder et al. (2019) was a pooled analysis, it scored poorly with the AMSTAR tool (4/11). Neither review indicated there was an *a priori* protocol available to guide the conduct of the review. Neither searched grey literature and only Fu et al. (2020) employed keywords in the search.

There is evidence of risk of cardiovascular disease and hypertension in the general population when exposed to BPA.

Cardiovascular disease

Fu et al. (2020) explored the association between urinary BPA exposure and cardiovascular disease in the general population (no age limit). BPA exposure was associated with incidence of cardiovascular disease (OR 1.19, 95%CI 1.03 to 1.37; 10 studies, 23,953 participants).

Hypertension

Rancière et al. (2015) reported the association between urinary BPA exposure and prevalent hypertension in adults (systolic blood pressure >140mmHg and/or diastolic blood pressure >90mmHg). BPA exposure was found to be associated with hypertension (OR 1.41 95%CI 1.12 to 1.79, 2 studies, 4,488 participants).

Serum lipids

One pooled analysis of surveillance data explored the association between urinary BPA exposure and serum lipid levels in children and adults (Dunder et al., 2019). Serum lipids encompass concentrations in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG) and apolipoprotein B (ApoB).

Overall findings across populations

BPA exposure was not associated with levels of LDL-C (β -0.02, 95%CI: -0.05 to 0.01, HDL-C (β -0.01, 95%CI: -0.02 to 0.00), TC (β -0.02, 95%CI: -0.04 to 0.00), TG (β -0.01, 95%CI: -0.03 to 0.01), ApoB (β -0.89, 95%CI: -1.843 to 0.06) in children and adults (15,593 participants).

Children

BPA exposure was not associated with levels of LDL-C (*standard adjusted* (β -0.005, 95%CI: -0.05 to 0.05); *fully adjusted* (β 0.003, 95%CI: -0.05 to 0.05)), HDL-C (*standard adjusted* (β -0.01, 95%CI: -0.02 to 0.002); *fully adjusted* (β -0.01, 95%CI: -0.02 to 0.002)), TC (*standard adjusted* (β 0.008, 95%CI: -0.03 to 0.05); *fully adjusted* (β 0.01, 95%CI: -0.03 to 0.05)), TG (*standard adjusted* (β 0.01, 95%CI: -0.02 to 0.05); *fully adjusted* (β 0.01, 95%CI: -0.02 to 0.05)) and ApoB (*standard adjusted* (β -0.48, 95%CI: -2.1 to1.2); *fully adjusted* (β -0.54, 95%CI: -2.3 to 1.2)) in children (4,604 participants). Note, standard adjusted referred to adjusted for urinary creatinine, age, sex and race. Fully adjusted referred to adjusted for urinary creatinine, age, sex and race, education/caregiver education, smoking (serum cotinine), income to poverty ratio and caloric intake.

Boys

BPA exposure was not associated with levels of LDL-C (β −0.03, 95%CI: −0.09 to 0.04), HDL-C (β -0.01, 95%CI: −0.03 to 0.003), TC (β 0.02, 95%CI: −0.04 to 0.07), TG (β 0.04, 95%CI −0.003 to 0.09) and ApoB (β -0.72, 95%CI: −2.8 to 1.4) (participants unspecified).

Girls

BPA exposure was not associated with levels of LDL-C (β 0.04, 95%CI: −0.04 to 0.11), HDL-C (β -0.01, 95%CI: −0.03 to 0.007), TC (β -0.02, 95%CI: −0.08 to 0.04), TG (β -0.02, 95%CI −0.07 to 0.03) and ApoB (β -0.18, 95%CI: −2.9 to 2.6) (participants unspecified).

Adults

BPA exposure was not associated with levels of LDL-C (*standard adjusted* (β -0.005, 95%CI: -0.05 to 0.05); *fully adjusted* (β -0.02, 95%CI: -0.05 to 0.01)); HDL-C (*standard adjusted* (β -0.012, 95%CI: -0.02

to 0.001); (*fully adjusted* (β -0.006, 95%CI: -0.01 to 0.003)), TC (*standard adjusted* (β -0.02, 95%CI: -0.04 to 0. 004); *fully adjusted* (β -0.02, 95%CI: -0.01 to 0.003)), TG (*standard adjusted* (β -0.02, 95%CI: -0.04 to 0.004); *fully adjusted* (β -0.021, 95%CI: -0.01 to 0.003)) and ApoB (*standard adjusted* (β -0.89, 95%CI: -1.8 to 0.06) in adults (10,989 participants). BPA exposure was associated with lower ApoB levels when using fully adjusted model (β -0.91, 95%CI: -1.82 to -0.02). Note, standard adjusted referred to adjusted for urinary creatinine, age, sex and race. Fully adjusted referred to adjusted for urinary creatinine, age, sex and race, education/caregiver education, smoking (serum cotinine), income to poverty ratio, physical activity, alcohol intake, caloric intake, statins and pregnancy.

Males

BPA exposure was not associated with levels of LDL-C (β −0.02, 95%CI: −0.07 to 0.02), HDL-C (β -0.008, 95%CI: −0.02 to 0.004), TC (β -0.02, 95%CI: −0.05 to 0.01), TG (β -0.01, 95%CI −0.04 to 0.02) and ApoB (β -0.66, 95%CI: −1.9 to 0.6) (participants unspecified).

Females

BPA exposure was not associated with levels of LDL-C (β −0.01, 95%CI: −0.05 to 0.03), HDL-C (β -0.01, 95%CI: −0.03 to 0.0002), TC (β -0.02, 95%CI: −0.05 to 0.02), TG (β -0.01, 95%CI −0.04 to 0.01) and ApoB (β -0.98, 95%CI: −2.3 to 0.4) (participants unspecified).

PLASTICISERS (PHTHALATES)

There were 16 systematic reviews, including 419 meta-analyses, that pooled data for outcomes related to phthalate and phthalate metabolite exposure (Cai et al., 2015, 2019; Dorman et al., 2018; Fu et al., 2020; Golestanzadeh et al., 2020, 2019; M. J. Kim et al., 2019; Lee et al., 2018; Li et al., 2017; Radke et al., 2020; Ribeiro et al., 2019; Shoshtari-Yeganeh et al., 2019; Song et al., 2016; Wen et al., 2015; Weixiang Wu et al., 2020; H. Zhang et al., 2020). No eligible reviews assessing human health effects for exposure to any other plasticisers were identified. Outcomes for which statistically pooled data were available were clustered into overarching health 'conditions' based on the ICD-11 (World Health Organization, 2020):

- Birth: birth weight, spontaneous pregnancy loss
- Child reproductive: anogenital distance and onset of puberty (abnormal breast development (thelarche), abnormal age of pubic hair development (pubarche) (girls), abnormal age of menarche, abnormal age of pubic hair development (pubarche) (boys), testicle volume, odds of precocious puberty)
- Adult reproductive (adults):
    - Women's reproductive health: endometriosis
    - Men's reproductive health: sperm concentration, sperm motility, sperm morphology, sperm volume, sperm motion (straight-line velocity), sperm motion (curvilinear velocity), sperm motion (linearity), comet assay (comet extent), comet assay (% DNA in tail), comet assay (tail distributed moment), sperm quality.
- Endocrine: Homeostatic model assessment (insulin resistance HOMA-IR) (general population), type 2 diabetes (adults) fasting glucose (adults), thyroid function (measured using free, total free thyroxine and thyrotropin) (general population)
- Child neurodevelopment: cognitive and language, psychomotor and cognitive or IQ
- Nutritional: BMI (children), BMI (adults), BMI Z-scores, waist circumferences (children and adults), obesity (as categorised using BMI) (children and adults)
- Circulatory: Incidence of cardiovascular disease (general population), systolic blood pressure (children), diastolic blood pressure (children), high-density lipoprotein (children), triglycerides (children)
- Respiratory: asthma (children and adults)

Abbreviations

ΣDEHP	Sum of all measured DEHP metabolites	**MCOP**	Monocarboxy-isooctyl phthalate
BBP	Butyl benzyl phthalate	**MECPP**	Mono (2-ethyl-5-carboxypentyl) phthalate
DBP	Dibutyl phthalate	**MEHP**	Mono-ethylhexyl phthalate
DEHP	Diethylhexyl phthalate	**MEHHP**	Mono (2-ethyl-5-hydroxyhexyl) phthalate
DiBP	Diisobutyl phthalate	**MEOHP**	Mono (2-ethyl-5-oxohexyl) phthalate
MCCP	Mono-(3-carboxypropyl) Phthalate	**MEP**	Monoethyl phthalate
MCNP	Mono-(carboxynonyl) phthalate	**MiBP**	Mono-iso-butyl phthalate
MBzP	Mono-benzyl phthalate	**MMP**	Mono-methyl phthalate
MnBP	Monobutyl phthalate	**MnBP**	Mono-n-butyl phthalate

Exposure description and measures

Phthalates (ortho-phthalate diesters) are synthetic chemical esters of ortho-phthalic acid and are a group of industrial chemicals, commonly used as plasticisers to impart flexibility, elasticity and durability in plastic products. Phthalates are readily metabolised by the human body and excreted in the urine (Cai et al., 2015) and exposure was commonly measured as mono-ester metabolites in nmol/mL, ng/mL or µg/g of either participant urine, or maternal urine for in utero exposure in birth

cohort studies. In some reviews, phthalate measurements were unspecified. Metabolism of phthalates is important, as in addition to effects of the parent compound used as plasticisers, the breakdown products following metabolism of the plasticiser may have separate biological effects. For additional details on phthalates, see Appendix 1.

Overall findings

In general, phthalate exposure had an impact on health outcomes, however, effects were inconsistent and varied amongst individual phthalates and phthalate metabolites. MEP was the only metabolite associated with decreased birth weight. MnBP, ΣDEHP, MEHP, MEHHP and MEOHP were associated with increased risk of spontaneous pregnancy loss but not the other metabolites investigated.

ΣDEHP was negatively associated with anogenital distance measures in boys. MEHHP and MEOHP were associated with an increased risk of abnormal timing of thelarche while the other phthalate metabolites investigated were not associated with abnormal timing of thelarche, abnormal timing of pubarche and abnormal age of menarche in girls. MnBP, MEHHP and MEOHP were associated with a decreased risk of abnormal timing of pubarche in boys while the other phthalate metabolites investigated were not associated with any risk of abnormal timing of pubarche and testicular volume levels. DEHP was associated with increased risk of precocious puberty and especially in a subgroup of studies conducted in China. In adult women, MEHHP increased the risk of endometriosis. There were inconsistent findings between various phthalate and phthalate metabolites and sperm/semen concentration, sperm motility, sperm morphology, semen volume, sperm motion (including curvilinear, straight-line velocity and linearity) and measures of sperm DNA damage.

Only MiBP was found to be associated with an increased risk of type 2 diabetes whilst MiBP, MBzP, ΣDEHP, MEHP, MEOHP, MECPP and MCPP were associated with insulin resistance levels. MEHHP was negatively associated with free thyroxine (fT4) in the general population but positively associated in a subgroup of children. MEOHP was also positively associated with fT4 in a subgroup of children. The other phthalate metabolites investigated were not associated with fT4, total free thyroxine (TT4) and thyrotropin (TSH).

Considering child neurodevelopment, prenatal ΣDEHP and current ΣDEHP exposure were negatively associated with psychomotor and cognitive or IQ measures in children, but not the other phthalates investigated.

MiBP and MEHHP were positively associated with BMI in children but not the other phthalate metabolites and not in adults. None of the phthalates and phthalate metabolites investigated were associated with change in BMI z scores in children. MEHP was positively associated with an increase in waist circumference in children and adults whilst MEHHP was only found to be positively associated in children. Inconsistent results were found with MBzP and the other phthalate metabolites investigated were not associated. MECPP was associated with an increased risk of obesity in adults whilst MEP and MEHP were not associated at all.

None of the phthalate metabolites were associated with an increased risk of cardiovascular disease in the general population. MEHHP and MEOHP were positively associated with systolic blood pressure and MEOHP was also positively associated with high-density lipoproteins in children. The other phthalate metabolites investigated were not associated with systolic and diastolic blood pressure, high-density lipoproteins and triglycerides.

MBzP was associated with an increased risk of asthma in general population, and in subgroups of children and adults. MBzP was also associated with an increased risk of asthma in children with prenatal exposure and in the European and North American population. MEHHP and MCOP were associated with an increased risk of asthma in children. MCNP was associated with an increased risk in asthma in Europe.

Table 3.3: Summary of health outcomes related to plasticisers (phthalate) exposure

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
			Birth outcomes			
BIRTH WEIGHT (Phthalates) – 1 review						
Infants; pre-natal exposure (measured in urine)	Golestanzadeh et al. 2019 (5/11)	MMP	β -0.05 (95% CI = -20.99 to 20.9)	2	4476	
		MEP	β -10.1 (95% CI = -18.57 to -1.6) *	3	4775	
		MnBP	β 0.05 (95% CI = -0.51 to 0.62)	4	5296	
		MiBP	β -0.11 (95% CI = -0.87 to 0.65)	2	820	
		MBzP	β -2.38 (95% CI = -9.2 to 3.53)	3	4294	
		ΣDEHP	β 3.85 (95% CI = -17.8 to 25.6)		4604	
		MEHP	β -0.79 (95% CI = -3.84 to 2.62)	4	4461	
		MEHHP	β -0.16 (95% CI = -1.27 to 0.9)	5	5424	
		MEOHP	β -0.39 (95% CI = -12.9 to 12.13)	5	5424	
		MECPP	β 16.15 (95% CI = -18.3 to 50.58)	3	1822	
MISCARRIAGE (SPONTANEOUS PREGNANCY LOSS) (Phthalates) – 1 review						
Adults; Reproductive women (measured in urine)	Zhang et al. 2020 (7/11)	MMP	OR 1.54 (95% CI = 0.91 to 2.6)	5	unsp.	
		MEP	OR 1.3 (95% CI = 0.84 to 2.03)	7	unsp.	
		MnBP	OR 1.34 (95% CI = 1.04 to 1.72) *	7	unsp.	
		MiBP	OR 1.31 (95% CI = 0.69 to 2.49)	4	unsp.	
		MBzP	OR 1.1 (95% CI = 0.74 to 1.64)	4	unsp.	
		ΣDEHP	OR 1.79 (95% CI = 1.27 to 2.53) *	3	unsp.	
		MEHP	OR 1.57 (95% CI = 1.29 to 1.9) *	7	unsp.	
		MEHHP	OR 1.59 (95% CI = 1.23 to 2.07) *	6	unsp.	
		MEOHP	OR 1.47 (95% CI = 1.15 to 1.89) *	6	unsp.	
		MECPP	OR 1.08 (95% CI = 0.8 to 1.46)	3	unsp.	
			Child reproductive health outcomes			
ANOGENITAL DISTANCE (Phthalates) – 1 review						
Infants (boys only); pre-natal exposure	Dorman et al. 2018 (8/11)	ΣDEHP	β -4.07% (95% CI = -6.49 to -1.66%) *	5	unsp.	% change per log10 change in DEHP
ONSET OF PUBERTY - Abnormal timing of breast development (thelarche) in girls (Phthalates) – 1 review						
Adolescents (7 to 19 years of age); Postnatal exposure	Golestanzadeh et al. 2020 (7/11)	MMP	OR 0.84 (95% CI = 0.67 to 1.01)	3	609	
		MEP	OR 0.82 (95% CI = 0.6 to 1.05)	3	609	
		MEHP	OR 1.16 (95% CI = 0.73 to 1.59)	3	609	
		MEHHP	OR 1.48 (95% CI = 1.11 to 1.85) *	2	387	
		MEOHP	OR 1.52 (95% CI = 1.15 to 1.88) *	2	387	
ONSET OF PUBERTY - Abnormal timing of pubic hair development (pubarche) in girls (Phthalates) – 1 review						
Adolescents (7 to 19 years of age); Postnatal exposure	Golestanzadeh et al. 2020 (7/11)	MMP	OR 0.95 (95% CI = 0.77 to 1.14)	3	609	
		MEP	OR 0.99 (95% CI = 0.81 to 1.17)	3	609	
		MnBP	OR 0.88 (95% CI = 0.59 to 1.16)	2	423	
		MEHP	OR 0.91 (95% CI = 0.74 to 1.08)	3	609	
		MEHHP	OR 0.96 (95% CI = 0.59 to 1.13)	2	387	
		MEOHP	OR 0.95 (95% CI = 0.66 to 1.23)	2	387	
ONSET OF PUBERTY - Abnormal age of menarche in girls (Phthalates) – 1 review						

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
Adolescents (7 to 19 years of age); Postnatal exposure	Golestanzadeh et al. 2020 (7/11)	MMP	OR 0.89 (95% CI = 0.68 to 1.1)	3	609	
		MEP	OR 0.89 (95% CI = 0.62 to 1.16)	3	609	
		MnBP	OR 1.01 (95% CI = 0.06 to 1.96)	2	423	
		MEHP	OR 0.89 (95% CI = 0.66 to 1.11)	3	609	
		MEHHP	OR 1.07 (95% CI = 0.14 to 2.01)	2	387	
		MEOHP	OR 1.08 (95% CI = 0.19 to 1.98)	2	387	
ONSET OF PUBERTY - Abnormal age of pubic hair development (pubarche) in boys (Phthalates) – 1 review						
Adolescents (7 to 19 years of age); Postnatal exposure	Golestanzadeh et al. 2020 (7/11)	MMP	OR 0.63 (95% CI = 0.23 to 1.03)	4	727	
		MEP	OR 1.01 (95% CI = 0.85 to 1.19)	3	609	
		MnBP	OR 0.66 (95% CI = 0.39 to 0.93) *	2	423	
		MEHP	OR 0.89 (95% CI = 0.62 to 1.16)	3	609	
		MEHHP	OR 0.61 (95% CI = 0.32 to 0.91) *	2	387	
		MEOHP	OR 0.61 (95% CI = 0.26 to 0.97) *	2	387	
ONSET OF PUBERTY - Testicular volume in boys (Phthalates) – 1 review						
Adolescents (7 to 19 years of age); Postnatal exposure	Golestanzadeh et al. 2020 (7/11)	MMP	OR 1.01 (95% CI = 0.59 to 1.44)	3	505	
		MEP	OR 0.99 (95% CI = 0.77 to 1.21)	2	387	
		MEHP	OR 1.13 (95% CI = 0.88 to 1.37)	2	387	
		MEHHP	OR 0.79 (95% CI = 0.44 to 1.14)	2	387	
PRECOCIOUS PUBERTY (Phthalates) – 1 review						
Girls (0.5 to 11.3 years of age); Postnatal exposure (measured in serum or urine)	Wen et al. 2015 (7/11)	MEP (urinary)	SMD 0.73 (95% CI = -0.4 to 1.86)	3	360	
		DnBP (serum)	OR 3.26 (95% CI = 0.69 to 15.42)	5	1149	
		DnBP (serum)	SMD 4.31 (95% CI = 2.67 to 5.95) *	5	1323	
		MnBP (serum)	SMD 0.01 (95% CI = -0.3 to 0.27)	3	774	
		MnBP (urinary)	SMD -0.11 (95% CI = -0.48 to 0.26)	3	360	
		MBzP (urinary)	SMD 0 (95% CI = -0.43 to 0.43)	4	419	
		DEHP (serum)	OR 4.09 (95% CI = 2.3 to 7.3) *	7	1390	
		DEHP (serum)	SMD 1.73 (95% CI = 0.54 to 2.91) *	7	1564	
		MEHP (serum)	SMD 0.18 (95% CI = -0.99 to 1.36)	4	895	
		Chinese studies only				
		MMP (urinary)	SMD 0.27 (95% CI = -0.21 to 0.76)	3	211	
		MEP (urinary)	SMD 0.16 (95% CI = -0.19 to 0.5)	2	152	
		DnBP (serum)	OR 2.74 (95% CI = 0.51 to 14.79)	4	1083	
		DnBP (serum)	SMD 6.33 (95% CI = 4.09 to 8.57) *	4	1083	
		MnBP (urinary)	SMD -0.21 (95% CI = -0.87 to 0.46)	2	152	
		MBzP (urinary)	SMD -0.04 (95% CI = -0.68 to 0.59)	3	211	
		DEHP (serum)	OR 3.58 (95% CI = 1.97 to 6.49) *	6	1324	
		DEHP (serum)	SMD 2.13 (95% CI = 0.86 to 3.4) *	6	1324	
		MEHP (serum)	SMD 1.38 (95% CI = -1.35 to 4.11)	2	599	
		MEHP (urinary)	SMD -0.44 (95% CI = -1.18 to 0.29)	3	unsp.	
Adult reproductive health outcomes (women)						
ENDOMETRIOSIS (Phthalates) – 1 review						
Women (18 to 54 years of age)	Cai et al. 2019 (7/11)	MEP	OR 1.073 (95% CI = 0.9 to 1.28)	6	unsp.	
		MBzP	OR 0.976 (95% CI = 0.81 to 1.176)	7	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		MEHP	OR 1.089 (95% CI = 0.858 to 1.383)	7	unsp.	
		MEHHP	OR 1.25 (95% CI = 1.003 to 1.55) *	6	unsp.	
		MEOHP	OR 1.282 (95% CI = 0.874 to 1.88)	6	unsp.	
		Adult reproductive health outcomes (men)				
LOW SPERM CONCENTRATION (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up; Measured in urine	Cai et al. 2015 (6/11)	*MMP*				
		medium levels	OR 0.89 (95% CI = 0.48 to 1.67)	6	unsp.	1.5-9.0 µg/L
		high levels	OR 0.96 (95% CI = 0.28 to 3.29)	6	unsp.	9.0-745.0 µg/L
		MEP				
		medium levels	OR 0.84 (95% CI = 0.43 to 1.63)	6	unsp.	3.3-49.8 µg/L
		high levels	OR 1.42 (95% CI = 0.84 to 2.42)	6	unsp.	77.2-11371 µg/L
		MnBP				
		medium levels	OR 2.6 (95% CI = 1.32 to 5.15) *	3	unsp.	7.4-25.3 µg/L
		high levels	OR 2.39 (95% CI = 1.26 to 4.53) *	5	unsp.	26.0-14459.0 µg/L
		continuous	β 0.04 (95% CI = -0.45 to 0.54)	3	unsp.	
		MBzP				
		medium levels	OR 1.24 (95% CI = 0.67 to 2.29)	6	unsp.	0-14.0 µg/L
		high levels	OR 2.23 (95% CI = 1.16 to 4.3) *	3	unsp.	14-540.2 µg/L
		ΣDEHP				
		medium levels	OR 1.2 (95% CI = 0.74 to 1.94)	6	unsp.	23.2–79.5 µg/L
		high levels	OR 1.32 (95% CI = 0.62 to 2.8)	6	unsp.	79.5–8,744.8 µg/L
		MEHP				
		medium levels	OR 8 (95% CI = 1 to 60.3)	6	unsp.	0.4–1.9 µg/L
		high levels	OR 0.99 (95% CI = 0.64 to 1.54)	6	unsp.	3.8–875.8 µg/L
		continuous	β -0.01 (95% CI = -0.17 to 0.17)	3	unsp.	
		MEOHP				
		medium levels	OR 1.66 (95% CI = 0.5 to 5.5)	6	unsp.	1.9–30.6 µg/L
		high levels	OR 1.3 (95% CI = 0.45 to 3.75)	6	unsp.	32.1–3063.0 µg/L
		MEHP + MEOHP (combined)				
		medium levels	OR 1.16 (95% CI = 0.67 to 2.03)	6	unsp.	2.2–84.2 µg/L
		high levels	OR 0.94 (95% CI = 0.48 to 1.81)	6	unsp.	93.9–3938.8 µg/L
LOW SPERM MOTILITY (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up; Measured in urine or seminal fluid	Cai et al. 2015 (6/11)	*MMP (urinary level)*				
		medium levels	OR 1.13 (95% CI = 0.53 to 2.39)	6	unsp.	1.5-9.0 µg/L
		high levels	OR 0.71 (95% CI = 0.39 to 1.32)	6	unsp.	9.0-745.0 µg/L
		MEP (urinary level)				
		medium levels	OR 0.77 (95% CI = 0.3 to 1.96)	6	unsp.	3.3-49.8 µg/L
		high levels	OR 0.89 (95% CI = 0.59 to 1.32)	6	unsp.	77.2-11371 µg/L
		MnBP (urinary level)				
		medium levels	OR 1.16 (95% CI = 0.58 to 2.34)	3	unsp.	7.4-25.3 µg/L
		high levels	OR 1.35 (95% CI = 0.86 to 2.11)	5	unsp.	26.0-14459.0 µg/L
		MBzP (urinary level)				
		medium levels	OR 1.2 (95% CI = 0.78 to 1.84)	6	unsp.	0-14.0 µg/L

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		high levels	OR 1.47 (95% CI = 0.91 to 2.36)	3	unsp.	14-540.2 µg/L
		DnBP (seminal fluid level)				
		continuous	β -0.19 (95% CI = -0.28 to -0.1) *	2	unsp.	
		ΣDEHP (urinary level)				
		medium levels	OR 1.01 (95% CI = 0.57 to 1.78)	6	unsp.	23.2–79.5 µg/L
		high levels	OR 0.88 (95% CI = 0.57 to 1.37)	6	unsp.	79.5–8,744.8 µg/L
		DEHP (seminal fluid level)				
		continuous	β -0.21 (95% CI = -0.3 to -0.12) *	2	unsp.	
		MEHP (urinary level)				
		medium levels	OR 0.7 (95% CI = 0.2 to 2)	6	unsp.	0.4–1.9 µg/L
		high levels	OR 1.17 (95% CI = 0.78 to 1.76)	6	unsp.	3.8–875.8 µg/L
		continuous	β 94.62 (95% CI = -176.54 to 365.77)	3	unsp.	
		MEOHP (urinary level)				
		medium levels	OR 0.84 (95% CI = 0.47 to 1.5)	6	unsp.	1.9–30.6 µg/L
		high levels	OR 0.66 (95% CI = 0.33 to 1.31)	6	unsp.	32.1–3063.0 µg/L
		MEHP + MEOHP (combined)				
		medium levels	OR 0.94 (95% CI = 0.62 to 1.43)	6	unsp.	2.2–84.2 µg/L
		high levels	OR 0.99 (95% CI = 0.62 to 1.60)	6	unsp.	93.9–3938.8 µg/L
LOW SPERM MORPHOLOGY (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	*MMP*				
		medium levels	OR 0.78 (95% CI = 0.43 to 1.4)	6	unsp.	1.5-9.0 µg/L
		high levels	OR 0.84 (95% CI = 0.44 to 1.6)	6	unsp.	9.0-745.0 µg/L
		MEP				
		medium levels	OR 0.88 (95% CI = 0.44 to 1.75)	6	unsp.	3.3-49.8 µg/L
		high levels	OR 1.21 (95% CI = 0.42 to 3.42)	6	unsp.	77.2-11371 µg/L
		MnBP				
		medium levels	OR 1 (95% CI = 0.59 to 1.71)	2	unsp.	7.4-25.3 µg/L
		high levels	OR 1.43 (95% CI = 0.83 to 2.47)	4	unsp.	26.0-14459.0 µg/L
		MBzP				
		medium levels	OR 0.7 (95% CI = 0.38 to 1.28)	6	unsp.	0-14.0 µg/L
		high levels	OR 1.27 (95% CI = 0.77 to 2.08)	3	unsp.	14-540.2 µg/L
		ΣDEHP				
		medium levels	OR 1.28 (95% CI = 0.85 to 1.93)	6	unsp.	23.2–79.5 µg/L
		high levels	OR 1.1 (95% CI = 0.54 to 2.25)	6	unsp.	79.5–8,744.8 µg/L
		MEHP				
		high levels	OR 1 (95% CI = 0.66 to 1.51)	6	unsp.	3.8–875.8 µg/L
		continuous	β 0.19 (95% CI = -0.4 to 0.79)	3	unsp.	
		MEOHP				
		medium levels	OR 1.4 (95% CI = 0.5 to 3.7)	6	unsp.	1.9–30.6 µg/L
		high levels	OR 0.59 (95% CI = 0.26 to 1.33)	6	unsp.	32.1–3063.0 µg/L
		MEHP + MEOHP (combined)				
		medium levels	OR 1.01 (95% CI = 0.56 to 1.81)	6	unsp.	2.2–84.2 µg/L
		high levels	OR 0.7 (95% CI = 0.41 to 1.2)	6	unsp.	93.9–3938.8 µg/L

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
LOW SEMEN VOLUME (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	*MnBP*				
		high levels	OR 0.8 (95% CI = 0.26 to 2.4)	2	unsp.	26.0-14459.0 µg/L
SPERM MOTION - Straight-line velocity (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	*MMP*				
		medium levels	β -0.14µm/s (95% CI = -1.76 to 1.49µm/s)	3	unsp.	1.5-8.3 µg/L
		high levels	β 0.79µm/s (95% CI = -1.29 to 2.88µm/s)	3	unsp.	8.3–278.1 µg/L
		MEP				
		medium levels	β 0.12µm/s (95% CI = -0.88 to 1.12µm/s)	3	unsp.	59.6–979.5 µg/L
		high levels	β 2.36µm/s (95% CI = 0.28 to 4.45µm/s) *	3	unsp.	979.5-11371 µg/L
		MnBP				
		medium levels	β -1.48µm/s (95% CI = -3.87 to 0.92µm/s)	3	unsp.	10.3–24.6 µg/L
		high levels	β -2.51µm/s (95% CI = -4.44 to -0.59µm/s) *	3	unsp.	24.6–14459.0 µg/L
		MBzP				
		medium levels	β -0.42µm/s (95% CI = -1.39 to 0.55µm/s)	3	unsp.	4.2–64.2 µg/L
		high levels	β -1.93µm/s (95% CI = -3.98 to 0.12µm/s)	3	unsp.	64.2–540.2 µg/L
		MEHP				
		medium levels	β -1.06µm/s (95% CI = -1.99 to -0.12µm/s) *	3	unsp.	3.1–208.1 µg/L
		high levels	β -1.76µm/s (95% CI = -3.83 to 0.31µm/s)	3	unsp.	208.1–875.8 µg/L
SPERM MOTION - Curvilinear velocity (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	*MMP*				
		medium levels	β -1.54 (95% CI = -4.31 to 1.24)	3	unsp.	1.5-8.3 µg/L
		high levels	β 0.18 (95% CI = -3.39 to 3.74)	3	unsp.	8.3–278.1 µg/L
		MEP				
		medium levels	β -0.21 (95% CI = -1.8 to 1.38)	3	unsp.	59.6–979.5 µg/L
		high levels	β 5.23 (95% CI = 1.67 to 8.8) *	3	unsp.	979.5-11371 µg/L
		MnBP				
		medium levels	β -2.6 (95% CI = -5.4 to 0.19)	3	unsp.	10.3–24.6 µg/L
		high levels	β -3.81 (95% CI = -6.74 to -0.87) *	3	unsp.	24.6–14459.0 µg/L
		MBzP				
		medium levels	β -0.44 (95% CI = -1.94 to 1.07)	3	unsp.	4.2–64.2 µg/L
		high levels	β -1.7 (95% CI = -5.21 to 1.82)	3	unsp.	64.2–540.2 µg/L
		MEHP				
		medium levels	β -1.48 (95% CI = -2.99 to 0.03)	3	unsp.	3.1–208.1 µg/L
		high levels	β -2.41 (95% CI = -5.96 to 1.15)	3	unsp.	208.1–875.8 µg/L
SPERM MOTION - Linearity (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	*MMP*				
		medium levels	β 0.99 (95% CI = -0.17 to 2.14)	3	unsp.	1.5-8.3 µg/L
		high levels	β 0.93 (95% CI = -0.61 to 2.47)	3	unsp.	8.3–278.1 µg/L
		MEP				
		medium levels	β 0.01 (95% CI = -0.82 to 0.85)	3	unsp.	59.6–979.5 µg/L
		high levels	β -0.44 (95% CI = -1.94 to 1.04)	3	unsp.	979.5-11371 µg/L
		MnBP				

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		medium levels	β -0.14 (95% CI = -2.64 to 2.36)	3	unsp.	10.3–24.6 µg/L
		high levels	β -0.7 (95% CI = -2.46 to 1.07)	3	unsp.	24.6–14459.0 µg/L
		MBzP				
		medium levels	β -0.22 (95% CI = -0.81 to 0.38)	3	unsp.	4.2–64.2 µg/L
		high levels	β -1.05 (95% CI = -2.51 to 0.4)	3	unsp.	64.2–540.2 µg/L
		MEHP				
		medium levels	β -0.43 (95% CI = -0.8 to -0.06) *	3	unsp.	3.1–208.1 µg/L
		high levels	β -0.43 (95% CI = -1.9 to 1.05)	3	unsp.	208.1–875.8 µg/L
SPERM DNA DAMAGE - Comet assay: comet extent (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	MMP	β -2.08 (95% CI = -10.89 to 6.73)	2	unsp.	
		MEP	β 4.22 (95% CI = 1.66 to 6.77) *	2	unsp.	IQR increase of 449.4 µg /L
		MnBP	β -0.3 (95% CI = -0.79 to 0.19)	2	unsp.	
		MBzP	β 3.57 (95% CI = 0.89 to 6.25) *	2	unsp.	IQR increase of 11.35 µg /L
		MEHP	β -0.16 (95% CI = -1.45 to 1.13)	2	unsp.	
SPERM DNA DAMAGE - Comet assay: % DNA in tail (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	MMP	β -2.44 (95% CI = -7.16 to 2.29)	2	unsp.	
		MEP	β -0.18 (95% CI = -0.79 to 0.44)	2	unsp.	
		MnBP	β 0.64 (95% CI = -0.94 to 2.23)	2	unsp.	
		MBzP	β 0.05 (95% CI = -0.38 to 0.48)	2	unsp.	
		MEHP	β 1.4 (95% CI = -1.6 to 4.4)	2	unsp.	
SPERM DNA DAMAGE - Comet assay: tail distributed moment (Phthalates) – 1 review						
Sub-fertile men undergoing infertility work-up	Cai et al. 2015 (6/11)	MMP	β 0.31 (95% CI = -1.23 to 1.84)	2	unsp.	
		MEP	β 1.64 (95% CI = 0.24 to 3.03) *	2	unsp.	IQR increase of 449.4 µg /L
		MnBP	β -0.122 (95% CI = -0.32 to 0.08)	2	unsp.	
		MBzP	β 1.72 (95% CI = 0.33 to 3.12) *	2	unsp.	IQR increase of 11.35 µg/L
		MEHP	β 0.01 (95% CI = -0.53 to 0.54)	2	unsp.	
Metabolic and endocrine outcomes						
TYPE 2 DIABETES (Phthalates) – 1 review						
Adults	Song et al. 2016 (6/11)	*high vs low exposure*				
		Total phthalates	RR 1.48 (95% CI = 0.98 to 2.25)	4	5307	
		MEP	RR 1.39 (95% CI = 0.55 to 3.48)	unsp.	unsp.	
		MiBP	RR 1.9 (95% CI = 1.17 to 3.09) *	unsp.	unsp.	
FASTING GLUCOSE (Phthalates) – 1 review						
Adults	Song et al. 2016 (6/11)	Total phthalates	MD 0.98mg/dL (95% CI = 0 to 1.97mg/dL)	3	3926	high vs low exposure
INSULIN RESISTANCE (HOMA-IR) (Phthalates) – 2 reviews						
children and adults (General population)	Song et al. 2016 (6/11) Shoshtari-Yeganeh et al. 2019 (4/11)	Total phthalates	WMD 0.71 (95% CI = 0.3 to 1.12) *	4	5396	
		Specific phthalate metabolites				
		MMP	β 0.02 (95% CI = -0.06 to 0.11)	3	2158	
		MEP	β 0.02 (95% CI = -0.04 to 0.08)	6	12455	
		MiBP	β 0.1 (95% CI = 0.03 to 0.17) *	4	6569	
		MBzP	β 0.05 (95% CI = 0.01 to 0.1) *	5	11439	
		ΣDEHP	β 0.26 (95% CI = 0.15 to 0.38) *	2	4997	
		MEHP	β 0.08 (95% CI = 0.03 to 0.12) *	7	13248	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		MEHHP	β 0.09 (95% CI = -0.01 to 0.18)	5	7795	
		MEOHP	β 0.1 (95% CI = 0.01 to 0.19) *	5	7795	
		MECPP	β 0.16 (95% CI = 0.05 to 0.27) *	2	1122	
		MCPP	β 0.15 (95% CI = 0.03 to 0.28) *	3	1908	
THYROID FUNCTION (fT4) (Phthalates) – 1 review						
children and adults (General population, including pregnant women)	Kim et al. 2019b (5/11)	*MEHP*				
		Main analysis	r -0.02 (95% CI = -0.05 to 0)	10	4673	
		Children	r 0.03 (95% CI = -0.01 to 0.08)	6	1832	
		Adults	r -0.03 (95% CI = -0.14 to 0.07)	2	1829	
		Pregnant women	r -0.04 (95% CI = -0.07 to 0)	4	2841	
		MEHHP				
		Main analysis	r -0.03 (95% CI = -0.05 to -0.01) *	10	10601	
		Children	r 0.06 (95% CI = 0.01 to 0.1) *	6	1832	
		Adults	r -0.08 (95% CI = -0.14 to -0.01) *	3	7832	
		Pregnant women	r -0.04 (95% CI = -0.08 to 0)	3	2766	
		MEOHP				
		Main analysis	r -0.01 (95% CI = -0.03 to 0.01)	10	10601	
		Children	r 0.05 (95% CI = 0 to 0.1)	6	1832	
		Adults	r -0.05 (95% CI = -0.1 to 0.01)	3	7832	
		Pregnant women	r 0.02 (95% CI = -0.05 to 0.1)	3	2766	
THYROID FUNCTION (TT4) (Phthalates) – 1 review						
children and adults (General population, including pregnant women)	Kim et al. 2019b (5/11)	*MEHP*				
		Main analysis	r 0.01 (95% CI = -0.03 to 0.06)	13	5097	
		Children	r 0.02 (95% CI = -0.04 to 0.07)	7	2061	
		Adults	r -0.04 (95% CI = -0.08 to 0.01)	4	2024	
		Pregnant women	r -0.01 (95% CI = -0.13 to 0.11)	4	2841	
		MEHHP				
		Main analysis	r 0.03 (95% CI = -0.01 to 0.08)	11	10830	
		Children	r 0.04 (95% CI = 0 to 0.09)	7	2061	
		Adults	r 0 (95% CI = -0.02 to 0.03)	3	7832	
		Pregnant women	r 0 (95% CI = -0.19 to 0.19)	3	2766	
		MEOHP				
		Main analysis	r 0.02 (95% CI = 0 to 0.04)	11	10830	
		Children	r 0.05 (95% CI = 0.01 to 0.1) *	7	2061	
		Adults	r 0.01 (95% CI = -0.01 to 0.03)	3	7832	
		Pregnant women	r -0.03 (95% CI = -0.13 to 0.08)	3	2766	
THYROID FUNCTION (TSH) (Phthalates) – 1 review						
children and adults (General population, including pregnant women)	Kim et al. 2019b (5/11)	*MEHP*				
		Main analysis	r -0.03 (95% CI = -0.07 to 0.01)	13	5096	
		Children	r -0.01 (95% CI = -0.05 to 0.04)	7	2060	
		Adults	r -0.04 (95% CI = -0.08 to 0.01)	4	2024	
		Pregnant women	r 0 (95% CI = -0.13 to 0.14)	4	2841	
		MEHHP				

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Main analysis	r -0.02 (95% CI = -0.07 to 0.03)	10	4826	
		Children	r 0 (95% CI = -0.05 to 0.05)	7	2060	
		Adults	r -0.04 (95% CI = -0.09 to 0)	2	1829	
		Pregnant women	r 0 (95% CI = -0.2 to 0.19)	3	2766	
		MEOHP				
		Main analysis	r -0.02 (95% CI = -0.07 to 0.03)	10	4826	
		Children	r 0 (95% CI = -0.04 to 0.05)	7	2060	
		Adults	r -0.1 (95% CI = -0.22 to 0.03)	2	1829	
		Pregnant women	r 0.03 (95% CI = -0.16 to 0.2)	3	2766	
Child neurodevelopmental outcomes						
NEURODEVELOPMENT - Performance on BSID II MDI +/- Bayley III Cognitive subscales (preschool cognitive/mental development) FSIQ of WISC (Phthalates) – 2 reviews						
Children (6 months to 12 years of age); Prenatal and current (measured in urine or plasma)	Radke et al. 2020 (8/11)	*MEP*				
		Main analysis	β 0.3 (95% CI = -0.3 to 0.9)	5	1791	
		Girls	β 0.3 (95% CI = -0.8 to 1.4)	unsp.	unsp.	
		Boys	β 0 (95% CI = -1.1 to 1.2)	unsp.	unsp.	
		MnBP				
		Main analysis	β -0.2 (95% CI = -0.7 to 0.4)	7	2536	
		Girls	β -0.8 (95% CI = -2.2 to 0.6)	unsp.	unsp.	
		Boys	β 0.4 (95% CI = -0.8 to 1.6)	unsp.	unsp.	
		MiBP				
		Main analysis	β -0.1 (95% CI = -0.6 to 0.4)	4	1361	
		Girls	β -0.8 (95% CI = -2.1 to 0.6)	unsp.	unsp.	
		Boys	β 0.8 (95% CI = -0.3 to 1.8)	unsp.	unsp.	
		MBzP				
		Main analysis	β -0.1 (95% CI = -0.8 to 0.5)	6	2119	
		Girls	β -0.7 (95% CI = -1.6 to 0.2)	unsp.	unsp.	
		Boys	β 0.8 (95% CI = -0.3 to 1.9)	unsp.	unsp.	
		ΣDEHP (prenatal)				
		Main analysis	β -0.1 (95% CI = -0.8 to 0.5)	7	2536	
		Girls	β -0.5 (95% CI = -2.2 to 1.2)	unsp.	unsp.	
		Boys	β 0.1 (95% CI = -1.2 to 1.3)	unsp.	unsp.	
	Lee et al. 2018 (7/11)	*DEHP metabolites*				
		prenatal exposure	β -0.36 (95% CI = -1.05 to 0.32)	5	871	
NEURODEVELOPMENT - Cognitive development or IQ (BSID II MDI, Bayley III Cognitive Development, WPPSI IQ or WISC IQ) (Phthalates) – 2 reviews						
Children (6 months to 12 years of age); Prenatal and current (measured in urine or plasma)	Lee et al. 2018 (7/11)	*DEHP metabolites*				
		prenatal exposure	β -0.14 (95% CI = -0.7 to 0.41)	8	1625	
		current exposure	β -1.03 (95% CI = -1.88 to -0.18) *	5	1462	
NEURODEVELOPMENT - Performance on BSID II/III PDI +/- Bayley III Fine Motor scales (preschool fine motor/ psychomotor development) (Phthalates) – 2 reviews						
Children (6 months to 12 years of age);	Radke et al. 2020 (8/11)	*MEP*				
		Main analysis	β 0 (95% CI = -0.6 to 0.6)	4	1361	
		Girls	β 0.4 (95% CI = -0.5 to 1.4)	unsp.	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
Prenatal and current (measured in urine or plasma)		Boys	β 0.4 (95% CI = -0.5 to 1.4)	unsp.	unsp.	
		MnBP				
		Main analysis	β -0.5 (95% CI = -1.5 to 0.5)	6	2119	
		Girls	β -0.7 (95% CI = -1.8 to 0.3)	unsp.	unsp.	
		Boys	β 0 (95% CI = -1.7 to 1.8)	unsp.	unsp.	
		MiBP				
		Main analysis	β -0.4 (95% CI = -1.1 to 0.3)	5	1689	
		Girls	β -0.5 (95% CI = -1.9 to 0.9)	unsp.	unsp.	
		Boys	β -0.1 (95% CI = -1.4 to 1.2)	unsp.	unsp.	
		MBzP				
		Main analysis	β -0.7 (95% CI = -1.4 to 0)	6	2119	
		Girls	β -1.6 (95% CI = -2.6 to -0.6) *	unsp.	unsp.	
		Boys	β 0.8 (95% CI = -0.2 to 1.9)	unsp.	unsp.	
		ΣDEHP (prenatal)				
		Main analysis	β -0.4 (95% CI = -1.4 to 0.7)	6	2106	
		Girls	β 0.2 (95% CI = -0.8 to 1.3)	unsp.	unsp.	
		Boys	β 0.1 (95% CI = -1.1 to 1.3)	unsp.	unsp.	
	Lee et al. 2018 (7/11)	*DEHP metabolites*				
		prenatal exposure	β -0.8 (95% CI = -1.48 to -0.12) *	5	871	
Nutritional outcomes						
BMI (Phthalates) – 2 reviews						
Children (< 18 years of age); postnatal exposure (measured in urine)	Golestanzadeh et al. 2019 (5/11)	MMP	β 0.09 (95% CI = -0.08 to 0.26)	6	1695	
		MEP	β 0.19 (95% CI = -0.09 to 0.46)	6	2545	
		MiBP	β 0.18 (95% CI = 0.002 to 0.35) *	3	950	
		MBzP	β 0.17 (95% CI = -0.09 to 0.43)	3	905	
		MEHP	β 0.15 (95% CI = -0.1 to 0.39)	9	3195	
		MEHHP	β 0.18 (95% CI = 0.04 to 0.31) *	9	2490	
		MEOHP	β -0.001 (95% CI = -0.09 to 0.09)	9	2490	
		MECPP	β -0.12 (95% CI = -0.27 to 0.03)	4	1059	
		MCPP	β 0.15 (95% CI = -0.1 to 0.41)	2	663	
Adults	Ribeiro et al. 2019 (6/11)	MEP	β 0.05 (95% CI = -0.06 to 0.16)	4	2512	
		MEHP	β -0.05 (95% CI = -0.15 to 0.05)	3	1298	
BMI (z-score) (Phthalates) – 2 reviews						
Children (< 18 years of age); postnatal exposure (measured in urine)	Ribeiro et al. 2019 (6/11)	MEP	β 0.02 (95% CI = -0.06 to 0.1)	3	820	
		MnBP	β 0 (95% CI = -0.11 to 0.12)	3	820	
		MiBP	β -0.01 (95% CI = -0.1 to 0.07)	3	820	
		MBzP	β -0.06 (95% CI = -0.15 to 0.04)	3	820	
		MCPP	β -0.12 (95% CI = -0.24 to 0)	3	820	
	Golestanzadeh et al. 2019 (5/11)	MEHP	β 0.16 (95% CI = -0.06 to 0.38)	2	629	
		MEHHP	β 0.2 (95% CI = -0.08 to 0.48)	2	629	
		MEOHP	β 0.12 (95% CI = -0.02 to 0.26)	2	629	
WAIST CIRCUMFERENCE (Phthalates) – 2 reviews						
	Golestanzadeh et al. 2019 (5/11)	MMP	β 0.06 (95% CI = -0.06 to 0.18)	3	777	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		MEP	β 0.17 (95% CI = -0.18 to 0.52)	3	922	
		MnBP	β 0.19 (95% CI = -0.19 to 0.58)	4	1043	
		MiBP	β -0.33 (95% CI = -1.11 to 0.45)	2	646	
		MBzP	β 0.12 (95% CI = 0.02 to 0.22) *	3	905	
		MEHP	β 0.13 (95% CI = 0.04 to 0.21) *	5	1301	
		MEHHP	β 0.28 (95% CI = 0.09 to 0.47) *	5	1301	
Children (< 18 years of age); postnatal exposure (measured in urine)		MEOHP	β 0.05 (95% CI = -0.02 to 0.13)	5	1301	
		MECPP	β -0.11 (95% CI = -0.24 to 0.03)	4	1059	
		MCPP	β -0.46 (95% CI = -1.42 to 0.51)	2	663	
	Ribeiro et al. 2019 (6/11)	MEP	β 0.47 (95% CI = -0.23 to 1.17)	3	820	
		MnBP	β 0.13 (95% CI = -0.86 to 1.13)	3	820	
		MiBP	β -0.62 (95% CI = -1.6 to 0.37)	3	820	
		MBzP	β -0.35 (95% CI = -1.16 to 0.48)	3	820	
		MCPP	β -0.73 (95% CI = -1.74 to 0.28)	3	820	
Adults	Ribeiro et al. 2019 (6/11)	MEHP	β 0.58 (95% CI = 0.55 to 0.62) *	3	2435	
OBESITY (Phthalates) – 1 review						
Children (< 18 years of age); postnatal exposure (measured in urine)	Ribeiro et al. 2019 (6/11)	MEHP	OR 0.78 (95% CI = 0.47 to 1.29)	3	773+	
Adults	Ribeiro et al. 2019 (6/11)	MEP	OR 1.22 (95% CI = 0.94 to 1.5)	4	3,701+	
		MEHP	OR 0.91 (95% CI = 0.66 to 1.27)	3	2,432+	
		MECPP	OR 1.67 (95% CI = 1.3 to 2.16) *	3	3,599+	
			Circulatory outcomes			
CARDIOVASCULAR DISEASE (Phthalates) – 1 review						
children and adults (General population; postnatal exposure (measured in urine)	Fu et al. 2020 (6/11)	MEP	OR 1.15 (95% CI = 0.99 to 1.34)	4	9261	
		MnBP	OR 1.02 (95% CI = 0.78 to 1.32)	4	9261	
		MiBP	OR 1.18 (95% CI = 0.99 to 1.38)	4	9261	
		MBzP	OR 1.19 (95% CI = 0.93 to 1.51)	4	9261	
		MEHP	OR 1.05 (95% CI = 0.97 to 1.13)	4	9261	
		MEHHP	OR 1.08 (95% CI = 0.95 to 1.23)	4	9261	
		MEOHP	OR 1.09 (95% CI = 0.93 to 1.26)	4	9261	
		MECPP	OR 1.15 (95% CI = 0.94 to 1.41)	4	9261	
SYSTOLIC BLOOD PRESSURE (Phthalates) – 1 review						
Children (< 18 years of age); postnatal exposure (measured in urine)	Golestanzadeh et al. 2019 (5/11)	MMP	β 0.09mmHg (95% CI = -0.03 to 0.2mmHg)	2	518	
		MBzP	β 0.09mmHg (95% CI = -0.11 to 0.29mmHg)	3	518	
		MEHP	β 0.13mmHg (95% CI = -0.02 to 0.28mmHg)	3	731	
		MEHHP	β 0.16mmHg (95% CI = 0.09 to 0.23mmHg) *	3	761	
		MEOHP	β 0.12mmHg (95% CI = 0.12 to 0.24mmHg) *	3	761	
DIASTOLIC BLOOD PRESSURE (Phthalates) – 1 review						
Children (< 18 years of age); postnatal exposure (measured in urine)	Golestanzadeh et al. 2019 (5/11)	MMP	β 0.02mmHg (95% CI = -0.06 to 0.11mmHg)	2	518	
		MBzP	β 0.04mmHg (95% CI = -0.05 to 0.12mmHg)	2	518	
		MEHP	β -0.01mmHg (95% CI = -0.09 to 0.08mmHg)	2	518	
		MEHHP	β 0.07mmHg (95% CI = -0.02 to 0.15mmHg)	2	518	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		MEOHP	β 0.03mmHg (95% CI = -0.06 to 0.12mmHg)	2	518	
HIGH-DENSITY LIPOPROTEIN CHOLESTEROL (Phthalates) – 1 review						
Children (< 18 years of age); postnatal exposure (measured in urine)	Golestanzadeh et al. 2019 (5/11)	MnBP	β -0.15 (95% CI = -0.88 to 0.58)	2	397	
		MBzP	β -0.11 (95% CI = -0.47 to 0.26)	3	1400	
		ΣDEHP	β 0.09 (95% CI = -0.26 to 0.44)	4	3231	
		MEHP	β -0.2 (95% CI = -0.42 to 0.03)	3	622	
		MEHHP	β 0.2 (95% CI = -0.23 to 0.63)	2	485	
		MEOHP	β 0.31 (95% CI = 0.25 to 0.37) *	2	485	
		MCPP	β 0.11 (95% CI = -0.1 to 0.33)	2	1158	
TRIGLYCERIDES (Phthalates) – 1 review						
Children (< 18 years of age); postnatal exposure (measured in urine)	Golestanzadeh et al. 2019 (5/11)	MnBP	β 0.08 (95% CI = -0.18 to 0.34)	2	397	
		MBzP	β 0.14 (95% CI = -0.1 to 0.37)	3	1400	
		ΣDEHP	β -0.11 (95% CI = -0.31 to 0.08)	4	3907	
		MEHP	β 0.2 (95% CI = -0.06 to 0.47)	3	787	
		MEHHP	β 0.01 (95% CI = -0.05 to 0.07)	2	485	
		MEOHP	β -0.06 (95% CI = -0.19 to 0.06)	2	485	
		MCPP	β -0.04 (95% CI = -0.09 to 0.02)	2	1158	
Respiratory outcomes						
ASTHMA (Phthalates) – 2 reviews						
Children (< 18 years of age); pre -and postnatal exposure (measured in urine)	Li et al. 2017 (9/11)	*MnBP*				
		Urinary prenatal	OR 0.83 (95% CI = 0.12 to 5.77)	2	unsp.	
		Urinary postnatal	OR 0.72 (95% CI = 0.48 to 1.1)	5	unsp.	
		MBzP				
		Urinary prenatal	OR 1.38 (95% CI = 1.09 to 1.75) *	3	unsp.	
		Urinary postnatal	OR 1.19 (95% CI = 0.79 to 1.8)	5	unsp.	
		DEHP metabolites				
		Urinary prenatal	OR 1.11 (95% CI = 0.97 to 1.26)	3	unsp.	ΣDEHP where available, otherwise most reliable individual DEHP metabolite
		Urinary postnatal	OR 0.76 (95% CI = 0.32 to 1.79)	5	unsp.	ΣDEHP where available, otherwise most reliable individual DEHP metabolite
		MCOP				
		Urinary postnatal	OR 1.21 (95% CI = 0.48 to 3.05)	2	unsp.	
		MiBP				
		Urinary postnatal	OR 1.06 (95% CI = 0.67 to 1.66)	3	unsp.	
	Wu et al. 2020b (5/11)	*MEP*				
		Main analysis	OR 1.02 (95% CI = 0.94 to 1.11)	10	unsp.	
		Urinary prenatal	OR 1.02 (95% CI = 0.93 to 1.12)	5	unsp.	
		MnBP				
		Main analysis	OR 0.97 (95% CI = 0.85 to 1.09)	8	unsp.	
		Urinary prenatal	OR 1.07 (95% CI = 0.8 to 1.42)	4	unsp.	
		MiBP				

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Main analysis	OR 1.04 (95% CI = 0.91 to 1.19)	7	unsp.	
		Urinary prenatal	OR 1.05 (95% CI = 0.88 to 1.24)	3	unsp.	
		MBzP				
		Main analysis	OR 1.17 (95% CI = 1.05 to 1.29) *	12	unsp.	
		Urinary prenatal	OR 1.15 (95% CI = 1.01 to 1.32) *	6	unsp.	
		DEHP metabolites				
		Main analysis	OR 0.87 (95% CI = 0.67 to 1.14)	8	unsp.	ΣDEHP where available, otherwise most reliable individual DEHP metabolite
		Urinary prenatal	OR 1.08 (95% CI = 0.92 to 1.26)	5	unsp.	ΣDEHP where available, otherwise most reliable individual DEHP metabolite
		MEHP				
		Main analysis	OR 1.04 (95% CI = 0.89 to 1.2)	5	unsp.	
		Urinary prenatal	OR 1.06 (95% CI = 0.91 to 1.23)	3	unsp.	
		Urinary postnatal	OR 0.78 (95% CI = 0.41 to 1.48)	3	unsp.	
		Males	OR 0.99 (95% CI = 0.81 to 1.19)	2	unsp.	
		MEHHP				
		Main analysis	OR 1.13 (95% CI = 1.03 to 1.24) *	5	unsp.	
		Urinary prenatal	OR 1.07 (95% CI = 0.96 to 1.2)	3	unsp.	
		Urinary postnatal	OR 1.3 (95% CI = 1.09 to 1.56) *	2	unsp.	
		MEOHP				
		Main analysis	OR 1.09 (95% CI = 0.77 to 1.53)	3	unsp.	
		Urinary prenatal	OR 1.19 (95% CI = 0.88 to 1.61)	2	unsp.	
		MECPP				
		Main analysis	OR 1.2 (95% CI = 1 to 1.42)	3	unsp.	
		Urinary prenatal	OR 1.23 (95% CI = 1.03 to 1.47) *	2	unsp.	
		MCOP				
		Main analysis	OR 1.19 (95% CI = 1.02 to 1.37) *	4	unsp.	
		Urinary prenatal	OR 1.17 (95% CI = 0.98 to 1.41)	2	unsp.	
		MCNP				
		Main analysis	OR 1.15 (95% CI = 1 to 1.31)	5	unsp.	
		Urinary prenatal	OR 1.14 (95% CI = 0.96 to 1.34)	2	unsp.	
		MCPP				
		Main analysis	OR 0.97 (95% CI = 0.83 to 1.13)	6	unsp.	
		Urinary prenatal	OR 0.99 (95% CI = 0.81 to 1.2)	3	unsp.	
General population	Wu et al. 2020b (5/11)	*MEP*				
		Main analysis	OR 1.03 (95% CI = 0.96 to 1.12)	11	unsp.	
		Urinary postnatal	OR 1.08 (95% CI = 0.95 to 1.23)	9	unsp.	
		Adults (postnatal/current)	OR 1.11 (95% CI = 0.89 to 1.39)	3	unsp.	
		Europe	OR 1.06 (95% CI = 0.9 to 1.24)	4	unsp.	
		North America	OR 1.03 (95% CI = 0.93 to 1.14)	7	unsp.	
		Asia	OR 1.03 (95% CI = 0.86 to 1.25)	3	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Males	OR 1.12 (95% CI = 0.97 to 1.31)	5	unsp.	
		Females	OR 0.94 (95% CI = 0.58 to 1.53)	3	unsp.	
		MnBP				
		Main analysis	OR 1.03 (95% CI = 0.85 to 1.24)	9	unsp.	
		Urinary postnatal	OR 0.95 (95% CI = 0.78 to 1.16)	7	unsp.	
		Adults (postnatal/current)	OR 1.35 (95% CI = 0.93 to 1.96)	3	unsp.	
		Europe	OR 0.98 (95% CI = 0.74 to 1.29)	4	unsp.	
		North America	OR 1.09 (95% CI = 0.89 to 1.33)	7	unsp.	
		Males	OR 0.98 (95% CI = 0.82 to 1.16)	4	unsp.	
		Females	OR 0.84 (95% CI = 0.56 to 1.25)	3	unsp.	
		MiBP				
		Main analysis	OR 1.05 (95% CI = 0.93 to 1.19)	8	unsp.	
		Urinary postnatal	OR 1.06 (95% CI = 0.89 to 1.27)	7	unsp.	
		Adults (postnatal/current)	OR 1.11 (95% CI = 0.84 to 1.47)	3	unsp.	
		Europe	OR 1.05 (95% CI = 0.9 to 1.23)	4	unsp.	
		North America	OR 1.06 (95% CI = 0.87 to 1.29)	6	unsp.	
		Males	OR 1.08 (95% CI = 0.88 to 1.33)	4	unsp.	
		Females	OR 0.81 (95% CI = 0.51 to 1.29)	3	unsp.	
		MBzP				
		Main analysis	OR 1.17 (95% CI = 1.06 to 1.28) *	13	unsp.	
		Urinary postnatal	OR 1.17 (95% CI = 1.03 to 1.33) *	10	unsp.	
		Adults (postnatal/current)	OR 1.17 (95% CI = 0.94 to 1.46)	3	unsp.	
		Europe	OR 1.16 (95% CI = 1.02 to 1.32) *	5	unsp.	
		North America	OR 1.23 (95% CI = 1.05 to 1.44) *	7	unsp.	
		Asia	OR 1.08 (95% CI = 0.37 to 3.19)	4	unsp.	
		Male	OR 1.19 (95% CI = 0.99 to 1.41)	5	unsp.	
		Female	OR 1.04 (95% CI = 0.77 to 1.42)	4	unsp.	
		ΣDEHP				
		Main analysis	OR 0.99 (95% CI = 0.8 to 1.22)	9	unsp.	
		Urinary postnatal	OR 1.04 (95% CI = 0.71 to 1.54)	7	unsp.	
		Adults (postnatal/current)	OR 1.27 (95% CI = 0.99 to 1.61)	3	unsp.	
		Europe	OR 1.16 (95% CI = 1 to 1.34)	4	unsp.	
		North America	OR 0.81 (95% CI = 0.57 to 1.17)	6	unsp.	
		Asia	OR 1.89 (95% CI = 0.79 to 4.53)	2	unsp.	
		MEHP				
		Europe	OR 1.04 (95% CI = 0.89 to 1.21)	3	unsp.	
		Asia	OR 1.14 (95% CI = 0.48 to 2.71)	3	unsp.	
		MEHHP				
		Europe	OR 1.11 (95% CI = 0.94 to 1.31)	3	unsp.	
		MCOP				
		Main analysis	OR 1.13 (95% CI = 0.99 to 1.28)	4	unsp.	
		Urinary postnatal	OR 1.08 (95% CI = 0.9 to 1.31)	3	unsp.	
		Europe	OR 1.13 (95% CI = 0.95 to 1.34)	2	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		North America	OR 1.1 (95% CI = 0.74 to 1.64)	3	unsp.	
		MCNP				
		Main analysis	OR 1.1 (95% CI = 0.98 to 1.24)	5	unsp.	
		Urinary postnatal	OR 1.07 (95% CI = 0.92 to 1.26)	5	unsp.	
		Adults (postnatal/current)	OR 1 (95% CI = 0.8 to 1.24)	2	unsp.	
		Europe	OR 1.18 (95% CI = 1.02 to 1.37) *	2	unsp.	
		North America	OR 0.99 (95% CI = 0.82 to 1.19)	5	unsp.	
		Males	OR 1.12 (95% CI = 0.95 to 1.33)	3	unsp.	
		Females	OR 1.02 (95% CI = 0.73 to 1.44)	2	unsp.	
		MCPP				
		Main analysis	OR 1.04 (95% CI = 0.91 to 1.19)	6	unsp.	
		Urinary postnatal	OR 1.09 (95% CI = 0.91 to 1.32)	5	unsp.	
		Adults (postnatal/current)	OR 1.32 (95% CI = 1 to 1.75)	2	unsp.	
		Europe	OR 0.96 (95% CI = 0.8 to 1.15)	2	unsp.	
		North America	OR 1.14 (95% CI = 0.94 to 1.4)	6	unsp.	
		Males	OR 0.93 (95% CI = 0.76 to 1.14)	4	unsp.	
		Females	OR 1.36 (95% CI = 0.98 to 1.88)	3	unsp.	
Skin-related outcomes – No data						
Cancer outcomes – No data						

Table legend:

** Indicates significant effect*

+ more participants indicated but exact number unspecified

Studies or participants unspecified (unsp.) indicates no data available from the reviews

Total phthalates composite measure of phthalate exposure which is the total concentration of all phthalate metabolites measured in the individual primary research study.

ΣDEHP composite measure of Diethylhexyl phthalate (DEHP) exposure as the sum of the individual DEHP metabolites measured in the individual primary research study, such as: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-carboxymethyl-5-hexyl) phthalate (MCMHP).

Note: MnBP refers to both MBP and MnBP. MnBP is the preferred term. For HOMA-IR and BMI, MBP and MnBP findings were excluded because authors reported findings for MnBP and MBP separately.

Descriptive summary of included plasticiser (phthalate) reviews

Presentation of studies in this section is in alphabetical order to facilitate rapid reference. This section includes details of exposures investigated, number and type of studies and total sample size, number of meta-analyses presented and various outcomes reported (Full details are available in Appendix 7). AMSTAR scores are provided for reference.

Cai et al. (2015)- *Human urinary/seminal phthalates or their metabolite levels and semen quality: a meta-analysis. No COIs declared, AMSTAR Score: 6/11.*

Cai et al. (2015) explored the association between DEHP phthalate and phthalate metabolites (MMP, MEP, MnBP, MBzP, MEHP, MEOHP, and combined MEHP and MEOHP) and sperm quality (measured through outcomes- sperm concentration, sperm motility, sperm morphology, semen volume, sperm motion parameters – straight-line velocity (VSL), curvilinear velocity (VCL) and linearity (LIN), comet assay parameters- comet extent, percent DNA in tails and tail distributed moment. The review included a total of 20 studies (however, only 14 were included in the meta-analyses), with most cross sectional (however, no specific numbers were reported), with a total of 4,945 men (studies used either subfertile men or healthy men from the general population of reproductive age; 20-50 years; 2 studies included younger men 18-22 years). The Elwood (1998) Critical Appraisal of Epidemiological Studies and Clinical Trials was used to assess the quality of included studies. Studies with a score no lower than –2 were included in the qualitative and quantitative analysis of the associations between phthalates or their metabolite levels in humans and semen quality. For studies measuring urinary phthalate metabolites, total quality scores varied from –3 to 3, with the median value being 1. For studies measuring phthalates in semen, scores were lower, which a range of –6 to 0 and a median of –1. The quality score of the only study measuring serum phthalate levels was 1. Three studies were removed due to poor quality. Exposure to phthalates was considered environmental. Phthalate levels were measured using urinary phthalates or metabolite levels; seminal phthalates levels; serum phthalates levels in µg/L. Exposure to MnBP measured at levels of 7.4-25.3 µg/L and 26.0-14459.0 µg/L was associated with increased sperm concentration.

There was a positive association between MnBP levels of 24.6–14,459.0 and straight-line velocity, and in curvilinear velocity. MBzP levels of 14-540.2 µg/L was positively associated with sperm concentration. There was a positive association between MBzP (IQR 11.35 µg/L) and tail distributed moment.

There was a positive association between MEP levels with straight-line velocity and curvilinear velocity and exposure to MEP (IQR 449.4 µg/L) and tail distributed moment. Exposure to lower levels of MEHP 3.1–208.1 was negatively associated with straight-line velocity and linearity.

Considering the analyses based on the 14 included studies, the authors concluded that specific phthalates or their metabolites may affect semen quality. However, the authors noted that longitudinal research is needed to help to confirm these tentative findings and to establish likelihood of causal relationships between these chemicals and semen quality.

Cai et al. (2019) - *Association between phthalate metabolites and risk of endometriosis: a meta-analysis. No COIs declared, AMSTAR Score: 7/11.*

Cai et al. (2019) explored the association between phthalate metabolites (MEP, MBzP, MEHP, MEHHP and MEOHP) and endometriosis among women (aged 18-54; n=2 studies did not state their age range). The review included a total of 13 studies - cross sectional (n= 1), case control (n= 5) and cohort (n= 7), with a total of 2,542 participants (cases n= 620; control n= 1,922). The Newcastle-Ottawa Scale was used to assess the quality of the included studies. All studies scored between 6-7 (scores could range from 0-9). Phthalate exposure and time was non-specific. Exposure measurement was from urine samples; however, participants were

unspecified. Outcome reported was endometriosis. MEHHP was associated with the risk of endometriosis in women, however, other metabolites investigated, MEP, MBzP, MEHP and MEOHP were not. When grouped by geographical location, MEHHP and MEP, exposure to participants in Asia was positively associated with endometriosis. There were no other associations found across the included metabolites for women in the USA, by study population (laparoscopic/laparotomy population or general population) or by study design (case control or cohort). The authors concluded that there was a statistically significant association between MEHHP exposure and endometriosis, and more specifically for this metabolite from studies conducted in Asia. However, no associations were found between the other phthalate metabolites and endometriosis.

Dorman et al. (2018) - *Systematic reviews and meta-analyses of human and animal evidence of prenatal diethylhexyl phthalate exposure and changes in male anogenital distance. No COIs declared, AMSTAR Score: 8/11.*

Dorman et al. (2018) explored the association between DEHP and anogenital distance in male babies (no further information was provided by the authors). The Office of Health Assessment appraisal tool (National Toxicology Program, 2015) was used to assess the quality of the included studies. Quality scores of (6 studies, 5 used in a meta-analysis), studies ranged from probable low risk to definitely low risk of bias. One study (Suzuki et al., 2012) was reported to have a high risk of bias; however, it was not included in the meta-analysis as it only reported results of AGD index. DEHP exposure was maternal exposure and was measured through maternal urine (ng/ml), for the in utero (ranged from 1st to 3rd trimester) period. Outcomes reported were measures of anogenital distance. The authors concluded a significant association per logarithmic rise in urinary DEHP metabolite concentrations and a reduced AGD in boys.

Fu et al. (2020) - *The association between environmental endocrine disruptors and cardiovascular disease: A systematic review and meta-analysis. No COI declared, AMSTAR Score: 6/11*.

Fu et al. (2020) explored the association between polychlorinated biphenyl (PCBs), any phthalate compound, BPA and the risk of cardiovascular disease among a general population in whom environmental exposure to endocrine disrupters could be determined. The review and meta-analyses included a total of 29 studies (cross-sectional studies (n=17), retrospective cohort (n=7), prospective cohort (n=4), case control (n=1)), with a total of 41,854 participants. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. The quality scores of studies ranged from 7 to 9 (all considered to be of high quality).

For exposure to BPA there was a significant positive association with risk of cardiovascular disease (no subgroup analysis conducted).

For exposure to any phthalate, there was a significant positive association with risk of cardiovascular disease. When grouped based on phthalate compound, there was no association between exposure to MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP and MECPP.

PCB exposure was via an unspecified route, the measure and timing of this exposure was unspecified by the authors. The only outcome reported was the risk of cardiovascular disease. For PCB exposure across populations, the authors concluded significant positive association with risk of cardiovascular disease. When grouped according to PCB congener, exposure to PCB 138 and PCB 153 were found to be positively associated with an increased risk of cardiovascular disease. There were no associations found for PCB 180 and total PCBs.

It should be noted that the combined analyses for PCBs and phthalates (and other composite exposure findings) were considered invalid, as data from studies were used repeatedly in the analyses (multiple counting same participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the

review. Where available, results of analysis of individual chemical exposures have been extracted instead.

The authors suggest that exposure to environmental endocrine disruptors is a risk factor for CVD. PCBs, BPA, pesticides (OCPs) and phthalates have a great impact on the development and progression of CVD. PCB 138, PCB 153 were risk factors for CVD mortality. However, the findings from the questionable combined analyses should be interpreted with caution.

Golestanzadeh et al. (2019) - *Association of exposure to phthalates with cardiometabolic risk factors in children and adolescents: a systematic review and meta-analysis. No COIs declared, AMSTAR Score: 5/11.*

Golestanzadeh et al. (2019) explored the association between phthalate exposure and cardiometabolic risk factors in children and adolescents. The review included a total of 35 studies – including cohort (n=17), case control (n=3), and cross sectional (n=15) with a total of 24,943 participants. The number of studies used in the meta-analysis was 23 with a total of 14,255 participants. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was reported as the critical appraisal tool; however, this is a reporting guideline and not a critical appraisal tool. Phthalate exposure was via maternal/prenatal exposure and childhood exposure (further details not reported), from urine and serum (measurement units were not reported), and the time period was not clearly reported. The outcomes reported were birthweight, BMI, BMI z-score, waist circumference, systolic and diastolic blood pressure, and lipids (High-density lipoprotein (HDL) and triglycerides). For both LMW and HMW phthalate exposure, authors concluded significant positive associations with BMI and BMI z-score but no significant association with birthweight and waist circumference. Phthalate exposure was positively associated with systolic blood pressure but not diastolic blood pressure or lipids. However, these combined analyses for the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting of same participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. β coefficients and z transformed correlation coefficients have been used interchangeably in analyses. Where available, results of analysis of individual chemical exposures have been extracted instead. Where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have been extracted and included, assuming these are mutually exclusive subgroups, however, there may be underestimate of true heterogeneity. However, for most of the phthalate metabolites and BMI z scores, the findings were not used in this review as data from one study were represented five times in the analysis. It is also worth noting that there was a significantly high level of heterogeneity found with most of the phthalate metabolites and outcomes investigated which make it difficult to estimate the true overall effect.

In the subgroup analyses exposure to MEP was positively associated with birthweight; exposure to MiBP was positively associated with BMI; exposure to MEHHP was positively associated with BMI, waist circumference and systolic blood pressure; exposure to MBzP was positively associated with waist circumference; MEHP was associated with waist circumference; MEOHP was positively associated with HDL lipids.

Golestanzadeh et al. (2020) - *Association of phthalate exposure with precocious and delayed pubertal timing in girls and boys: a systematic review and meta-analysis. No COIs declared, AMSTAR Score: 7/11.*

Golestanzadeh et al. (2020) explored the association between different compounds of phthalates and pubertal development outcomes among adolescent boys and girls, ranging from 7 years to 19 years old. The review included 39 studies – (cohort (n=17), case control (n=13), cross sectional (n=9)), with a total of 10,524 participants. The number of studies included in the meta-analysis was 4 with 609 participants. The STROBE checklist was used to

evaluate the quality of the included studies and the results of appraisal were non-specific. Phthalate exposure was via an unspecified route, measured in either the blood or urine (units unspecified), for an unspecified period. Outcomes reported were abnormal breast development ages; abnormal age of pubic hair development; abnormal age of menarche and testicular volume. Analysis was conducted based on individual phthalate exposure. There were positive associations between exposure to MEOHP and an abnormal age of pubic hair development for boys; exposure to MEHHP and abnormal breast development age; and exposure to MnBP and abnormal age of pubic hair development for boys. There were no associations found for the phthalate subtypes MEP, MMP, MnBP, MEHP, MEHHP and MEOHP with any other reported outcome. The authors of the review have stated that there was a moderate association between exposure to different phthalates and pubertal timing and status of puberty for both genders. Exposure to phthalates may alter physiological development of humans such as pubic hair and breast development, menarche, production rates of hormones, as well as the size of ovaries, uterus and testicles.

Kim et al. (2019) - *Association between diethylhexyl phthalate exposure and thyroid Function: a meta-analysis. No COIs declared, AMSTAR score: 5/11.*

Kim et al. (2019) explored the association between the DEHP metabolites MEHP, MEHHP, and MEOHP, and thyroid function among children (neonates excluded) and adolescents (aged < 18 years), pregnant women, adults (aged ≥ 18 years), and the general population. The review included 13 studies – cross sectional, case control and cohort (numbers not reported) with 12,674 participants. No critical appraisal of studies was undertaken. Exposure of MEHP was measured in urine samples. Outcomes reported were levels of free thyroxine (fT4), total free thyroxine (TT4), and thyrotropin/thyroid stimulating hormone (TSH). For MEHHP exposure across populations, the authors concluded a significant negative association with fT4. When grouped by age, MEHHP was found to be significantly positively associated with fT4 and TT4 in children and adolescents. For MEOHP across populations, the authors concluded a significant positive association with TT4. When grouped by age, MEOHP was found to be significantly positively associated with children and adolescents. No associations were found between MEHP and fT4, TT4 or TSH.

Lee et al. (2018) - *Prenatal and postnatal exposure to di-(2-ethylhexyl) phthalate and neurodevelopmental outcomes: A systematic review and meta-analysis. No COI declared, AMSTAR score: 7/11.*

Lee et al. (2018) explored the association between DEHP exposure and neurodevelopment among children aged six months to 12 years. The review included 10 studies –cross sectional (n=2) and cohort (n=8), with 2,496 participants; all were used in the meta-analyses. The Newcastle-Ottawa Scale was used to assess the quality of all the included studies. Quality scores ranged from seven to eight; all studies were of high quality. Exposure to DEHP was measured in urine samples in µg/g or mmol/L; prenatal maternal urine was used in eight studies; child's urine in two studies, and three studies collected both. Outcomes reported were neurodevelopment measured with Wechsler Intelligence Scale for Children (WISC) and Bayley Scales of Infant Development (BSID). Longitudinal and cross-sectional data were analysed separately involving a total of 1,625 and 1,462 participants respectively.

For DEHP exposure across populations using longitudinal data, the authors concluded a significant negative association with the Psychomotor Development Index (PDI), but not the Mental Development Index (MDI) of the BSID, nor overall for the WISC and BSID combined. For DEHP exposure across populations using cross-sectional data, the authors concluded a significant negative association with neurodevelopment overall. It should be noted that where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have been extracted and included, assuming these are mutually exclusive subgroups, however, there may be underestimate of true heterogeneity.

Authors concluded that exposure to DEHP was shown to carry risks of disturbed neurodevelopment in children.

Li et al. (2017) - *Phthalate esters and childhood asthma: A systematic review and congener-specific meta-analysis. No COIs declared, AMSTAR Score: 9/11.*

Li et al. (2017) explored the association between phthalate exposure and childhood asthma among children. The review included a total of nine studies – including case control (n=3), cross sectional (n=4) and cohort (n=2), with a total of 3,406 participants. All studies were used in the meta-analysis. The Newcastle-Ottawa scale used to assess the quality of all the included studies. Quality scores ranged from moderate to high quality. Phthalate exposure was via maternal/pre- and postnatal exposure (no other descriptions regarding route or exposure time were reported), measured in urine and dust (units were not reported), and the time period was not reported. The outcome reported was risk of childhood asthma. For BBzP exposure, the authors concluded a significant association with childhood asthma risk (ORs differed depending on different exposure measure combination strategies (prenatal or postnatal data and dust or urine samples). However, only those which directly measured exposure via urine were reported in this review.

Radke et al. (2020) - *Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence. No COIs declared, AMSTAR Score: 8/11.*

Radke et al. (2020) explored the association between different phthalate compounds and mental development among newborns from birth to the age of 11. The review included 26 studies – (prospective cohort (n=25), case control (n=1)) with a total of 5,573 participants. The number of studies included in the meta-analysis was 7 with 2,536 participants. The ROBINS-I tool was used to assess the quality of the included studies. Four studies were classified as high confidence, ten studies were classified as medium confidence and three were classified as low confidence. Phthalate exposure was via an unspecified, measured in the urine or plasma (units combined from different studies in meta-analysis), for an unspecified period. Outcomes reported were performance on the Psychomotor Development Index (PDI) and the metal development index (MDI) and analysed using beta-coefficient effect size (natural units of the Bayley Scales of Infant Development). There were no associations found for any phthalate subgroup (DEHP, BBP, DBP, DEP, DIBP) and their metabolites on any of the outcomes reported. No subgroup analyses were conducted. The authors concluded no clear pattern of association with prenatal phthalate exposures and neurodevelopment.

Ribeiro et al. (2019) - *Association between the exposure to phthalates and adiposity: A meta-analysis in children and adults. No COIs declared (Funding body acknowledged), AMSTAR Score: 6/11.*

Ribeiro et al. (2019) explored the association between different phthalate compounds and outcomes related to obesity in the general population (no age limitations used, and age limiters are unclear). The review included 29 studies – (cross-sectional (n=25), prospective cohort (n=1), case control (n=3)), with a total of 26,968 participants. The number of studies included in the meta-analysis was 8 with 5,574 participants. The STROBE checklist was used to assess the quality of the included studies. Only 4 of the included studies were considered as 'low' quality. Phthalate exposure was via an unspecified route, measured in an unspecified manner (only regression coefficients have been reported), combining both pre- and postnatal exposure. Outcomes reported were BMI, waist circumference and incidence of obesity. Analysis was conducted based on phthalate compound and children and adult data as it was not possible to do a combined analysis of children and adult due to high heterogeneity reported. There were positive associations between exposure to MEHP and waist circumference and exposure to MECPP and the odds of obesity. No associations were found for the individual phthalate metabolites MEP, MnBP, MiBP, MBzP and MCCP and any of the reported outcomes. The authors have stated that the inconsistency in the results and the fact

that most of them reported associations that were not statistically significant require some putative explanations, such as: 1) the study design and the short-half life of phthalates, 2) the lipophilic capacity of phthalates, 3) gender and age differences.

Shoshtari-Yeganeh et al. (2019) - *Systematic review and meta-analysis on the association between phthalates exposure and insulin resistance - No COIs declared (No acknowledgement of a funding source or source of support), AMSTAR Score: 4/11.*

Shoshtari-Yeganeh et al. (2019) explored the association between any phthalate exposure and Homeostatic Model Assessment – Insulin Resistance (HOMA-IR) among participants from the general population, aged from 12-79 years old. The review and meta-analysis included eight cross-sectional studies, with a total of 13,808 participants. The authors indicated study quality was assessed with "Cochrane checklist"; the results of this assessment are not provided in the manuscript or as supplementary material. Phthalate exposure was unspecified, postnatal route, measured in an unspecified manner (only regression coefficients have been reported). Outcomes reported were HOMA-IR. The authors reported a statistically significant increase in HOMA-IR with increased phthalate exposure across populations. However, the combined analyses for the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly (multiple counting of participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted.

When grouped based on phthalate compound, positive associations (increased HOMA-IR) were identified for the following compounds: MiBP, MBzP, ΣDEHP, MEHP, MEOHP, MECPP and MCCP. This association remained significant even after adjusting the analysis for multiple confounding variables. No association was found for MMP, MEP and MEHHP.

Song et al. (2016) - *Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. No COIs declared, AMSTAR Score: 6/11.*

Song et al. (2016) explored the association between endocrine-disrupting chemical exposure and risk of type 2 diabetes and diabetes-related metabolic traits. The review included a total of 49 studies- including cross sectional (n=41) and cohort (n=8), with a total of 55,774 participants. Thirty-two studies were included in the meta-analysis for polychlorinated biphenyls (PCBs; n=21), phthalates (n=7) and bisphenol A (BPA; n=4). Critical appraisal was not undertaken. Exposure routes were not reported; exposure was measured in serum or urine as pg/ml, pg/g or ng/g lipid. The outcome reported was type 2 diabetes and it was analysed comparing highest versus lowest exposure categories (no further details of the categories reported). For exposure to PCBs and BPA across populations, the authors concluded a significant positive association with type 2 diabetes risk. No association was found for phthalate exposure and type 2 diabetes risk. It should be noted that multiple subgroups from within a single study were included within an analysis of individual chemical exposures (BPA, phthalates and PCBs) and these data have been extracted and included, assuming these are mutually exclusive subgroups; however, this may underestimate true heterogeneity.

Wen et al. (2015) - *Association of PAEs with precocious puberty in children: A systematic review and meta-analysis. No COIs declared, AMSTAR Score: 7/11.*

Wen et al. (2015) explored the association between exposure to different phthalate compounds and the prevalence of precocious puberty among female children aged between 0.5 and 11.3 years. The review included 14 case-control studies with 2,223 participants. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. Seven studies were considered as moderate risk of bias (scores of 5 and 6), the others were assessed as low risk of bias (scores of 7 and 8). Phthalate exposure was via an unspecified route, measured as a concentration in the blood (metrics combined for meta-analysis), for an unspecified period. Outcome was the prevalence of precocious puberty. There was a positive association between

DEHP and DBP and the prevalence of precocious puberty. Subgroup analysis revealed that there were positive associations based on the studies conducted in China for DEHP. The authors summarise their results stating phthalate exposure and precocious puberty might be a potential risk for girls.

Wu et al. (2020) - *Association between phthalate exposure and asthma risk: A meta-analysis of observational studies. No COIs declared, AMSTAR Score: 5/11.*

Wu et al. (2020) explored the association between exposure to different phthalate compounds and the prevalence of asthma among men and women of any age from the general population. The review and meta-analyses included 14 studies – (cohort (n=7), case-control (n=2), cross sectional (n=5)), with a total of 1,731 cases (authors only provide the number of cases in the review, not total number of participants). The Newcastle-Ottawa Scale was used to assess the quality of the included studies. Quality ranged from 7 to 9 in the cohort studies, 7–8 in the case-control studies, and 6–8 in the cross-sectional studies, which indicated moderate to high quality in the included studies. Phthalate exposure was via an unspecified route, measured in the urine (µg/L), for an unspecified period (but subgrouping was conducted based on prenatal or postnatal exposure). Outcome was the prevalence and/or incidence of asthma. For exposure to MBzP and MEHHP there was a positive association with asthma. For MBzP, subgroup analysis was conducted based on age (no difference), study location (positive associations found from studies from North America and Europe, but not from Asia), exposure time (positive association for postnatal exposure but not prenatal exposure) and gender (no differences). For MEHHP, subgroup analysis was conducted based on location (a positive association was found for studies from Asia, but no difference for studies from North America or Europe) and exposure time (positive association was found for postnatal exposure, but no association was found for prenatal exposure). For MEP, MnBP, MiBP, ΣDEHP, MEHP, MEOHP, MECCP, MCOP, MCNP and MCCP, there was no association. Subgroup analysis was conducted based on age (no difference), study location (no difference), exposure time (no difference) and gender (no difference). The authors concluded that urine levels of MBzP, MEHHP and MECPP were associated with the risk of asthma.

It should be noted that the combined analyses for the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting of same participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review.

Zhang et al. (2020) - *Associations between phthalate exposure and risk of spontaneous pregnancy loss: A systematic review and meta-analysis. No COIs declared, AMSTAR score: 7/11.*

Zhang et al. (2020) explored the association between exposure to individual phthalate metabolites and spontaneous pregnancy loss amongst reproductive women. The review included studies; case-control (n=4), prospective cohort studies (n=4) with a total of 4713 participants (n=651 cases and n=4,063 controls). Critical appraisal was undertaken using the Newcastle-Ottawa Scale. The authors deemed all articles to be of high quality. Exposure of phthalates was via the mother (prenatal exposure), however, no detail was provided how mothers were exposed. The exposure was measured through urinary phthalates levels (measurements noted: µg/g, ng/mL, µg/L). Outcomes reported were spontaneous pregnancy loss.

The combined analysis for the overall summary (and other composite exposure findings) was invalid as data from studies were used repeatedly in the analyses (multiple counting of same participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted. There was a significant positive association between MBP, MEHP, MEHHP, MEOHP and ΣDEHP and spontaneous pregnancy

loss. There was no association between MMP, MEP, MiBP, MBzP and MECCP and spontaneous pregnancy loss in reproductive women.

Critical appraisal of included plasticiser (phthalate) reviews

The methodological quality of the 16 systematic reviews with meta-analyses included is presented in the following table.

Table 3.4: Critical appraisal of phthalate reviews

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Cai et al. (2015)	N	CA	N	N	N	Y	Y	Y	Y	Y	Y	**6**	This review was not supported by an *a priori* protocol (Q1). The review reported that two people undertook study searching, but no further details re if two members of the team completed data extraction (Q2). The study searched two databases, but only used key words (Q3). No grey literature searching occurred (Q4). No list of included or excludes studies was provided in the review or supplementary materials (Q5). Conflict of interest in the individual review was discussed but not for all included articles (Q11).
Cai et al. (2019)	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	**7**	This review was not informed by *a priori* protocol (Q1). Authors did use three databases to perform their search with dates (PubMed, EMBASE, and Web of Science from 1 January 1995 to 3 March 2019), however, they did not report the use of MESH terms in their search (Q3). No grey literature search was conducted (Q4). No list of the included or excluded studies were included in their literature review or supplementary information (Q5). The authors declared no conflict of interest for their study, but not for individual studies included (Q11).
Dorman et al. (2018)	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	**8**	No grey literature search undertaken (Q4); no list of excluded studies available (Q5); conflict of interest in the individual review was discussed but not for all included articles(Q11)
Fu et al. (2020)	N	CA	Y	N	N	Y	Y	Y	CA	Y	Y	**6**	No *a priori* protocol (Q1); Study selection completed in duplicate; however, not clear if extraction was done in duplicate or if any strategy was undertaken to check the data extraction (Q2); no grey literature search undertaken (Q4); no list of excluded studies available (Q5); table and narrative appear to be presented with relevant details. NB. an exclusion criterion in this study was to exclude those for which an OR could not be calculated (~33 studies) - this is acceptable practice for conduct of a meta-analysis, however, the SR is likely at risk of bias - evidence has been omitted on this basis (Q6); Combined analyses for BPA were valid, however, for phthalates and PCBs, the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Golestanzadeh et al. (2019)	N	CA	Y	N	N	Y	Y	N	CA	Y	Y	**5**	No *a priori* protocol (Q1); Not clear about duplicate selection of studies (Q2); no grey literature search undertaken (Q4); no list of excluded studies available (Q5); authors attempted to appraise the quality of included studies, however, they used the STROBE checklist which as reporting guideline and not a critical appraisal tool (Q7); quality of studies not assessed correctly and not used in formulating conclusions (Q8); combined analyses for the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore these results have not been extracted for the

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		review. Where available, results of analysis of individual chemical exposures have been extracted instead. Where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have been extracted and included, assuming these are mutually exclusive subgroups, however, there may be an underestimate of true heterogeneity (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Golestanzadeh et al. (2020)	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	**7**	No a priori protocol (Q1); Not clear about duplicate selection of studies (Q2); no list of excluded studies available (Q5); authors attempted to appraise the quality of included studies, however, they used the STROBE checklist which as reporting guideline and not a critical appraisal tool (Q7); quality of studies not assessed correctly and not used in formulating conclusions (Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Kim et al. (2019)	N	Y	N	N	N	Y	N	N	Y	Y	Y	**5**	No *a priori* protocol (Q1); no supplemental search undertaken (Q3); no grey literature search undertaken (Q4); no list of excluded studies available (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Lee et al. (2018)	N	CA	Y	N	N	Y	Y	Y	Y	Y	Y	**7**	No *a priori* protocol (Q1); Duplicate screening and selection done, however, not clear about duplicate extractions and decisions in extracting data (Q2); no search of grey literature (Q4); no list of excluded studies (Q5); note: Where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have been extracted and included, assuming these are mutually exclusive subgroups, however, there may be underestimate of true heterogeneity (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Li et al. (2017)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	**9**	The overall quality was high, the main concerns were unpublished literature were not searched and a list of excluded studies was not provided by authors. Authors declared no conflict of interest in theory review, but not for individual studies included.
Radke et al. (2020)	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	**8**	The only areas of concern were there was no indication that a source of grey literature was searched (Q4) and there was no list of excluded studies included or referenced by the authors (Q5). There was also no formal assessment of publication bias made by the authors (Q10).
Ribeiro et al. (2019)	N	Y	N	N	N	Y	Y	N	Y	Y	Y	**6**	No *a priori* protocol (Q1); Search was undertaken only in PubMed (Q3); No search of grey literature undertaken (Q4); no list of excluded studies available (Q5); has a table of included studies but no sample/population size available (Q6); authors attempted to appraise the quality of included studies, however, they used the STROBE checklist which as reporting guideline and not a critical appraisal tool (Q7); quality of studies not assessed correctly and not used in formulating conclusions (Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Shoshtari-Yeganeh et al. (2019)	N	Y	N	Y	N	Y	CA	N	N	Y	N	**4**	No *a priori* protocol (Q1); comprehensive range of databases was searched, however, only a few keywords were presented (Q3); no list of excluded studies available (Q5); Cochrane checklist was used to assess study quality but results were not presented and therefore could not be assessed if used appropriately in the findings and recommendations (Q7 & Q8); combined analyses for the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead (Q9); no declarations were made regarding conflicts of interests (Q11).

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Song et al. (2016)	Y	Y	CA	N	N	Y	N	N	Y	Y	Y	**6**	Search was undertaken only in MEDLINE as written in the published paper; however, in the PROSPERO version, both MEDLINE and Embase and reference list were searched (Q3); No search of grey literature (Q4); no list of excluded studies (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8). Note: Multiple subgroups within a study were included within an analysis of individual chemical exposures (BPA, phthalates and PCBs) and these data have been extracted and included, assuming these are mutually exclusive subgroups; however, this may be an underestimate of true heterogeneity (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Wen et al. (2015)	N	CA	Y	Y	N	Y	Y	Y	Y	N	Y	**7**	No *a priori* protocol (Q1); Not clear about decisions in extracting data (Q2); no list of excluded studies available (Q5); combined analyses for BPA, PCBs and total phthalates are appropriate but not for DEHP metabolites; therefore, only the relevant and appropriate data were extracted and used (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Wu et al. (2020)	N	Y	Y	N	N	N	Y	N	CA	Y	Y	**5**	No *a priori* protocol (Q1); No search of grey literature undertaken (Q4); no list of excluded studies available (Q5); details provided in table appear to be bare basics, particularly regarding the exposure; other detail of studies, analyses, adjustments etc. have not been provided (Q6); quality of studies not assessed correctly and not used in formulating conclusions (Q8); provide indication that fixed model was preferred for heterogeneity, however, no indication of cut-off value for this, nor is the model used reported in the results to make any assessment. Assumptions of random effects may be more appropriate. Inclusion of adult/child population from same study in same analyses likely infringes independence of measurements and skews estimate of heterogeneity in some instances (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Zhang et al. (2020)	N	Y	Y	N	N	Y	Y	Y	CA	Y	Y	**7**	No a priori protocol (Q1); No search of grey literature undertaken (Q4); no list of excluded studies available (Q5); combined analyses for the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; only relevant analysis of individual chemical exposures have been extracted (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).

*Legend: Y = Yes, N = No, CA = Can't Answer

Phthalates and birth outcomes

Two reviews explored the association between prenatal exposure to phthalates and their metabolites and birth outcomes in children and the women (Golestanzadeh et al., 2019; H. Zhang et al., 2020). Outcomes reported were birth weight (Golestanzadeh et al., 2019) and spontaneous pregnancy loss (H. Zhang et al., 2020). The reviews included a combination of cohort, case-control and cross-sectional studies.

Quality of the reviews informing birth outcomes was moderate ranging from 5-8/11 in the AMSTAR tool. Both reviews did not have an *a priori* protocol, did not conduct a grey literature search and no list of excluded studies were provided. Golestanzadeh et al. (2019) used STROBE checklist in an attempt to assess the quality of included studies, instead of a legitimate appraisal tool. The overall summary analyses by Golestanzadeh et al. (2019) were considered invalid and therefore not included in this report, furthermore β coefficients and z transformed correlation coefficients have been used interchangeably in analyses. The data from individual studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits. Therefore, where available, results of analysis of individual chemical exposures have been included in this report. Where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have also been included in this report, assuming these are mutually exclusive subgroups. The review by Zhang et al. (2020) did not have identifiable issues with the analyses.

Of the phthalate metabolites investigated, only MEP was found to be associated with a decrease in birth weight, whilst the other phthalate metabolites, MMP, MnBP, MBzP, and ΣDEHP were not found to be associated. There were no associations between phthalate metabolites MMP, MEP, MiBP, MBzP and the DEHP metabolite, MECCP and spontaneous pregnancy loss, but MnBP, ΣDEHP and DEHP metabolites MEHP, MEHHP and MEOHP were associated with an increased risk of spontaneous pregnancy loss.

Birth weight

Only one review reported on birth weight (Golestanzadeh et al., 2019). MEP was associated with reduced birth weight (β -10.1g, 95%CI: -18.57g to -1.6g; 3 studies, 4,775 participants). The other phthalate metabolites MMP (β -0.05, 95%CI: -20.99 to 20.90; 2 studies, 4,476 participants), MnBP (β 0.05, 95%CI: -0.51 to 0.62; 4 studies, 5,296 participants), MiBP (β -0.11, 95%CI: -0.87 to 0.65; 2 studies, 820 participants), MBzP (β −2.38, 95%CI: -9.20 to 3.53; 3 studies, 4,294 participants) and **Σ**DEHP (β 3.85, 95%CI: −17.8 to 25.6; 4,604 participants) and DEHP metabolites MEHP (β −0.79, 95%CI: − 3.84 to 2.62; 4 studies, 4,461 participants), MEHHP (β −0.16, 95%CI: −1.27 to 0.9; 5 studies, 5,424 participants), MEOHP (β −0.39, 95%CI: −12.9 to 12.13; 5 studies, 5,424 participants) and MECPP (β 16.15,95%CI: −18.3 to 50.58; 3 studies, 1,822 participants) were not found to be significantly associated with birth weight.

Spontaneous pregnancy loss

Only one review addressed spontaneous pregnancy loss in reproductive women Zhang et al. (2020). The phthalate metabolite MnBP (OR 1.34, 95%CI: 1.04 to 1.72; 7 studies, participants unspecified), ΣDEHP (OR 1.79, 95%CI: 1.27 to 2.53; 3 studies, participants unspecified) and DEHP metabolites, MEHP (OR 1.57, 95%CI: 1.29 to 1.90; 7 studies, participants unspecified), MEHHP (OR 1.59, 95%CI: 1.23 to 2.07; 6 studies, participants unspecified) and MEOHP (OR 1.47, 95%CI: 1.15 to 1.89; 6 studies, participants unspecified) were found to be associated with an increased risk of spontaneous pregnancy loss. There were no associations found between phthalate metabolites MMP (OR 1.54, 95%CI 0.91 to 2.60; 5 studies, participants unspecified), MEP (OR: 1.30, 95%CI 0.84 to 2.03;7 studies, participants unspecified), MiBP (OR 1.31, 95%CI 0.69 to 2.49; 4 studies, participants unspecified) and MBzP (OR 1.10, 95%CI 0.74 to 1.64; 4 studies, participants unspecified) and the DEHP metabolite, MECPP (OR 1.08, 95%CI 0.80 to 1.46; 3 studies, participants unspecified) and spontaneous pregnancy loss.

Phthalates and child reproductive health outcomes

Three reviews explored the association of phthalates and child reproductive outcomes. One review investigated prenatal DEHP exposure and anogenital distance (predominantly determined by measures of anoscrotal distance) in boys (Dorman et al., 2018). The other two reviews investigated postnatal exposure and puberty outcomes in adolescents (Golestanzadeh et al., 2020; Wen et al., 2015). Golestanzadeh et al. (2020) included adolescent boys and girls from 7 to 19 years of age, whilst Wen et al. (2015) only included female children with ages ranging from 0.5 to 11.3 years of age. Onset of puberty outcomes were reported by Golestanzadeh et al. (2020) in terms of abnormal timing of thelarche (breast development), pubarche (pubic hair development in girls and boys), abnormal age of menarche (first menstrual cycle) and testicular volume and by Wen et al. (2015) in terms of precocious puberty (the appearance of secondary sex characteristics before 8 years of age) in girls. Onset before 8 or after 13 years of age were considered as abnormal timing; however, for testicular volume, it was unclear how the outcome was dichotomised by the reviewers. These studies included data from cohort, case-control and cross-sectional studies.

The quality of the reviews informing child reproductive outcomes was moderate, ranging from 7-8/11 with the AMSTAR tool. Of the three reviews, only Dorman et al. (2018) had an *a priori* protocol. All three reviews conducted an extensive search of the literature, however, Dorman et al. (2018) failed to conduct a grey literature search. None of the reviews included the list of excluded studies. None of the included reviews appeared to have identifiable issues with their data analyses.

There was a negative association found between prenatal phthalate exposure (ΣDEHP and MEHP) and AGD in male infants.

DEHP metabolites MEHHP and MEOHP were found to be associated with an increased risk of abnormal timing of thelarche and MnBP, MEHHP and MEOHP were found to be associated with a decreased risk in abnormal timing of pubarche in boys. No associations were found for other phthalate metabolites and DEHP metabolites and puberty outcomes.

DEHP and DEHP serum concentration levels were found to be associated with an increased risk of precocious puberty in girls and in a subgroup of studies conducted in China. No associations were found for DnBP and its metabolite MnBP and the DEHP metabolite, MEHP and precocious puberty in girls. However, serum DnBP concentration levels significantly increased in girls and in subgroup of studies conducted in China.

<u>Anogenital distance</u>

One review explored the association between prenatal ΣDEHP and MEHP exposure (Dorman et al., 2018). There was a negative association between phthalate exposure and anogenital distance in male infants (β -4.07, 95%CI: -6.49 to -1.66; 5 studies, participants unspecified; % change per log10 change ΣDEHP).

<u>Onset of puberty</u>

Two reviews explored the association between postnatal exposure to individual phthalate metabolites and outcomes related to the onset of puberty (Golestanzadeh et al., 2020; Wen et al., 2015).

Abnormal timing of thelarche (breast development)

Golestanzadeh et al. (2020) found urinary MEHHP (OR 1.48, 95%CI: 1.11 to 1.85; 2 studies, 387 participants) and urinary MEOHP (OR 1.52, 95%CI: 1.15, 1.88; 2 studies, 387 participants) were associated with an increased risk of thelarche in girls. No association was found for the following urinary phthalate metabolites: MMP (OR 0.84,95%CI: 0.67 to 1.01; 3 studies, 609 participants), MEP (OR 0.82, 95%CI: 0.6 to 1.05; 3 studies, 609 participants) and MEHP (OR 1.16, 95%CI: 0.73 to 1.59; 3 studies, 609 participants).

Abnormal timing of pubarche in girls

Golestanzadeh et al. (2020) found no association between the following urinary phthalate metabolites and abnormal timing of pubarche in girls: MMP (OR 0.95, 95% CI: 0.77 to 1.14; 3 studies, 609 participants), MEP (OR 0.99, 95%CI: 0.81 to 1.17; 3 studies, 609 participants), MnBP (OR 0.88, 95% CI: 0.59 to 1.16, 2 studies, 423 participants), MEHP (OR 0.91, 95CI: 0.74 to 1.08, 3 studies, 609 participants), MEHHP (OR 0.96, 95% CI: 0.59 to 1.13; 2 studies, 387 participants) and MEOHP (OR 0.95 95% CI: 0.66 to 1.23; 2 studies, 387 participants).

Abnormal age of menarche

Golestanzadeh et al. (2020) found no association between the following urinary phthalate metabolites and abnormal age of menarche: MMP (OR 0.89, 95%CI: 0.68 to 1.10; 3 studies, 609 participants), MEP (OR 0.89, 95%CI: 0.62 to 1.16;3 studies, 609 participants), MnBP (OR 1.01, 95%CI: 0.06 to 1.96; 2 studies, 423 participants), MEHP (OR 0.89, 95%CI: 0.66 to 1.11; 3 studies, 609 participants), MEHHP (OR 1.07, 95%CI: 0.14 to 2.01; 2 studies, 387 participants) and MEOHP (OR 1.08, 95% CI:0.19 to 1.98, 2 studies, 387 participants).

Abnormal timing of pubarche in boys

Golestanzadeh et al. (2020) found urinary MnBP (OR 0.66, 95%CI: 0.39 to 0.93; 2 studies, 423 participants), MEHHP (OR 0.61, 95%CI: 0.32 to 0.91; 2 studies, 387 participants) and MEOHP (OR 0.61, 95%CI: 0.26 to 0.97; 2 studies, 387 participants) were associated with an decreased risk in abnormal pubarche in boys. No association was found for the following urinary phthalate metabolites: MMP (OR 0.63, 95% CI: 0.23 to 1.03; 4 studies, 727 participants), MEP (OR 1.01, 95%CI: 0.85 to 1.19; 3 studies, 609 participants) and MEHP (OR 0.89, 95%CI: 0.62 to 1.16; 3 studies, 609 participants).

Testicular volume levels

Golestanzadeh et al. (2020) found no association between the following urinary phthalate metabolites and testicular volume levels: MMP (OR 1.01, 95%CI: 0.59 to 1.44; 3 studies, 505 participants), MEP (OR 0.99, 95%CI: 0.77 to 1.21; 2 studies, 387 participants), MEHP (OR 1.13, 95%CI: 0.88 to 1.37; 2 studies, 387 participants) and MEHHP (OR 0.79, 95%CI: 0.44 to 1.14; 2 studies, 387 participants)

Precocious puberty

Wen et al. (2015) reported that serum DEHP was associated with an increased risk in precocious puberty in girls (OR 4.09, 95%CI: 2.3 to 7.3; 7 studies, 1,390 participants), The serum concentration of DEHP in the girls with precocious puberty was higher than those in the control group (SMD 1.73, 95%: 0.54 to 2.91; 7 studies, 1,564 participants). In a subgroup of studies conducted in China, serum DEHP was associated with an increased risk in precocious puberty (OR 3.58, 95%CI:1.97 to 6.49; 6 studies, 1,324 participants). The serum concentration of those with precocious puberty was higher than those in the control group in the subgroup of Chinese studies (SMD 2.13, 95%CI 0.86 to 3.4; 6 studies, 1,324 participants). No association was found for exposure to DnBP (OR 3.26, 95%CI: 0.69 to 15.42; 5 studies, 1,149 participants) and even in a subgroup of studies conducted in China (OR 2.74, 95%CI:0.51 to 14.79, 4 studies, 1,083 participants); however, the serum concentration levels for both were significant: DnBP SMD 4.31, 95%CI: 2.67 to 5.95; 5 studies, 1,323 participants and DnBP in subgroup SMD 6.33, 95%CI: 4.09 to 8.57; 4 studies, 1,083 participants. No association was found for serum concentration levels of metabolites MnBP (SMD 0.01, 95%CI: -0.3 to 0.27; 3 studies, 774 participants) and MEHP (SMD 0.18, 95%CI: -0.99 to 1.36; 4 studies, 895 participants) and MEHP in a subgroup of studies conducted in China (SMD 1.38, 95%CI: -1.35 to 4.11; 2 studies, 599 participants). No associations were found for urinary concentration levels of the following metabolites and precocious puberty: MMP in studies conducted in China (SMD 0.27, 95%CI: -0.21 to 0.76; 3 studies, 211 participants), MEP (SMD 0.73, 95%CI: -0.40 to 1.86; 3 studies, 360 participants) and MEP in subgroup of studies conducted in China (SMD 0.16, 95%CI: -0.19, 0.50; 2 studies, 152 participants), MnBP (SMD -0.11, 95%CI: -0.48 to 0.26; 3 studies, participants unspecified) and MnBP in subgroup of studies conducted in China (SMD -0.21, 95%CI: -0.87 to 0.46; 2 studies, participants unspecified), MBzP (SMD 0.00, 95%CI: -0.43 to 0.43; 4 studies, 419 participants) and MBzP in subgroup of studies conducted in

China (SMD -0.04, 95%CI: -0.68, 0.59; 3 studies, 211 participants) and MEHP in studies conducted in China (SMD -0.44, 95%CI: -1.18 to 0.29; 3 studies, participants unspecified).

Phthalates and adult reproductive health outcomes

Two reviews included data exploring the association between phthalate exposure and reproductive health outcomes. One review included outcomes related to female reproductive health (Cai et al., 2019) and one on male reproductive health (Cai et al., 2015). The female reproductive health outcome reported was endometriosis. Outcomes pertinent to male reproductive health included sperm concentration, sperm motility, sperm morphology, sperm volume, sperm motion (straight-line velocity), sperm motion (curvilinear velocity), sperm motion (linearity), comet assay (comet extent), comet assay (% DNA in tails), and comet assay (tail distributed moment). The majority of studies included in Cai et al. (2015) included sub fertile males as their eligible population as well as a subset of studies that included healthy males of reproductive age. Female and male reproductive health outcomes have been separated below. These reviews contained data from cohort, case-control and cross-sectional studies.

Quality of the three reviews informing reproductive outcomes was moderate, with scores on the AMSTAR tool ranging from 6-7/11. No reviews were informed by an *a priori* protocol. There were concerns about the search strategy and source selection in all articles, these ranged from not using MESH terms, no grey literature searching, to not enough information provided to determine if duplicate search or selection occurred. None of the reviews had a list of excluded studies. Wen et al. (2015) conducted combined analyses for BPA, PCBs and total phthalates, which were appropriate but not appropriate for the DEHP metabolites due to repeated use of data from studies in the analyses; therefore, only the relevant data were extracted and reported in this review. There were no concerns with the analyses by Cai et al. (2015) and Cai et al. (2019) in their reviews. No reviews included conflict of interest for individual studies.

Results suggest an increased risk of endometriosis with the DEHP metabolite, MEHHP. No association was observed for any of the phthalate metabolites MEP, MBzP, MEHP and MEOHP and endometriosis. There is evidence that some phthalate metabolites may affect outcomes indicative of semen quality. However, it is important to note that in the majority of included studies, subfertile males were included in the populations of these reviews.

Female reproductive health outcomes

<u>Endometriosis</u>

One review explored the association between exposure to phthalate metabolites (exposure measure not specified) and incidence of endometriosis (Cai et al., 2019). Cai et al. (2019) reported an increased risk in endometriosis and MEHHP (OR 1.25, 95% CI 1.003 to 1.55; 6 studies, participants unspecified) but not with MEP (OR 1.073, 95%CI: 0.90 to 1.28; 6 studies, participants unspecified), MBzP (OR 0.976; 95%CI: 0.810 to 1.176; 7 studies, participants unspecified), MEHP (OR 1.089, 95% CI 0.858 to 1.383; 7 studies, participants unspecified) and MEOHP (OR 1.282, 95%CI: 0.874 to 1.88; 6 studies, participants unspecified).

Male reproductive health outcomes

One review reported on the association between various surrogate outcomes indicative of sperm quality and phthalate metabolites (Cai et al., 2015). The included review presented analyses for the metabolites according to medium and high levels of exposure. The association between phthalate metabolite exposure and risk of reduced or low parameters (odds ratio; OR) indicative of semen quality were compared to a reference value in men at or above a sperm concentration of $\geq 20 \times 10^6$ *m*L, motility of ≥ 50% motile, and morphology of ≥ 4% normal morphology. Pooled regression and correlation coefficients were used to assess measures of sperm motion and DNA damage. This review included subfertile males of reproductive age who were currently involved in infertility workups.

<u>Low sperm concentration</u>

MMP

No association was reported between medium urinary MMP levels of 1.5-9.0 µg/L (OR 0.89, 95%CI: 0.48 to 1.67; 6 studies, participants unspecified), nor high urinary MMP levels of 9.0-745.0 µg/L (OR 0.96, 95% CI: 0.28–3.29; 6 studies, participants unspecified), and reduced sperm concentration.

MEP

No association was found between medium urinary MEP levels of 3.3-49.8 µg/L (OR 0.84, 95%CI: 0.43 to 1.63; 6 studies, participants unspecified), nor high urinary MEP levels of 77.2-11371 µg/L (OR 1.42, 95%CI: 0.84 to 2.42; 6 studies, participants unspecified), and low sperm concentration.

MnBP

Medium urinary MnBP levels of 7.4-25.3 µg/L were positively associated with decreased sperm concentration (OR 2.6, 95%CI: 1.32 to 5.15, 3 studies, participants unspecified). Similarly, high urinary MnBP levels of 26.0-14459.0 µg/L were positively associated with decreased sperm concentration (OR 2.39, 95%CI: 1.26 to 4.53, 5 studies, participants unspecified). There was no association observed between urinary MnBP levels and sperm concentration using regression analysis (β 0.04, 95%CI: -0.45 to 0.54, 3 studies, participants unspecified).

MBzP

No association was reported between medium urinary MBzP levels of 0-14.0 µg/L and decreased sperm concentration (OR 1.24, 95%CI: 0.67 to 2.29, 6 studies, participants unspecified). However, high urinary MBzP levels of 14-540.2 µg/L were positively associated with decreased sperm concentration (OR 2.23, 95%OR: 1.16 to 4.30, 3 studies, participants unspecified).

ΣDEHP

No association was found between medium urinary ΣDEHP levels of 23.2–79.5 µg/L (OR 1.20, 95%CI: 0.74 to 1.94; 6 studies, participants unspecified), nor high urinary ΣDEHP levels of 79.5–8744.8 µg/L (OR 1.32, 95%CI: 0.62 to 2.80; 6 studies participants unspecified), and low sperm concentration.

MEHP

No association was found between medium urinary MEHP levels of 0.4–1.9 µg/L (OR 8.00, 95%CI: 1.00 to 60.30; 6 studies, participants unspecified) nor high urinary MEHP levels of 3.8–875.8 µg/L and reduced sperm concentration (OR 0.99, 95% CI: 0.64 to 1.54; 6 studies, participants unspecified). In addition, regression analysis suggested no association between urinary MEHP levels and sperm concentration (β -0.01, 95%CI: -0.17 to 0.17, 3 studies, participants unspecified).

MEOHP

No association was reported between medium urinary MEOHP levels of 1.9–30.6 µg/L (OR 1.66, 95% CI: 0.50 to 5.50; 6 studies, participants unspecified), nor high MEOHP levels of 32.1–3063.0 µg/L (OR 1.30, 95%CI: 0.45 to 3.75; 6 studies, participants unspecified) and low sperm concentration.

MEHP and MEOHP (combined)

No association was found between combined medium urinary MEHP and MEOHP levels of 2.2–84.2 µg/L and reduced sperm concentration (OR=1.16, 95%CI: 0.67 to 2.03; 6 studies, participants unspecified). Similarly, no association between combined high urinary MEHP and MEOHP levels of 93.9–3,938.8 µg/L and low sperm concentration (OR 0.94, 95%CI: 0.48 to 1.81; 6 studies, participants unspecified).

<u>Low sperm motility</u>

DnBP

DnBP in semen was negatively associated with decreased sperm motility (β -0.19, 95%CI: -0.28 to -0.1; 2 studies, participants unspecified).

MMP

No association was reported between medium urinary MMP levels of 1.5-9.0 µg/L (OR 1.13, 95%CI: 0.53 to 2.39; 6 studies participants unspecified), nor high urinary MMP levels of 9.0-745.0 µg/L (OR 0.71, 95%CI: 0.39 to 1.32, 6 studies, participants unspecified) and low sperm motility.

MEP

No association was reported between medium urinary MEP levels of 3.3-49.8 µg/L (OR 0.77, 95%CI: 0.30 to 1.96; 6 studies participants unspecified), nor high urinary MEP levels of 77.2-1,1371 µg/L and low sperm motility (OR 0.89, 95%CI: 0.59 to 1.32; 6 studies, participants unspecified).

MnBP

No association was found between medium urinary MnBP levels of 7.4-25.3 µg/L (OR 1.16, 95%CI: 0.58 to 2.34; 3 studies, participants unspecified), nor high urinary MnBP levels of 26.0-14,459.0 µg/L (OR 1.35, 95%CI: 0.86 to 2.11, 5 studies, participants unspecified) and low sperm motility.

MBzP

No association was found between medium urinary MBzP levels of 0-14.0 µg/L (OR 1.20, 95%CI: 0.78 to 1.84; 6 studies, participants unspecified), nor urinary MBzP levels of 14-540.2 µg/L (OR 1.47, 95%CI: 0.91 to 2.36, 3 studies, participants unspecified) and low sperm motility.

ΣDEHP

No association was found between medium urinary ΣDEHP levels of 23.2–79.5 µg/L and low sperm motility (OR 1.01, 95%CI: 0.57 to 1.78; 6 studies, participants unspecified). There was no association between high urinary ΣDEHP levels of 79.5–8744.8 µg/L and low sperm motility (OR 0.88, 95%CI: 0.57 to 1.37; 6 studies, participants unspecified).

DEHP

Seminal DEHP levels were negatively associated with decreased sperm motility (β -0.21, 95%CI: -0.3 to - 0.12; 2 studies, participants unspecified).

MEHP

No association was reported between medium urinary MEHP levels of 0.4–1.9 µg/L and low sperm motility (OR 0.70, 95%CI: 0.20 to 2.00; 6 studies, participants unspecified). There was no association between high urinary MEHP levels of 3.8–875.8 µg/L and reduced sperm motility (OR 1.17, 95%CI: 0.78 to 1.76; 6 studies, participants unspecified). In addition, regression analysis suggested no association between urinary MEHP levels and sperm motility in males of reproductive age (β 94.62, 95%CI: -176.54 to 365.77; 3 studies, participants unspecified).

MEOHP

No association was reported between medium urinary MEOHP levels of 1.9–30.6 µg/L and low sperm motility (OR 0.84, 95%CI: 0.47 to 1.50; 6 studies, participants unspecified). Similarly, no association was found between high urinary MEOHP levels of 32.1–3063.0 µg/L and low sperm motility (OR 0.66, 95%CI: 0.33 to 1.31; 6 studies, participants unspecified).

MEHP and MEOHP

No association was reported between medium urinary MEHP and MEOHP levels of 2.2–84.2 µg/L and low sperm motility (OR 0.94, 95% CI:0.62–1.43; 6 studies, participants unspecified). No association was found between high urinary MEHP and MEOHP levels of 93.9–3938.8 µg/L and low sperm motility (OR 0.99, 95%CI: 0.62 to 1.60; 6 studies, participants unspecified).

<u>Low sperm morphology</u>

MMP

No association was found between medium urinary MMP levels of 1.5-9.0 µg/L (OR 0.78, 95% CI: 0.43 to 1.40; 6 studies, participants unspecified), nor high urinary MMP levels of 9.0-745.0 µg/L (OR 0.84, 95%CI: 0.44 to 1.60; 6 studies, participants unspecified) and low sperm morphology.

MEP

No association was found between medium urinary MEP levels of 3.3-49.8 µg/L (OR 0.88, 95%CI: 0.44 to 1.75; 6 studies, participants unspecified), nor high urinary MEP levels of 77.2-11371 µg/L and low sperm morphology (OR 1.21, 95%CI: 0.42 to 3.42; 6 studies, participants unspecified).

MnBP

No association was reported between medium urinary MnBP levels of 7.4-25.3 µg/L and low sperm morphology (OR 1.00, 95%CI: 0.59 to 1.71; 2 studies, participants unspecified). Similarly, no association was found between high urinary MnBP levels of 26 -14,459.08 µg/L and low sperm morphology (OR 1.43, 95%CI: 0.83 to 2.47; 4 studies, participants unspecified).

MBzP

No association was found between medium urinary MBzP levels of 0-14.0 µg/L (OR 0.70, 95%CI: 0.38 to 1.28; 6 studies, participants unspecified), nor high urinary MBzP levels of 14-540.2 µg/L and low sperm morphology (OR 1.27, 95%CI: 0.77 to 2.08, 3 studies, participants unspecified).

ΣDEHP

No association was reported between medium urinary ΣDEHP levels of 23.2–79.5 µg/L and low sperm morphology (OR 1.28, 95%CI: 0.85 to 1.93; 6 studies, participants unspecified). Similarly, no association was found between high urinary **Σ**DEHP levels of 79.5–8744.8 µg/L and low sperm morphology (OR 1.10, 95% CI: 0.54 to 2.25; 6 studies, participants unspecified).

MEHP

No association was found between high urinary MEHP levels of 3.8–875.8 µg/L and low sperm morphology (OR 1.00, 95%CI: 0.66 to 1.51; 6 studies, participants unspecified). In addition, no linear association between urinary MEHP and sperm morphology was observed (β 0.19, 95%CI: -0.40 to 0.79; 3 studies, participants unspecified).

MEOHP

No association was reported between medium urinary MEOHP levels of 1.9–30.6 µg/L (OR 1.40, 95%CI: 0.50 to 3.70; 6 studies, participants unspecified), nor high urinary MEOHP levels of 32.1–3063.0 µg/L (OR 0.59, 95%CI: 0.26 to 1.33; 6 studies, participants unspecified) and low sperm morphology.

<u>Low semen volume</u>

MnBP

No association was reported between high urinary MnPB levels of 26.0-14459.0 µg/L and low semen volume (OR 0.80, 95%CI: 0.26 to 2.40; 2 studies, participants unspecified).

<u>Sperm motion (straight-line velocity)</u>

MMP

No association was found between medium urinary MMP levels of 1.5–8.3 µg/L (β -0.14 µm/s, 95%CI: -1.76 to 1.49; 3 studies, participants unspecified), nor high urinary MMP levels of 8.3–278.1 µg/L (β 0.79 µm/s, 95%CI: -1.29 to 2.88; 3 studies, participants unspecified) and straight-line velocity.

MEP

No association was reported between medium urinary MEP levels of 59.6–979.5 µg/L and straight-line velocity (β 0.12µm/s, 95%CI: -0.88 to 1.12; 3 studies, participants unspecified). There was a significant association between exposure to high urinary MEP levels of 979.5–11,371.0 µg/L (β 2.36µm/s, 95%CI: 0.28 to 4.45; 3 studies, participants unspecified) and increased straight-line velocity.

MnBP

No association was found between medium urinary MnBP levels of 10.3–24.6 µg/L and straight-line velocity (β -1.48 µm/s, 95%CI: -3.87 to 0.92; 3 studies, participants unspecified). There was a significant association between exposure to high urinary MnBP levels of 24.6–14,459.0 µg/L and decreased straight-line velocity (β -2.51 µm/s, 95%CI: -4.44 to -0.59; 3 studies, participants unspecified).

MBzP

No association was reported between medium urinary MBzP levels of 4.2–64.2 µg/L and straight-line (β -0.42 µm/s, 95%CI: -1.39 to 0.55; 3 studies, participants unspecified). Similarly, no association was found between high urinary MBzP levels of 64.2–540.2 µg/L and straight-line velocity (β -1.93 µm/s, 95%CI: -3.98 to 0.12; 3 studies, participants unspecified).

MEHP

There was a significant association between medium urinary MEHP levels of 3.1–208.1 µg/L and decreased straight-line velocity (β -1.06 µm/s, 95%CI: -1.99 to -0.12; 3 studies, participants unspecified). However, no association was found between high urinary MEHP levels of 208.1–875.8 µg/L and straight-line velocity (β -1.76 µm/s, 95%CI: -3.83 to 0.31; 3 studies, participants unspecified).

Sperm motion (curvilinear velocity)

MMP

No association was found between medium urinary MMP levels of 1.5–8.3 µg/L and curvilinear velocity (β -1.54 µm/s, 95%CI: -4.31 to 1.24; 3 studies, participants unspecified). Similarly, no association was reported between high urinary MMP levels of 8.3–278.1 µg/L and curvilinear velocity (β 0.18 µm/s 95%CI: -3.39 to 3.74; 3 studies, participants unspecified).

MEP

No association was reported between medium urinary MEP levels of 59.6–979.5 µg/L and curvilinear velocity (β -0.21 µm/s, 95%CI: -1.80 to 1.38; 3 studies, participants unspecified). However, there was a significant association between high urinary MEP levels of 979.5–11,371.0 µg/L and increased curvilinear velocity (β 5.23 µm/s, 95%CI: 1.67 to 8.80; 3 studies, participants unspecified).

MnBP

No association was found between medium urinary MBP levels of 10.3–24.6 µg/L and curvilinear velocity (β -2.60 µm/s, 95%CI: -5.40 to 0.19 µm/s; 3 studies, participants unspecified). However, there was a significant association between high urinary MBP levels 24.6–14,459.0 µg/L and decreased curvilinear velocity (β = -3.81µm/s, 95%CI: -6.74 to -0.87; 3 studies, participants unspecified).

MBzP

No association was reported between medium urinary MBzP levels of 4.2–64.2 µg/L and curvilinear velocity (β -0.44 µm/s, 95%CI: -1.94 to 1.07; 3 studies, participants unspecified). Similarly, no association was found between high urinary MBzP levels of 64.2–540.2 µg/L and curvilinear velocity (β -1.70 µm/s, 95%CI: -5.21 to 1.82; 3 studies, participants unspecified).

MEHP

No association was found between medium urinary MEP levels of 3.1–208.1 µg/L (β -1.48 µm/s, 95%CI: -2.99 to 0.03; 3 studies, participants unspecified), nor high urinary MEHP levels of 208.1–875.8 µg/L (β -2.41 µm/s, 95%CI: -5.96 to 1.15; 3 studies, participants unspecified), and curvilinear velocity.

Sperm motion (linearity)

MMP

No association was found between medium urinary MMP levels of 1.5–8.3 µg/L and linearity (β 0.99 µm/s 95%CI: -0.17 to 2.14; 3 studies, participants unspecified), nor high urinary MMP levels of 8.3–278.1 µg/L (β 0.93 µm/s 95%CI: -0.61 to 2.47; 3 studies, participants unspecified) and linearity.

MEP

No association was reported between medium urinary MEP levels of 59.6–979.5 µg/L and linearity (β 0.01 µm/s, 95%CI: -0.82 to 0.85; 3 studies, participants unspecified). Similarly, no association between was found between high urinary MEP levels of 979.5–11,371.0 µg/L and linearity (β -0.44 µm/s, 95%CI: -1.94 to 1.04; 3 studies, participants unspecified).

MnBP

No association was reported between medium urinary MnBP levels of 10.3–24.6 µg/L (β -0.14 µm/s, 95%CI: -2.64 to 2.36; 3 studies, participants unspecified), nor high urinary MBP levels of 24.6–14,459.0 µg/L (β -0.70 µm/s, 95%CI: -2.46 to 1.07; 3 studies, participants unspecified) and linearity.

MBzP

No association was found between medium urinary MBzP levels of 4.2–64.2 µg/L and linearity (β -0.22 µm/s, 95%CI: -0.81 to 0.38 µm/s; 3 studies, participants unspecified). Similarly, no association was found between high urinary MBzP levels of 64.2–540.2 µg/L and linearity (β -1.05 µm/s, 95%CI: -2.51 to 0.40; 3 studies, participants unspecified).

MEHP

There was a significant association between medium urinary MEHP levels of 3.1–208.1 µg/L and decreased linearity (β -0.43 µm/s, 95%CI: -0.80 to -0.06; 3 studies, participants unspecified). No association was found between high urinary MEHP levels of 208.1–875.8 µg/L and linearity (β -0.43 µm/s, 95%CI: -1.90 to 1.05; 3 studies, participants unspecified).

Sperm DNA damage - COMET ASSAY (comet extent)

MMP

No association was reported between urinary MMP levels (IQR 8.85 µg/L) and comet extent (β -2.08, 95%CI: -10.89 to 6.73; 2 studies, participants unspecified).

MEP

A significant association was found between urinary MEP levels (IQR 449.4 µg/L) and increased comet extent (β 4.22, 95%CI: 1.66 to 6.77; 2 studies, participants unspecified).

MnBP

No association was reported between urinary MnBP levels (IQR 20.75 µg/L) and comet extent (β -0.30, 95% CI: -0.79 to 0.19; 2 studies, participants unspecified).

MBzP

A significant association was found between urinary MBzP levels (IQR 11.35 µg/L) and increased comet extent (β 3.57, 95% CI: 0.89 to 6.25; 2 studies, participants unspecified).

MEHP

No association was reported between urinary MEHP levels (IQR 14.35 µg/L) and comet extent (β -0.16, 95%CI: -1.45 to 1.13; 2 studies, participants unspecified).

Sperm DNA damage - COMET ASSAY (% DNA in tail)

MMP

No association was reported between urinary MMP levels (IQR 8.85 µg/L) and %DNA in tail (β -2.44, 95%CI: -7.16 to 2.29; 2 studies, participants unspecified).

MEP

No association was reported between urinary MEP levels (IQR 449.4 µg/L) and %DNA in tail (β -0.18, 95%CI: -0.79 to 0.44; 2 studies, participants unspecified).

MnBP

No association was reported between urinary MnBP levels (IQR 20.75 µg/L) and %DNA in tail (β 0.64, 95%CI: -0.94 to 2.23; 2 studies, participants unspecified).

MBzP

No association was reported between urinary MBzP levels (IQR 11.35 µg/L) and %DNA in tail (β 0.05, 95% CI: -0.38 to 0.48; 2 studies, participants unspecified).

MEHP

No association was reported between urinary MEHP levels (IQR 14.35 µg/L) and %DNA in tail (β 1.40, 95%CI: -1.60 to 4.40; 2 studies, participants unspecified).

Sperm DNA damage - COMET ASSAY (tail distributed moment)

MMP

No association was reported between urinary MMP levels (IQR 8.85 µg/L) and tail distributed moment (β 0.31, 95%CI: -1.23, to 1.84; 2 studies, participants unspecified).

MEP

A significant association was found between urinary MEP levels (IQR 449.4 µg/L) and increased tail distributed moment (β 1.64, 95%CI: 0.24 to 3.03; 2 studies, participants unspecified).

MnBP

No association was reported between urinary MnBP levels (IQR 20.75 µg/L) and tail distributed moment (β -0.122, 95% CI: -0.32 to 0.08; 2 studies, participants unspecified).

MBzP

A significant association was found between urinary MBzP levels (IQR 11.35 µg/L) and increased tail distributed moment (β 1.72, 95%CI: 0.33 to 3.12; 2 studies, participants unspecified).

MEHP

No association was reported between urinary MEHP levels (IQR 14.35 µg/L) and tail distributed moment (β 0.01, 95%CI: -0.53 to 0.54; 2 studies, participants unspecified).

Phthalates and endocrine and metabolic outcomes

Three reviews explored the association between exposure to phthalates and metabolic or endocrine outcomes (M. J. Kim et al., 2019; Shoshtari-Yeganeh et al., 2019; Song et al., 2016). The outcomes included were insulin resistance, measured using the Homeostatic Model Assessment (HOMA-IR), fasting glucose, incidence of type 2 diabetes and thyroid function. Kim et al. (2019) and Shoshtari-Yeganeh et al. (2019) reported on a general population of children and adults and Song et al. (2016) reported on adults only. Kim et al. (2019)also included pregnant women in the review general population. Shoshtari-Yeganeh et al. (2019) and Song et al. (2016) conducted analyses on exposure to phthalates and phthalate metabolites, while Kim et al. (2019) focused on DEHP metabolites. These reviews included data from cohort, case-control and cross-sectional studies.

Quality of the reviews informing metabolic outcomes was poor to moderate, with scores on the AMSTAR ranging from 4-6/11. Shoshtari-Yeganeh et al. (2019) and Kim et al. (2019) were not informed by an *a priori* protocol and search strategies of both reviews were limited to key words only. Kim et al. (2019) and Song et al. (2016) did not report any critical appraisal, whilst Shoshtari-Yeganeh et al. (2019) stated that they did conduct quality assessment; however, the results could not be located in either report or supplementary information. No reviews included a list of excluded studies. Kim et al. (2019) conducted analyses of pooled correlation coefficients that were first z transformed for analyses and subsequently converted back to values of Pearson's r. The combined analyses by Shoshtari-Yeganeh et al. (2019) for the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting of same participants), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted and included. Shoshtari-Yeganeh et al. (2019) also conducted separate analyses for phthalate metabolite MBP and MnBP and which are identical as acknowledged in the review. The difference in the results cannot be explained and therefore, these results have not been extracted for the review.

Only MiBP was associated with an increased risk of type 2 diabetes and no association was found for total phthalates and MEP in the adult population. No association was found for total phthalates and

fasting glucose in adults. There was evidence of positive association between total phthalates, MiBP, MBzP, ΣDEHP, MEHP, MEOHP, MECPP and MCPP and HOMA-IR, but not with, MMP, MEP and MEHPP. Urinary MEHHP was negatively associated with fT4 in the general population of children and adults and adults alone, and positively associated with fT4 in children. MEOHP was positively associated with TT4 in children and none of the DEHP metabolites investigated (MEHP, MEHHP, MEOHP) were associated with TSH.

Type 2 diabetes

The review by Song et al. (2016) found MiBP to be associated with an increased risk of type 2 diabetes (RR 1.90, 95%CI: 1.17 to 3.09; studies unspecified, participants unspecified). No association was found for total phthalates (RR 1.48, 95%CI: 0.98 to 2.25; 4 studies, 5,307 participants) nor MEP (RR 1.39, 95%CI: 0.55 to 3.48; 4 studies, participants unspecified).

Fasting glucose

One review reported no association for total phthalates between highest (>17.5 ng/mL) and lowest (≤7.2 ng/mL) concentration (MD 0.98 mg/dL, 95% CI 0.00 to 1.97 mg/dL; 3 studies, 3926 participants) (Song et al., 2016).

Insulin resistance (HOMA-IR)

Two reviews explored the association between exposure to total phthalates and specific phthalate metabolites and insulin resistance (Shoshtari-Yeganeh et al., 2019; Song et al., 2016). Song et al. (2016) found a significant association between total phthalates and increased insulin resistance (WMD 0.71, 95% CI 0.30 to 1.12; 4 studies, 5396 participants). Shoshtari-Yeganeh et al. (2019) found positive associations for MiBP (β 0.10, 95%CI: 0.03 to 0.17; 4 studies, 6569 participants), MBzP (β 0.05, 95%CI: 0.01 to 0.10; 5 studies, 11439 participants), ΣDEHP (β 0.26, 95%CI 0.15 to 0.38; 2 studies 4997 participants), MEHP (β 0.08, 95%CI: 0.03 to 0.12; 7 studies, 13248 participants), MEOHP (β 0.10, 95%CI: 0.01 to 0.19; 5 studies, 7,795 participants), MECPP (β 0.16, 95%CI: 0.05 to 0.27; 2 studies, 1122 participants and MCPP (β 0.15, 95%CI: 0.03 to 0.28; 3 studies, 1,908 participants). No association was found for MMP (β 0.02, 95%CI: -0.06, 0.11; 3 studies, 2,158 participants), MEP (β 0.02, 95%CI: -0.04 to 0.08; 6 studies, 12455 participants) and MEHHP (β 0.09, 95%CI: -0.01 to 0.18; 5 studies, 7,795 participants). *Note, MnBP findings were not included because Shoshtari-Yeganeh et al.* (2019) *reported for MnBP and MBP separately.*

Thyroid function

One review explored the association between thyroid function and urinary DEHP metabolites, MEHP, MEHHP and MEOHP (M. J. Kim et al., 2019). This review also included three different measures of thyroid function; concentrations of free thyroxine (fT4), total thyroxine (TT4) and Thyrotropin/thyroid stimulating hormone (TSH).

Free thyroxine fT4

No associations were found with urinary MEHP (r -0.02, 95%CI: -0.05 to 0.00; 10 studies, 4673 participants). When grouped based on age and pregnancy status there was no association found for children (r 0.03, 95%CI: -0.01 to 0.08; 6 studies, 1,832 participants), adults (r -0.03, 95%CI: -0.14 to 0.07; 2 studies, 1,829 participants) or pregnant women (r -0.04, 95%CI: -0.07 to 0.00; 4 studies, 2841 participants).

Urinary MEHHP was found to have a negative association with concentration of fT4 (r -0.03, 95%CI: -0.05 to -0.01; 10 studies, 10,601 participants). When grouped based on age and pregnancy status there was a positive association for children (r 0.06, 95%CI: 0.01 to 0.10; 6 studies, 1,832 participants) a negative association for adults (r -0.08, 95%CI: -0.14 to -0.01; 3 studies, 7,832 participants) but no association for pregnant women when considered alone (r -0.04, 95%CI: -0.08 to 0.00; 3 studies, 2,766 participants).

There was no association between urinary MEOHP and concentration of fT4 (r -0.01, 95%CI: -0.03 to 0.01; 10 studies, 10,601 participants). When grouped based on age and pregnancy status, there was

no association for children (r 0.05, 95%CI: 0.00 to 0.10; 6 studies, 1,832 participants), adults (r -0.05, 95%CI: -0.10 to 0.01; 3 studies, 7,832 participants) or pregnant women (r 0.02, 95%CI: -0.05 to 0.10; 3 studies, 2,766 participants).

Total thyroxine (TT4)

No association was found between urinary MEHP and concentration of TT4 (r 0.01, 95%CI: -0.03 to 0.06; 13 studies, 5097 participants). When grouped based on age and pregnancy status there was no association found for children (r 0.02, 95%CI: -0.04 to 0.07; 7 studies, 2,061 participants), adults (r -0.04, 95%CI: -0.08 to 0.01; 4 studies, 2024 participants) or pregnant women (r -0.01, 95%CI: -0.13 to 0.11; 4 studies, 2,841 participants).

No association was found between urinary MEHHP and concentration of TT4 (r 0.03, 95%CI: -0.01 to 0.08; 11 studies, 10,830 participants). When grouped based on age and pregnancy status there was no association for children (r 0.04, 95%CI: 0.00 to 0.09; 7 studies, 2061 participants), or adults (r 0.00, 95%CI: -0.02 to 0.03; 3 studies, 7,832 participants) and pregnant women (r -0.00, 95%CI: -0.19 to 0.19; 3 studies, 2,766 participants).

Urinary MEOHP had no association with concentration of TT4 (r 0.02, 95%CI: 0.00 to 0.04; 11 studies, 10,830 participants) across the general population. When grouped based on age and pregnancy status, there was a positive association for children (r 0.05, 95%CI: 0.01 to 0.10; 7 studies, 2,061 participants), but no association for adults (r 0.01, 95%CI: -0.01 to 0.03; 3 studies, 7,832 participants) or pregnant women (r -0.03, 95%CI: -0.13 to 0.08, 3 studies; 2,766 participants).

Thyrotropin/thyroid stimulating hormone (TSH)

No association was found between urinary MEHP and concentration of TSH (r -0.03, 95%CI: -0.07, 0.01, 13 studies, 5,096 participants). When grouped based on age and pregnancy status there was no association found for children (r -0.01, 95%CI: -0.05 to 0.04; 7 studies, 2,060 participants), adults (r -0.04, 95%CI: -0.08 to 0.01; 4 studies, 2024 participants) or pregnant women (r 0.00, 95%CI: -0.13 to 0.14; 4 studies, 2,841 participants).

No association was found between urinary MEHHP and concentration of TSH (r -0.02, 95%CI -0.07 to 0.03; 10 studies, 4,826 participants). When grouped based on age and pregnancy status there was no association for children (r 0.00, 95%CI: -0.05 to 0.05; 7 studies, 2,060 participants), adults (r -0.04, 95%CI: -0.09 to 0.00; 2 studies, 1,829 participants) or pregnant women (r 0.00, 95%CI: -0.20 to 0.19; 3 studies, 2,766 participants).

There was no association between urinary MEOHP and concentration of TSH (r -0.02, 95%CI: -0.07 to 0.03; 10 studies, 4,826 participants). When grouped based on age and pregnancy status, there was no association for children (r 0.00, 95%CI -0.04 to 0.05; 7 studies, 2,060 participants), adults (r -0.10, 95%CI: -0.22 to 0.03; 2 studies, 1,829 participants) or pregnant women (r 0.03, 95%CI: -0.16 to 0.20; 3 studies, 2,766 participants).

Phthalates and child neurodevelopmental outcomes

Two reviews explored the association between phthalate exposure and child neurodevelopmental outcomes (Lee et al., 2018; Radke et al., 2020). The specific outcomes included cognitive and language development (measured using the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID)), psychomotor development (measured using the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development (BSID)) and cognitive development or intelligence quotient (IQ) (measured using of the Bayley Scales of Infant Development (BSID) III Cognitive Development, Wechsler Preschool and Primary Scale of Intelligence (WPPSI) IQ or full-scale intelligence quotient (FSIQ) of the Weschsler Intelligence Scale for Children (WISC)). These studies included children younger than 12 years of age and included data from cohort, case-control and cross-sectional studies.

Quality of the reviews informing child neurodevelopmental outcomes was moderate, ranging from 7-8/11 with the AMSTAR tool. Only Radke et al. (2020) had an *a priori* protocol available and neither review included a search for grey literature nor provided a list of excluded studies. Lee et al. (2018) used sum of DEHP metabolites where available, or best available single metabolite where not available. Lee et al. (2018) conducted subgroup analyses and where multiple subgroups within a study were included within an analysis of individual chemical exposures or outcome, these data have been extracted and included. The review by Radke et al. (2020) did not have issues with the analyses but did not assess publication bias.

Overall, prenatal and current exposure to ΣDEHP and DEHP metabolites were negatively associated with psychomotor development and cognitive development or IQ outcomes. There were no associations found for the phthalates and their metabolites (MEP, MnBP, MiBP and MBzP) and prenatal ΣDEHP and cognitive and mental development. MEP, MnBP, MiBP and MBzP were not associated with changes in psychomotor development.

Child neurodevelopment outcomes

Two reviews explored the association between phthalate metabolites and the neurodevelopment of children, with ages ranging from 6 months to 12 years of age (Lee et al., 2018; Radke et al., 2020). Lee et al. (2018) specifically investigated prenatal (from longitudinal data) and current (from cross-sectional data) ΣDEHP exposure, whilst Radke et al. (2020) investigated prenatal exposure of a variety of phthalates measured by their metabolites MEP, MnBP, MiBP, MBzP and ΣDEHP in children four years old and younger.

Cognitive performance and intelligent quotient

Both reviews found no association between prenatal DEHP metabolite exposure (β -0.36 95%CI -1.05 to 0.32, 5 studies, 871 participants) (Lee et al., 2018), and ΣDEHP exposure (β -0.01, 95%CI: -0.8 to 0.5, 7 studies, 2,536 participants)(Radke et al., 2020) and cognitive development. Radke et al. (2020) found no association between prenatal exposure to MEP (β 0.3, 95%CI: -0.3 to 0.9; 5 studies, 1,791 participants), MnBP (β -0.2, 95%CI: -0.7 to 0.4; 7 studies, 2,536 participants), MiBP (β -0.1, 95%CI: -0.6 to 0.4; 4 studies, 1,361 participants) and MBzP (β -0.1, 95%CI: -0.8 to 0.5; 6 studies, 2,119 participants), and cognitive development.

Current DEHP metabolite exposure was found to be negatively associated with measures of cognitive development and IQ (β -1.03, 95%CI -1.88 to -0.18, 5 studies, 1,462 participants) but prenatal DEHP metabolite exposure was not (β -0.14, 95%CI: -0.70 to 0.41; 8 studies, 1,625 participants) (Lee et al., 2018).

Girls

There were no associations found between cognitive or mental development in girls and prenatal exposure to MEP (β 0.3, 95%CI: −0.8 to 1.4; studies and participants unspecified), MnBP (β −0.8, 95%CI: −2.2 to 0.6; studies and participants unspecified), MiBP (β −0.8, 95%CI: −2.1 to 0.6; studies and participants unspecified), MBzP (β −0.7, 95%CI: −1.6 to 0.2; studies and participants unspecified) and ΣDEHP (β −0.5, 95%CI: −2.2 to 1.2; studies and participants unspecified) (Radke et al., 2020).

Boys

There were no associations found between cognitive or mental development in boys and prenatal exposure to MEP (β 0.0, 95%CI: −1.1 to 1.2; studies and participants unspecified), MnBP (β 0.4, 95%CI: −0.8 to 1.6; studies and participants unspecified), MiBP (β 0.8, 95%CI: −0.3 to 1.8; studies and participants unspecified), MBzP (β 0.8, 95%CI: −0.3 to 1.9; studies and participants unspecified) and ΣDEHP (β 0.1, 95%CI: −1.2 to 1.3; studies and participants unspecified) (Radke et al., 2020).

Fine motor performance

Prenatal DEHP metabolites (β -0.80, 95%CI -1.48 to -0.12, 5 studies, 871 participants) were negatively associated with fine motor development (Lee 2018). Conversely, there was no association found by Radke et al. (2020) with prenatal exposure to ΣDEHP (β -0.4, 95%CI: -1.4 to 0.7; 6 studies, 2,106

participants) and fine motor development. Similarly, there were no associations between prenatal exposure to MEP (β 0.0, 95%CI: -0.6 to 0.6; 4 studies, 1,361 participants), MnBP (β -0.5, 95%CI: -1.5 to 0.5; 6 studies, 2,119 participants), MiBP (β -0.4, 95%CI: -1.1 to 0.3; 5 studies, 1,689 participants) and MBzP (β -0.7, 95%CI: -1.4 to 0.0; 6 studies, 2,119 participants) and fine motor development.

Girls

Prenatal exposure to MBzP was negatively associated with psychomotor development in girls (β −1.6, 95%CI: −2.6 to −0.6; studies and participants unspecified). Conversely there were no associations found between prenatal exposure to MEP (β 0.4, 95%CI: −0.5 to 1.4; studies and participants unspecified), MnBP (β −0.7, 95%CI: −1.8 to 0.3; studies and participants unspecified), MiBP (β −0.5, 95%CI: −1.9 to 0.9; studies and participants unspecified) and ΣDEHP (β 0.2, 95%CI: −0.8 to 1.3; studies and participants unspecified) and psychomotor development in girls (Radke et al., 2020).

Boys

There were no associations found between psychomotor development in boys and prenatal exposure to MEP (β 0.4, 95%CI: −0.5 to 1.4; studies and participants unspecified), MnBP (β 0.0, 95%CI: −1.7 to 1.8; studies and participants unspecified), MiBP (β −0.1, 95%CI: −1.4 to 1.2; studies and participants unspecified), MBzP (β 0.8, 95%CI: −0.2 to 1.9; studies and participants unspecified) and ΣDEHP (β 0.1, 95%CI: −1.1 to 1.3; studies and participants unspecified) (Radke 2020).

Phthalates and nutritional outcomes (obesity & anthropometrics)

Two reviews explored the association between phthalate exposure and nutritional outcomes (Golestanzadeh et al., 2019; Ribeiro et al., 2019). The outcomes included were BMI, BMI z-scores, waist circumference and obesity. Golestanzadeh et al. (2019) only included children (18 years of age or younger), while Ribeiro et al. (2019) included general population (children and adults) but did not combine children and adult data in the meta-analyses due to high heterogeneity. These reviews contained data from cohort, case-control and cross-sectional studies.

Quality of the two reviews informing nutritional outcomes was moderate, with scores on the AMSTAR tool ranging from 5-6/11. No reviews were informed by an *a priori* protocol. There were concerns over the search conducted by Ribeiro et al. (2019), as it only included one database. Neither review conducted a search for grey literature nor provided a full list of the excluded studies. Both reviews used the STROBE checklist to conduct critical appraisal, which is not a critical appraisal tool. The overall summary analyses by Golestanzadeh et al. (2019)were found to be invalid and therefore not included in this report. The data from the studies were used repeatedly in the analyses (multiple counting of same participant), artificially increasing the sample size and constraining confidence limits. Where available, results of analysis of individual chemical exposures have been included in this report. Where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have also been included in this report, assuming these are mutually exclusive subgroups. Golestanzadeh et al. (2019) also conducted separate analyses for phthalate metabolite MBP and MnBP and BMI, which are the same phthalate metabolite. The difference in the results cannot be explained and therefore, these results have not been extracted for the review. There were no identifiable issues with the individual chemical exposure analyses undertaken by Ribeiro et al. (2019).

There were positive associations between MiBP and the DEHP metabolite, MEHHP and BMI in children, but not for MMP, MEP, MBzP and other DEHP metabolites, MEHP, MEOHP, MECPP and MCPP in children. No association was found for MEP and MEHP and BMI in adults. DEHP, its metabolites and MCOP were positively associated with BMI z scores in children. However, there was inconsistent evidence of association for the other phthalate metabolites MEP, MnBP, MiBP, MBzP and MCPP and BMI z-scores in children. MEHP and MEHHP were positively associated with waist circumference in children, however, no association was found for the other phthalate metabolites MMP, MEP, MnBP, MiBP and MCPP. Inconsistent evidence of association was found for MBzP and waist circumference in children. MEHP was positively associated with waist circumference in adults.

MEHP was not associated with obesity in children and adults. MECPP was associated with an increased risk of obesity in adults but not MEP.

BMI

Golestanzadeh et al. (2019) investigated phthalate metabolites and its association with BMI in children and Ribeiro et al. (2019) considered this outcome for adults.

Children

Positive association was observed for MiBP (β 0.18, 95%CI: 0.002 to 0.35; 3 studies, 950 participants) and MEHHP (β 0.18, 95%CI: 0.04 to 0.31; 9 studies, 2,490 participants). No associations were found for the following: MMP (β 0.09, 95%CI: −0.08 to 0.26; 6 studies, 1,695 participants), MEP (β 0.19, 95%CI: −0.09 to 0.46; 6 studies, 2545 participants), MBzP (β 0.17, 95%CI: −0.09 to 0.43; 3 studies, 905 participants), MEHP (β 0.15, 95%CI: −0.10 to 0.39; 9 studies, 3,195 participants), MEOHP (β −0.001, 95%CI: −0.09 to 0.09; 9 studies, 2,490 participants), MECPP (β −0.12, 95%CI: − 0.27 to 0.03; 4 studies, 1059 participants) and MCPP (β 0.15, 95%CI: −0.10 to 0.41; 2 studies, 663 participants). *Note, MnBP findings were not included because authors reported for MnBP and MBP separately.*

Adults

In adults, both urinary MEP (β 0.05 kg/m^2, 95%CI: -0.06 to 0.16; 3 studies, 2,512 participants) and MEHP (β -0.05 kg/ m^2, 95%CI: -0.15 to 0.05; 3 studies, 1,298 participants) and were not associated with any change in BMI.

BMI z-scores

Golestanzadeh et al. (2019) and Ribeiro et al. (2019)reported on the association between phthalates, their metabolites and BMI z-scores (BMI standard deviation scores) in children. Ribeiro et al. (2019) reported no associations for MEP (β 0.02, 95%CI: -0.06 to 0.10; 3 studies, 820 participants), MnBP (β 0.00, 95%CI: -0.11 to 0.12; 3 studies, 820 participants), MiBP (β -0.01, 95%CI: -0.10 to 0.07; 3 studies, 820 participants), MBzP (β -0.06, 95%CI: -0.15 to 0.04; 3 studies, 820 participants), and MCPP (β -0.12, 95%CI: -0.24 to 0.00; 3 studies, 820 participants). Golestanzadeh et al. (2019) reported no associations for MEHP (z 0.16, 95%CI: −0.06 to 0.15; 2 studies, 629 participants), MEHHP (z 0.20, 95%CI: −0.08 to 0.48; 2 studies, 629 participants), MEOHP (z 0.12, 95%CI: −0.02 to 0.26; 2 studies, 629 participants). *Note, only MEHP, MEHHP and MEOHP were reported from Golestanzadeh et al.* (2019)*, because the other phthalate metabolite findings were analysed from multiple repeated data from one study.*

Waist circumference

Both reviews included analyses assessing the relationship between phthalate metabolites and waist circumference (Golestanzadeh et al., 2019; Ribeiro et al., 2019).

Children

Golestanzadeh et al. (2019) reported a positive association between urinary MBzP (β 0.12, 95%CI: 0.02 to 0.22, 3 studies, 905 participants), MEHP (β 0.13, 95%CI: 0.04 to 0.21; 5 studies, 1,301 participants) and MEHHP (β 0.28, 95%CI: 0.09 to 0.47, 5 studies, 1,301 participants) and waist circumference. No association was found for MMP (β 0.06, 95%CI: −0.06 to 0.18; 3 studies, 777 participants), MEP (β 0.17, 95%CI: −0.18 to 0.52; 3 studies, 922 participants), MnBP (β 0.19, 95%CI: −0.19 to 0.58; 4 studies, 1,043 participants), MiBP (β −0.33, 95%CI: −1.11 to 0.45; 2 studies, 646 participants), MEOHP (β 0.05, 95%CI: −0.02 to 0.13; 5 studies, 1,301 participants), MECPP (β −0.11, 95%CI: −0.24 to 0.03: 4 studies, 1,059 participants) and MCPP (β −0.46, 95%CI: −1.42 to 0.51; 2 studies, 663 participants).

Ribeiro et al. (2019) reported no association between urinary MEP (β 0.47 cm, 95%CI: -0.23, 1.17; 3 studies, 820 participants), MnBP (β 0.13 cm, 95%CI: -0.86 to 1.13; 3 studies, 820 participants), MiBP (β -0.62 cm, 95%CI: -1.6 to 0.37; 3 studies, 820 participants), MBzP (β -0.35 cm, 95%CI: -1.16 to 0.48 cm; 3 studies, 820 participants), MCCP (β -0.73 cm, 95%CI -1.74 to 0.28 cm; 3 studies, 820 participants) and waist circumference in children.

Adults

Ribeiro et al. (2019) reported a positive association between urinary MEHP and waist circumference (β 0.58 cm, 95%CI: 0.55 to 0.62 cm; 3 studies, 2,435 participants).

Obesity

Obesity was reported in one review (Ribeiro et al., 2019).

Children

There was no association between urinary MEHP and obesity (OR 0.78, 95%CI: 0.47 to 1.29; 3 studies, at least 773 participants).

Adults

Three estimates were provided exploring the association between phthalate and obesity in adults. There was a positive association between urinary MECPP and obesity in adults (OR 1.67, 95%CI: 1.3 to 2.16; 3 studies, at least 3,599 participants), but there was no observed association for urinary MEP (OR1.22, 95%CI: 0.94 to 1.5; 4 studies, at least 3,701 participants) and MEHP (OR 0.91, 95%CI: 0.66 to 1.27; 3 studies, at least 2,432 participants).

Phthalates and circulatory outcomes

Two reviews explored the association between urinary phthalate exposure and circulatory outcomes (Fu et al., 2020; Golestanzadeh et al., 2019). Exposure was postnatal for children. Fu et al. (2020) reported the incidence of cardiovascular disease whilst Golestanzadeh et al. (2019) reported systolic blood pressure, diastolic blood pressure, high-density lipoprotein and triglycerides. Fu et al. (2020) considered a general population of children and adults, whilst Golestanzadeh et al. (2019) included a child population (18 years of age or less). These reviews synthesised data from cohort, case-control and cross-sectional studies.

Quality of the reviews informing circulatory outcomes was moderate, with scores ranging from 5-6/11 in the AMSTAR tool. Both reviews presented a comprehensive literature search, a table of included studies and conducted a test for publication bias. Neither review was informed by an *a priori* protocol, was clear whether data extraction was done in duplicate, conducted a grey literature search nor provided a list of excluded studies. Golestanzadeh et al. (2019) attempted to perform critical appraisal, however, used the STROBE checklist, which is a reporting guideline and not an appraisal tool. The overall (all phthalates) summary analyses in both reviews were found to be invalid and therefore not included in this report. The data from the studies were used repeatedly in the analyses (multiple counting from same participant), artificially increasing the sample size and constraining confidence limits. Where available, results of analysis of individual chemical exposures have been extracted and included in this report. Where multiple subgroups within a study were included within an analysis of individual chemical exposures these data have also been included in this report, assuming these are mutually exclusive subgroups.

There is evidence of an association between the DEHP metabolites, MEHHP and MEOHP, and increased systolic blood pressure, and also with MEOHP and increased HDL, in children. No associations were found for other phthalate metabolites and other circulatory outcomes.

Cardiovascular disease

Fu et al. (2020) explored the association between urinary phthalate exposure and cardiovascular disease in the general population (no age limit). None of the phthalate metabolites were associated with incidence of cardiovascular disease: MEP (OR 1.15, 95%CI:0.99 to 1.34; 4 studies, 9,261 participants), MnBP (OR 1.02, 95%CI:0.78 to 1.32; 4 studies, 9,261 participants), MBzP (OR 1.19, 95%CI: 0.93 to 1.51; 4 studies, 9,261 participants), MEHP (OR 1.05, 95%CI: 0.97 to 1.13; 4 studies, 9,261 participants), MEOHP (OR 1.09, 95%CI: 0.93 to 1.26; 4 studies, 9,261 participants), MEHHP (OR 1.08, 95%CI: 0.95 to 1.23; 4 studies, 9,261 participants), MECPP (OR 1.15, 95%CI: 0.94 to 1.41; 4 studies, 9,261 participants), MiBP (OR 1.18, 95%CI: 0.99 to 1.38; 4 studies, 9,261 participants).

Systolic blood pressure

Golestanzadeh et al. (2019) explored the association between urinary phthalate exposure and systolic blood pressure in children 18 years of age or younger. There were associations found with the DEHP metabolites, MEHHP (β 0.16 mmHg, 95%CI: 0.09, 0.23 mmHg; 3 studies, 761 participants) and MEOHP (β 0.12 mmHg, 95%CI: 0.12, 0.24 mmHg; 3 studies, 761 participants). No associations were found for the following: MMP (β 0.09 mmHg, 95%CI: −0.03 to 0.20 mmHg: 2 studies, 518 participants), MBzP (β 0.09 mmHg, 95%CI: −0.11 to 0.29 mmHg; 3 studies, 518 participants) and MEHP (β 0.13 mmHg, 95%CI: −0.02 to 0.28 mmHg; 3 studies, 731 participants).

Diastolic blood pressure

Golestanzadeh et al. (2019) found there was no association between the phthalate metabolites investigated in urine and diastolic blood pressure in children: MMP (β 0.02 mmHg, 95%CI: −0.06 to 0.11 mmHg; 2 studies, 518 participants), MBzP (β 0.04 mmHg, 95%CI:− 0.05 to 0.12 mmHg; 2 studies, 518 participants), MEHP (β − 0.01 mmHg, 95%CI: −0.09 to 0.08 mmHg; 2 studies, 518 participants), MEHHP (β 0.07 mmHg, 95%CI: −0.02 to 0.15 mmHg; 2 studies, 518 participants) and MEOHP (β 0.03 mmHg, 95%CI: −0.06 to 0.12 mmHg; 2 studies, 518 participants).

High-density lipoprotein

Golestanzadeh et al. (2019) also explored the association between urinary phthalate metabolite exposure and high-density lipoprotein (HDL) in children. The DEHP metabolite MEOHP was associated with an increase in HDLs (β 0.31, 95%CI: 0.25, 0.37; 2 studies, 485 participants). No other associations were found for MnBP (β− 0.15, 95%CI: − 0.88 to 0.58; 2 studies, 397 participants), MBzP (β −0.11, 95%CI: −0.47 to, 0.26; 3 studies, 1,400 participants), ΣDEHP (β 0.09, 95%CI: − 0.26 to 0.44; 4 studies, 3,231 participants), MEHP (β −0.20, 95%CI: −0.42 to 0.03; 3 studies, 622 participants), MEHHP (β 0.20, 95%CI: −0.23 to 0.63; 2 studies, 485 participants) and MCPP (β 0.11, 95%CI: −0.10 to 0.33; 2 studies, 1,158 participants).

Triglycerides

Golestanzadeh et al. (2019) also explored the association between urinary phthalate metabolite exposure and triglycerides. No associations were found with any of the phthalate metabolites investigated and levels of triglycerides: MnBP (β 0.08, 95%CI: −0.18 to 0.34; 2 studies, 397 participants), MBzP (β 0.14, 95%CI: −0.10 to 0.37; 3 studies, 1,400 participants), ΣDEHP (β −0.11, 95%CI: −0.31 to 0.08; 4 studies, 3,907 participants), MEHP (β 0.2, 95%CI: −0.06 to 0.47; 3 studies, 787 participants), MEHHP (β 0.01, 95%CI: −0.05 to 0.07; 2 studies, 485 participants), MEOHP (β −0.06, 95%CI: −0.19 to 0.06; 2 studies, 485 participants) and MCPP (β −0.04, 95%CI: −0.09, 0.02; 2 studies, 1,158 participants).

Phthalates and respiratory outcomes

Two reviews explored the association between phthalates and individual phthalate metabolites on respiratory health outcomes (Li et al., 2017; Weixiang Wu et al., 2020). Outcomes included were risk of asthma and allergic rhinitis. Li et al. (2017) limited the population to children, while Wu et al. (2020) studied the general population. Both reviews analysed subgroups based on pre- or postnatal exposure. The studies informing these reviews were a mixture of cohort, case-control and cross-sectional studies.

Quality of the reviews informing respiratory outcomes ranged from low to high, with scores on the AMSTAR tool ranging from 5-9/11. Only Li et al. (2017)had an *a priori* protocol. Both reviews did not search for grey literature and did not provide a list of excluded studies. Wu et al. (2020) provided limited participant characteristics, and did not assess quality of studies correctly. Wu et al. (2020) opted for fixed effect model rather than random effects in the presence of heterogeneity. In addition, inclusion of adult/child population from same study in the same analyses likely infringes independence of measurements and skews estimate of heterogeneity in some instances.

There is limited evidence from the reviews that demonstrate an association between exposure to phthalates and increased risk of asthma in children.

Asthma

Children

Two reviews included outcome data related to asthma specific to children (Li et al., 2017; Weixiang Wu et al., 2020). Subgroup analyses were also reported in terms of prenatal and postnatal exposures in some DEHP metabolites.

MEP

Wu et al. (2020) found no association between urinary MEP and asthma (OR 1.02, 95%CI:0.94 to 1.11; 10 studies participants unspecified) in children. Similarly, no association was found with prenatal exposure only (OR 1.02, 95CI:0.93 to 1.12; 5 studies, participants unspecified).

MnBP

Wu et al. (2020) found no association between urinary MnBP and asthma (OR 0.97, 95%CI:0.85 to 1.09; 8 studies, participants unspecified) in children, nor when considering prenatal exposure only (OR 1.07, 95%CI:0.8 to 1.42; 4 studies, participants unspecified). When grouped by exposure, Li et al. (2017)found no associations for prenatal exposure (OR 0.83, 95%CI: 0.12 to 5.77; 2 studies, participants unspecified) and postnatal exposure (OR 0.72, 95%CI: 0.48 to 1.10; 5 studies, participants unspecified).

MiBP

Wu et al. (2020) found no association between urinary MiBP and asthma (OR 1.04, 95%CI: 0.91 to 1.19; 7 studies, participants unspecified) in children and with prenatal exposure only (OR 1.05, 95%CI: 0.88 to 1.24; 3 studies, participants unspecified). When grouped by exposure, Li et al. (2017) similarly found no associations for postnatal exposure (OR 1.06, 95%CI: 0.67 to 1.66; 3 studies, participants unspecified).

MBzP

Wu et al. (2020) reported that urinary MBzP was associated with an increased risk of developing asthma in children (OR 1.17, 95%CI: 1.05 to 1.29; 12 studies, participants unspecified), this significant association was maintained with prenatal exposure only (OR 1.15, 95%CI: 1.01 to 1.32, 6 studies, participants unspecified). Similarly, Li et al. (2017) found an increased risk of asthma in subgroups of studies considering prenatal exposure (OR 1.38, 95%CI: 1.09 to 1.75; 3 studies, participants unspecified) but found no association with postnatal exposure (OR 1.19, 95%CI: 0.79 to 1.80; 5 studies, participants unspecified).

DEHP metabolites (ΣDEHP where available, otherwise most reliable individual DEHP metabolite)

Wu et al. (2020) found no association between urinary DEHP metabolite and asthma (OR 0.87, 95%CI: 0.67 to 1.14; 8 studies, participants unspecified) in children nor with prenatal exposure only (OR 1.08, 95%CI: 0.92 to 1.26; 5 studies, participants unspecified). Similarly, when grouped by timing of exposure, Li et al. (2017) found no associations for prenatal exposure, (OR 1.11, 95%CI: 0.97 to 1.26; 3 studies, participants unspecified) and postnatal exposure (OR 0.76, 95%CI: 0.32 to 1.79; 5 studies, participants unspecified).

MEHP

Wu et al. (2020) found no association between urinary MEHP and asthma (OR 1.04, 95%CI: 0.89 to 1.20; 5 studies, participants unspecified) in children. When grouped by exposure, Wu et al. (2020) still found no associations for prenatal exposure (OR 1.06, 95%CI 0.91 to 1.23; 3 studies, participants unspecified) nor for postnatal exposure (OR 0.78, 95%CI: 0.41 to 1.48; 3 studies, participants unspecified). No association was found for boys when analysed separately (OR 0.99, 95%CI: 0.81 to 1.19; 2 studies, participants unspecified).

MEHHP

Wu et al. (2020) reported that urinary MEHP was associated with an increased risk of developing asthma (OR 1.13, 95%CI: 1.03 to 1.24; 5 studies, participants unspecified) in children and when grouped by postnatal exposure (OR 1.30, 95%CI: 1.09 to 1.56; 2 studies, participants unspecified), but not for prenatal exposure (OR 1.07, 95%CI: 0.96 to 1.20; 3 studies, participants unspecified).

MEOHP

Wu et al. (2020) reported that urinary MEOHP was not associated with asthma (OR 1.09, 95%CI: 0.77 to 1.53; 3 studies, participants unspecified) in children. However, when grouped by exposure, prenatal urinary MEOHP was found to be associated with an increased risk of developing asthma (OR 1.19, 95%CI: 0.88 to 1.61; 2 studies, participants unspecified).

MECPP

Wu et al. (2020) found an association between urinary MECPP and asthma (OR 1.2, 95%CI: 1.0 to 1.42; 3 studies, participants unspecified) in children. When grouped by exposure, prenatal urinary MECPP was also found to be associated with an increased risk of developing asthma (OR 1.23, 95%CI: 1.03 to 1.47; 2 studies, participants unspecified).

MCOP

Wu et al. (2020) found that urinary MCOP was associated with an increased risk in asthma (OR 1.19, 95%CI: 1.02 to 1.37; 4 studies, participants unspecified) in children, however, in the subgroup of studies considering prenatal exposure only, this association was no longer significant (OR 1.17, 95%CI: 0.98, 1.41; 2 studies, participants unspecified). Li et al. (2017) found no associations for subgroups of studies considering prenatal exposure (OR 1.21, 95%CI: 0.48 to 3.05; 2 studies, participants unspecified).

MCNP

Wu et al. (2020) reported an association between urinary MCNP and risk of asthma (OR 1.15, 95%CI: 1.00 to 1.31; 5 studies, participants unspecified) in children, however, this association was no longer statistically significant in the subgroup of studies considering prenatal exposure only (OR 1.14, 95%CI: 0.96 to 1.34; 2 studies, participants unspecified).

MCPP

Wu et al. (2020) reported no association between urinary MCPP and risk in asthma in children (OR 0.97, 95%CI: 0.83 to 1.13; 6 studies, participants unspecified) and in studies considering prenatal exposure only (OR 0.99, 95%CI: 0.81 to 1.2; 3 studies, participants unspecified).

General population

The review by Wu et al. (2020) presented individual analyses for exposure to specific phthalate metabolites in the general population and where possible, subgroups based on age, location, timing of exposure and gender.

MEP

There was no association between urinary MEP and asthma in the general population (OR 1.03, 95%CI: 0.96 to 1.12; 11 studies, participants unspecified), with postnatal exposure in the general population (OR 1.08, 95%CI: 0.95 to 1.23; 9 studies, participants unspecified), or in adults (postnatal/current exposure) only (OR 1.11, 95%CI: 0.89 to 1.39; 3 studies, participants unspecified). No association was maintained in subgroup analysis of studies that were conducted in Europe (OR 1.06, 95%CI: 0.9 to 1.24; 4 studies), North America (OR 1.03, 95%CI: 0.93 to 1.14; 7 studies, participants unspecified) or Asia (OR 1.03, 95%CI: 0.86 to 1.25; 3 studies, participants unspecified). No association was found for analyses within males (OR 1.12, 95%CI 0.97 to 1.31; 5 studies, participants unspecified) or females (OR 0.94, 95%CI: 0.58 to 1.53; 3 studies, participants unspecified).

MnBP

There was no association observed between urinary MnBP and asthma in the general population (OR 1.03, 95%CI: 0.85 to 1.24; 9 studies, participants unspecified), postnatal exposure in the general

population (OR 0.95, 95%CI: 0.78 to 1.16; 7 studies, participants unspecified), or in adults (postnatal/current exposure) only (OR 1.35, 95%CI: 0.93 to 1.96; 3 studies, participants unspecified). and No association was reported when considering the location of studies, irrespective of whether from Europe (OR 0.98, 95%CI: 0.74 to 1.29; 4 studies, participants unspecified) or North America (OR 1.09, 95%CI: 0.89 to 1.33; 7 studies, participants unspecified). Similarly, there was no association for males (OR 0.98, 95%CI: 0.82 to 1.16; 4 studies, participants unspecified) or females (OR 0.84, 95%CI: 0.56 to 1.25; 3 studies, participants unspecified) when analysed separately.

MiBP

There was no association between urinary MiBP and asthma in the general population (OR 1.05, 95%CI 0.93 to 1.19; 8 studies) or adults (OR 1.11, 95%CI: 0.84 to 1.47; 3 studies, participants unspecified). Wu 2020b found no associations for postnatal exposure in the general population (OR 1.06, 95%CI: 0.89 to 1.27; 7 studies, participants unspecified). Similarly, there was no association for studies from Europe (OR 1.05, 95%CI: 0.90 to 1.23; 4 studies, participants unspecified) or North America (OR 1.06, 95%CI: 0.87 to 1.29; 6 studies, participants unspecified). There was no association in males (OR 1.08, 95%CI: 0.88 to 1.33; 4 studies, participants unspecified) or females (OR 0.81, 95%CI: 0.51 to 1.29; 3 studies, participants unspecified).

MBzP

There was an increased risk of asthma with increased urinary MBzP in the general population (OR 1.17, 95%CI: 1.06 to 1.28; 13 studies, participants unspecified). Likewise, there was an increase in risk of asthma with postnatal exposure in the general population (OR 1.17, 95%CI: 1.03 to 1.33; 10 studies, participants unspecified). No association was found in adults with postnatal/current (OR 1.17, 95%CI: 0.94, 1.46; 3 studies, participants unspecified). Other subgroup analyses were conducted based on location, where positive associations were found for studies from Europe (OR 1.16, 95%CI: 1.02 to 1.32; 5 studies, participants unspecified) and North America (OR 1.23, 95%CI: 1.05 to 1.44; 7 studies, participants unspecified), but no association was found for studies from Asia (OR 1.08, 95%CI: 0.37 to 3.19; 4 studies, participants unspecified). The final subgroup analysis was conducted based on gender. No associations were found when the analysis was restricted to either males only (OR 1.19, 95%CI 0.99 to 1.41; 5 studies, participants unspecified) or females only (OR 1.04, 95%CI: 0.77 to 1.42; 4 studies, participants unspecified).

ΣDEHP

There was no association between ΣDEHP metabolites and asthma in the general population (OR 0.99, 95%CI: 0.8 to 1.22; 9 studies, participants unspecified) and in adults with postnatal/current exposure (OR 1.27, 95%CI: 0.99 to 1.61; 3 studies, participants unspecified) when analysed separately. When grouped by timing of exposure, no association was found with postnatal (OR 1.04, 95%CI: 0.71 to 1.54; 7 studies, participants unspecified) exposure. There was no association reported when considering studies from Europe (OR 1.16, 95%CI: 1.0 to 1.34; 4 studies, participants unspecified), North America, (OR 0.81, 95%CI: 0.57 to 1.17; 6 studies, participants unspecified) and Asia (OR 1.89, 95%CI: 0.79 to 4.53; 2 studies, participants unspecified).

MEHP

No association was found between urinary MEHP and asthma in studies conducted in Europe (OR 1.04, 95%CI: 0.89 to 1.21; 3 studies, participants unspecified) or from Asia (OR 1.14, 95%CI: 0.48 to 2.71; 3 studies, participants unspecified).

MEHHP

No association was found between urinary MEHHP and asthma in studies from Europe (OR 1.11, 95%CI: 0.94 to 1.31; 3 studies, participants unspecified).

MCOP

There was no association between MCOP and asthma in the general population (OR 1.13, 95%CI: 0.99 to 1.28; 4 studies, participants unspecified). No association was found with postnatal exposure only in

the general population (OR 1.08, 95%CI: 0.9 to 1.31; 3 studies, participants unspecified) exposures. No association was reported irrespective of whether studies were conducted in Europe (OR 1.13, 95%CI: 0.95 to 1.34; 2 studies, participants unspecified) or North America (OR 1.10, 95%CI: 0.74 to 1.64; 3 studies, participants unspecified).

MCNP

There was no association between MCNP and asthma in the general population (OR 1.10, 95%CI: 0.98 to 1.24; 5 studies, participants unspecified) and in adults (current/postnatal exposure) (OR 1.0, 95%CI: 0.8 to 1.24; 2 studies, participants unspecified) when considered separately. No association was found with postnatal exposure in the general population (OR 1.07, 95%CI: 0.92 to 1.26; 5 studies, participants unspecified). A positive association was found for studies from Europe (OR 1.18, 95%CI: 1.02 to 1.37; 2 studies, participants unspecified) whereas there was no association for studies exclusively from North America (OR 0.99, 95%CI: 0.82 to 1.19; 5 studies, participants unspecified). There was no association for males (OR 1.12, 95%CI: 0.95 to 1.33; 3 studies) or females (OR 1.02, 95%CI: 0.73 to 1.44; 2 studies, participants unspecified).

MCPP

There was no association between the nonspecific phthalate metabolite MCPP and risk of asthma in the general population (OR 1.04, 95%CI: 0.91 to 1.19; 6 studies, participants unspecified) and in adults with current/postnatal exposure (OR 1.32, 95%CI: 1.0 to 1.75; 2 studies, participants unspecified). Considering the timing of exposure, no association was found with postnatal exposure in the general population (OR 1.09, 95%CI: 0.91 to 1.32; 5 studies, participants unspecified). Similarly, no association was discernable when considering the origin of studies whether from Europe (OR 0.96, 95%CI: 0.8 to 1.15; 2 studies, participants unspecified) or North America (OR 1.14, 95%CI: 0.94 to 1.4; 6 studies, participants unspecified). There was no association reported when analyses were conducted separately for males (OR 0.93, 95%CI: 0.76 to 1.14; 4 studies, participants unspecified) or females (OR 1.36, 95%CI: 0.98 to 1.88; 3 studies, participants unspecified).

FLAME RETARDANTS (PCB AND PBDE)

There were 15 systematic reviews (Cano-Sancho et al., 2019; Catalani et al., 2019; Fu et al., 2020; Lam et al., 2017; Leng et al., 2016; Nieminen et al., 2013; Park et al., 2016; Roy et al., 2015; Song et al., 2016; Zani et al., 2017, 2013; Zhang et al., 2015; Zhao et al., 2017, 2015; Zou et al., 2019) and four pooled analyses (Gascon et al., 2014; Govarts et al., 2012; Li et al., 2015; Wu et al., 2013), that together include 160 meta-analyses that pooled data for outcomes related to flame retardant exposure. No systematic reviews were found for human health effects of other plastic-associated brominated flame retardants, or of plastic-associated, nonhalogenated flame retardants. Outcomes for which analyses were available were clustered into overarching health conditions based on ICD-11 (World Health Organization, 2020):

- Birth – Birth weight, birth length, head circumference, secondary sex ratio
- Reproductive health (adults)
    - Women – endometriosis
- Metabolic - Thyroid function, type 2 diabetes, fasting glucose, 2-hour glucose, fasting insulin, 2-hour insulin, HOMA-IR, hepatic disease mortality
- Child neurodevelopment – intelligence quotient (IQ)
- Circulatory – Incidence of cardiovascular disease, cardiovascular disease mortality, cerebrovascular disease mortality, hypertension, hypertension mortality
- Respiratory – Bronchitis, wheeze
- Cancer – Breast, non-Hodgkin's lymphoma including chronic lymphocytic leukemia, diffuse large B-cell lymphoma and follicular lymphoma, cancer-related mortality
- Mortality - All-cause mortality

Abbreviations

PCBs	Polychlorinated biphenyls	**HOMA-IR**	Homeostatic Model Assessment of Insulin Resistance
PBDEs	Polybrominated diphenyl ethers	**IQ**	Intelligent quotient

Exposure description and measures

Flame retardant plastic additives are compounds added to plastics to inhibit, suppress or delay combustion. Exposure to flame retardants can be from a variety of sources in the environment depending on the flame retardant. Specific exposure routes (e.g. dermal, inhalation or ingestion) were rarely reported by review and pooled analysis authors; with the exception of those in high-risk environments such as occupational exposure and populations that were known to be exposed due to a chemical spill accident or through prenatal exposure. Only two classes of flame retardants were reported in included studies in this Evidence Review: polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). For additional details on flame retardants, see Appendix 1.

Across all exposures, the levels for flame retardants were commonly measured in ng/g, ng/mL, µg/L, µg/kg or mmol/L, in blood (whole, serum or plasma), cord serum or plasma, breast milk, adipose tissue. Individuals working as electrical workers, telecommunication transformer and capacitor workers are those commonly exposed to PCBs by the nature of their job description. Therefore, the term 'special PCB exposure by occupation' was used in this review to describe their exposure. Populations (Japan and Taiwan) exposed to PCB ingestion of contaminated rice oil were described as 'special PCB exposure by poisoning'. For both these groups, the measurement and reporting of exposure was by group rather than by individual.

Overall findings

Overall, exposure to PCB 153 and total PCBs resulted in lower birth weight but there was no association found with secondary sex ratio. Total PCB exposure was associated with increase in risk in endometriosis, type 2 diabetes risk and fasting glucose but not with 2 hr glucose, fasting insulin, 2 hr insulin and HOMA-IR. PCB exposure by poisoning was associated with hepatic disease mortality. PCB 138 and 153 were found to be associated with cardiovascular disease but not total PCBs, special PCB exposure by poisoning was associated with cardiovascular disease mortality but not with hypertension, hypertension mortality and cerebrovascular disease mortality. PCB 153 exposure was reported to be associated with bronchitis in infants but not with wheeze and not with combined bronchitis and/or wheeze. Lastly, special PCB exposure by poisoning was found to be associated with all-cause mortality and specifically in males. Exposure to PCB 187, 105, 99, 183 resulted in an increase in risk of developing breast cancer. Inconsistent findings were reported for total PCBs and increased risk of developing non-Hodgkin's lymphoma in children and adults. PCB exposure by poisoning was found to be associated with all cancer mortality and lung cancer mortality and especially in males and liver cancer mortality in females. No associations were found for PCB exposure by poisoning and other cancer-related mortality. Occupational PCB exposure was associated with melanoma mortality but not with non-Hodgkin's lymphoma mortality.

Exposure to total PBDEs was associated with decreased birth weight in infants and BDE 47 with lower IQ in children. Total PBDE exposure was also associated with increased TT4 levels but not with TSH levels.

Table 3.5: Summary of health outcomes related to flame retardant exposure

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
			Birth outcomes			
BIRTH WEIGHT (PCBs) - 1 review, 1 pooled analysis						
Infants; Prenatal - general environment (measured in cord plasma or serum/maternal serum or blood/breast milk)	Govarts et al. 2012 (3/11) [p]	PCB 153	β -0.15g (95% CI = -0.24 to -0.05g) *	12	7666	per ng/L PCB-153 in cord serum
Infants; Prenatal; general environment (measured in maternal serum/cord blood)	Zou et al. 2019 (4/11)	Total PCBs	β -0.59g (95% CI = -0.852 to -0.343g) *	7	8054	
		Trimester of exposure				
		First trimester	β -0.39g (95% CI = -0.56 to -0.21g) *	3	unsp.	
		Second trimester	β -0.49g (95% CI = -0.66 to -0.33g) *	2	unsp.	
		Third trimester	β -0.66g (95% CI = -0.91 to -0.41g) *	6	unsp.	
		Geographically				
		Asia	β -0.4g (95% CI = -0.52 to -0.27g) *	2	680	
		Europe	β -0.6g (95% CI = -0.65 to -0.55g) *	3	5618	
		America	β -0.88g (95% CI = -1.64 to -0.11g) *	2	1756	
		Specimen type				
		cord serum	β -0.83g (95% CI = -1.7 to -0.03g) *	2	1004	
		maternal serum	β -0.5g (95% CI = -0.79 to -0.22g) *	5	7050	
		Study type				
		prospective studies	β -0.63g (95% CI = -0.91 to -0.35g) *	6	unsp.	
BIRTH WEIGHT (PBDEs) - 1 review						
Infants; Prenatal - general environment (measured in serum)	Zhao et al. 2017 (9/11)	Total PBDEs	β -50.6g (95% CI = -95.91 to -5.28g) *	5	1332	correlation with log PBDEs (ng/g lipids)
		Sex				
		Male infants	β -121.456g (95% CI = -230.139 to -12.773g) *	2	296	
		Female infants	β 37.766g (95% CI = -81.425 to 156.957g)	2	265	
		Both males and females	β -54.388g (95% CI = -115.98 to 7.206g)	3	771	
		Congener				
		BDE-47	β -41.54g (95% CI = -90.35 to 7.28g)	3	601	
		BDE-99	β -29.78g (95% CI = -95.09 to 35.53g)	3	601	
		BDE-100	β -28.55g (95% CI = -91.19 to 34.1g)	3	768	
		BDE-153	β -41.22g (95% CI = -102.73 to 20.29g)	3	768	
BIRTH LENGTH (PBDEs) - 1 review						
Infants; Prenatal - general environment (measured in serum)	Zhao et al. 2017 (9/11)	Total PBDEs	β -0.33cm (95% CI = -0.74 to 0.07cm)	2	320	
HEAD CIRCUMFERENCE (PBDEs) - 1 review						
Infants; Prenatal - general environment (measured in serum)	Zhao et al. 2017 (9/11)	Total PBDEs	β -0.175cm (95% CI = -0.42 to 0.07cm)	2	320	
SECONDARY SEX RATIO (PCBs) - 1 review						
Infants;	Nieminen et al. 2013 (3/11)	Total PCBs	Ratio 0.5 (95% CI = 0.45 to 0.55)	9	unsp.	High and low maternal exposure

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
Prenatal exposure - general and highly exposed environment (measured in maternal blood, paternal blood, cord blood or mother's breast milk)						
		Child reproductive health outcomes - No data				
		Adult reproductive health outcomes (women)				
ENDOMETRIOSIS (PCBs) - 2 reviews		**Range of effects:**	**OR 1.70 to 1.91 (95% CI = 1.05 to 5.54) ***	**6 to 9**	**1380 to 31041**	
Adults; General population of women (measured in serum)	Cano-Sancho et al. 2019 (8/11)	Total PCBs	OR 1.7 (95% CI = 1.2 to 2.39) *	9	31041	
		Specimen type				
		Adipose	OR 1.42 (95% CI = 0.91 to 2.21)	3	28770	
		Serum	OR 2.02 (95% CI = 1.2 to 3.4) *	6	2271	
		Geographically				
		Europe	OR 2.35 (95% CI = 1.44 to 3.82) *	4	385	
		US	OR 1.08 (95% CI = 0.93 to 1.26)	5	30656	
		study type				
		Population-based	OR 1.14 (95% CI = 0.88 to 1.48)	3	unsp.	
		Operative case control	OR 2.08 (95% CI = 1.4 to 3.08) *	6	unsp.	
		outcome				
		Deep endometriosis	OR 1.76 (95% CI = 1.35 to 2.28) *	2	unsp.	
		Total endometriosis	OR 1.73 (95% CI = 1.08 to 2.76) *	7	unsp.	without peritoneal form
		Exposure contract				
		Continuous	OR 1.51 (95% CI = 0.89 to 2.57)	4	unsp.	
		Categorical	OR 1.86 (95% CI = 1.21 to 2.86) *	5	unsp.	
		risk of bias				
		Tier 2	OR 1.57 (95% CI = 1.18 to 2.09) *	4	unsp.	
		Tier 1	OR 1.78 (95% CI = 1.02 to 3.12) *	5	unsp.	
		laparoscopy among controls				
		With laparoscopy	OR 1.78 (95% CI = 1.02 to 3.13) *	5	unsp.	
		No laparoscopy	OR 1.57 (95% CI = 1.18 to 2.09) *	4	unsp.	
	Roy et al. 2015 (3/11)	Total PCBs	OR 1.91 (95% CI = 1.05 to 5.54) *	6	1380	
		Metabolic and endocrine outcomes				
TYPE 2 DIABETES (PCBs) - 2 reviews						
General and high-risk (occupational exposure workers and population living in areas with PCB exposure) population (measured in serum)	Song et al. 2016 (6/11)	Total PCBs	RR 2.39 (95% CI = 1.86 to 3.08) *	21	21530	High vs low exposure
		Study type				
		cross-sectional studies	RR 2.9 (95% CI = 2.14 to 3.92) *	13	13419	
		prospective studies	RR 1.63 (95% CI = 1.15 to 2.33) *	8	4681	
		Sex				
		females	RR 2.65 (95% CI = 1.57 to 4.48) *	unsp.	unsp.	
		males	RR 1.73 (95% CI = 0.8 to 3.75)	unsp.	unsp.	
		Race				
		white race	RR 1.94 (95% CI = 1.43 to 2.62) *	unsp.	unsp.	
		non-white race	RR 2.91 (95% CI = 1.6 to 5.3) *	unsp.	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
	Wu et al. 2013 (4/11)	Total PCBs	OR 1.7 (95% CI = 1.28 to 2.27) *	7	3508	
		Total PCBs	OR 2.05 (95% CI = 1.41 to 2.98) *	5	2035	Two meta-analyses excluded (Yucheng cohort)
		Congener or group				
		PCB 118 (group II)	OR 1.2 (95% CI = 0.73 to 1.96)	4	2471	
		PCB 138 (group II)	OR 1.36 (95% CI = 0.69 to 2.68)	2	1820	
		PCB 153 (group III)	OR 1.06 (95% CI = 0.79 to 1.42)	3	2742	
		PCB 180 (group III)	OR 1.46 (95% CI = 0.77 to 2.77)	3	2000	
FASTING GLUCOSE (PCBs) - 1 review						
General and high-risk (occupational exposure workers and population living in areas with PCB exposure) population (measured in serum)	Song et al. 2016 (6/11)	Total PCBs	MD 3.27 (95% CI = 1.87 to 4.67) *	3	2882	highest versus lowest exposure categories
2 HR GLUCOSE (PCBs) - 1 review						
General and high-risk (occupational exposure workers and population living in areas with PCB exposure) population (measured in serum)	Song et al. 2016 (6/11)	Total PCBs	MD 0.72 (95% CI = -7.44 to 8.87)	2	836	highest versus lowest exposure categories
FASTING INSULIN (PCBs) - 1 review						
General and high-risk (occupational exposure workers and population living in areas with PCB exposure) population (measured in serum)	Song et al. 2016 (6/11)	Total PCBs	MD -0.48 (95% CI = -2.06 to 1.09)	3	2882	highest versus lowest exposure categories
2 HR INSULIN (PCBs) - 1 review						
General and high-risk (occupational exposure workers and population living in areas with PCB exposure) population (measured in serum)	Song et al. 2016 (6/11)	Total PCBs	MD -17.56 (95% CI = -59.06 to 23.93)	2	836	highest versus lowest exposure categories
INSULIN RESISTANCE (HOMA-IR) (PCBs) - 1 review						
General and high-risk (occupational exposure workers and population living in areas with PCB exposure) population (measured in serum)	Song et al. 2016 (6/11)	Total PCBs	MD -2.05 (95% CI = -4.65 to 0.56)	3	933	highest versus lowest exposure categories
HEPATIC DISEASE MORTALITY (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Males and Females	SMR 1.5 (95% CI = 1 to 2.4) *	2	3467	*Special PCB exposure (poisoning)*
		Males	SMR 1.9 (95% CI = 1.3 to 2.8) *	2	1690	*Special PCB exposure (poisoning)*
		Females	SMR 1 (95% CI = 0.5 to 1.9)	2	1777	*Special PCB exposure (poisoning)*

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
THYROID FUNCTION (TSH) (PBDEs) - 1 review						
children and adults; General population (measured in serum lipid standardised (ng/g))	Zhao et al. 2015 (9/11)	Random effects	z -0.07 (95% CI = -0.14 to 0)	10	1064	median PBDEs levels < 30 ng/g lipids
		Fixed effects	z -0.07 (95% CI = -0.13 to -0.01) *	10	1064	median PBDEs levels < 30 ng/g lipids
THYROID FUNCTION (TT4) (PBDEs) - 1 review						
children and adults; General population (measured in serum lipid standardised (ng/g))	Zhao et al. 2015 (9/11)	Random and fixed effects	z 0.15 (95% CI = 0.06 to 0.24) *	3	466	median PBDEs levels between 35 ng/g and 100 ng/g lipids
Child neurodevelopmental outcomes						
INTELLIGENCE QUOTIENT (IQ) - FSIQ or McCarthy Scale (PBDEs) - 1 review						
Children (4-7 years); Prenatal (measured in umbilical cord blood or maternal serum)	Lam et al. 2017 (11/11)	BDE-47	β -3.7points (95% CI = -6.56 to -0.83points) *	4	595	per 10-fold increase in lipid-adjusted PBDE concentration (PBDE concentration range: <limits of detection–761 ng/g lipid)
Nutritional outcomes - no data						
Circulatory outcomes						
CARDIOVASCULAR DISEASE (PCBs) - 1 review						
children and adults; General population (measured in plasma, serum or urine)	Fu et al. 2020 (6/11)	Total PCBs	OR 1.32 (95% CI = 0.97 to 1.78)	4	8826	
		Congener or group				
		PCB 138 (group II)	OR 1.35 (95% CI = 1.1 to 1.66) *	7	13409	
		PCB 153 (group III)	OR 1.35 (95% CI = 1.13 to 1.62) *	10	49326	
		PCB 180 (group III)	OR 1.19 (95% CI = 0.98 to 1.45)	9	14735	
CARDIOVASCULAR DISEASE MORTALITY (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Males and Females	SMR 1.3 (95% CI = 1 to 1.7) *	2	3467	*Special PCB exposure (poisoning)*
CEREBROVASCULAR DISEASE MORTALITY (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Males and Females	SMR 1 (95% CI = 0.8 to 1.29)	2	3467	*Special PCB exposure (poisoning)*
		Males	SMR 0.9 (95% CI = 0.6 to 1.2)	2	1690	*Special PCB exposure (poisoning)*
		Females	SMR 1.1 (95% CI = 0.8 to 1.5)	2	1777	*Special PCB exposure (poisoning)*
HYPERTENSION (PCBs) - 1 review						
General population (measured in serum (lipid) or adipose tissue)	Park et al. 2016 (7/11)	*Congener or group*				
		PCB 118 (group II)	OR 1.26 (95% CI = 1 to 1.58) *	5	9134	
		PCB 153 (group III)	OR 1.09 (95% CI = 0.97 to 1.23)	6	9431	
		Dioxin-like PCBs (group II)	OR 1.45 (95% CI = 1 to 2.12) *	5	8793	
		Non-dioxin-like PCBs	OR 1 (95% CI = 0.89 to 1.12)	3	2048	
HYPERTENSION MORTALITY (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but	Li et al. 2015 (4/11) [p]	Males and Females	SMR 1.6 (95% CI = 0.9 to 2.9)	2	3467	*Special PCB exposure (poisoning)*
		Males	SMR 1.5 (95% CI = 0.7 to 3.4)	2	1690	*Special PCB exposure (poisoning)*
		Females	SMR 1.4 (95% CI = 0.3 to 5.6)	2	1777	*Special PCB exposure (poisoning)*

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
reference to PCB levels in blood of affected population)						
Respiratory outcomes						
BRONCHITIS (PCBs) - 1 pooled analysis						
Infants (< 18 months); prenatal (measured in maternal whole blood or serum/ cord plasma or serum/breast milk)	Gascon et al. 2014 (3/11) [p]	*PCB 153*				
		per doubling exposure	RR 1.06 (95% CI = 1.01 to 1.12) *	7	2990	
		Medium vs low exposure	RR 1.13 (95% CI = 0.98 to 1.31)	7	2990	
		High vs low exposure	RR 1.17 (95% CI = 0.97 to 1.41)	7	2990	
BRONCHITIS AND/OR WHEEZE (PCBs) - 1 pooled analysis						
Infants (< 18 months); prenatal (measured in maternal whole blood or serum/ cord plasma or serum/breast milk)	Gascon et al. 2014 (3/11) [p]	*PCB 153*				
		per doubling exposure	RR 1.02 (95% CI = 0.96 to 1.08)	9	4394	
		Medium vs low exposure	RR 1.04 (95% CI = 0.92 to 1.18)	9	4394	
		High vs low exposure	RR 0.95 (95% CI = 0.75 to 1.21)	9	4394	
WHEEZE (PCBs) - 1 pooled analysis						
Infants; prenatal (measured in maternal whole blood or serum/ cord plasma or serum/breast milk)	Gascon et al. 2014 (3/11) [p]	*PCB 153; < 18 months*				
		per doubling exposure	RR 1.01 (95% CI = 0.94 to 1.09)	8	3675	
		Medium vs low exposure	RR 1.06 (95% CI = 0.89 to 1.25)	8	3675	
		High vs low exposure	RR 0.92 (95% CI = 0.68 to 1.25)	8	3675	
		PCB 153; 18 to 49 months				
		per doubling exposure	RR 1.06 (95% CI = 0.98 to 1.15)	6	1754	
		Medium vs low exposure	RR 1.02 (95% CI = 0.87 to 1.19)	6	1754	
		High vs low exposure	RR 1.12 (95% CI = 0.95 to 1.32)	6	1754	
Skin-related outcomes – no data						
Cancer outcomes						
BREAST CANCER (PCBs) - 4 reviews		**Range of effects (Total PCBs):**	**OR 1.09 to 1.33 (95% CI = 0.72 to 2.65)**	**6 to 25**	**2458 to 128**	
Women; general environment (measured in serum, plasma or fat)	Roy et al. 2015 (3/11)	Total PCBs	OR 1.33 (95% CI = 0.72 to 2.65)	6	2458	High vs low exposure
	Zani et al. 2013 (2/11)	Total PCBs	OR 1.15 (95% CI = 0.92 to 1.43)	18	11645	High vs low exposure
		Study type				
		cohort studies	OR 1.01 (95% CI = 0.78 to 1.31)	6	unsp.	
		case-control studies	OR 1.19 (95% CI = 0.92 to 1.43)	12	unsp.	
	Zhang et al. 2015 (8/11)	*Total PCBs*	OR 1.09 (95% CI = 0.97 to 1.22)	25	12866	High vs low exposure
		Study type				
		Sensitivity analysis	OR 1.06 (95% CI = 0.98 to 1.15)	22	11729	excluding 3 retrospective studies with divergent ORs
		prospective studies	OR 1.02 (95% CI = 0.85 to 1.23)	9	unsp.	
		retrospective studies	OR 1.12 (95% CI = 0.96 to 1.3)	16	unsp.	
		Specimen type				
		Serum/plasma	OR 1.12 (95% CI = 0.95 to 1.32)	14	7556	
		Adipose tissue	OR 1.06 (95% CI = 0.7 to 1.6)	2	985	
		retrospective studies by geographical region				
		North America	OR 1.08 (95% CI = 1.01 to 1.16) *	12	unsp.	
		Asia	OR 1.91 (95% CI = 0.34 to 10.68)	3	unsp.	
	Leng et al. 2016 (8/11)	*PCB group 1: potentially oestrogenic*				

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		PCB 187	OR 1.18 (95% CI = 1.01 to 1.39) *	7	1456	
		PCB group 2: potentially antiestrogenic dioxin-like				
		PCB 118	OR 1.32 (95% CI = 0.98 to 1.78)	9	2446	
		PCB 118 (Cases ≥ 100)	OR 1.07 (95% CI = 0.87 to 1.32)	7	2346	
		PCB 118 (Cases < 100)	OR 3.72 (95% CI = 2.16 to 6.42) *	2	100	
		PCB 138	OR 1.08 (95% CI = 0.99 to 1.17)	11	2911	
		PCB 156	OR 1.19 (95% CI = 0.85 to 1.67)	6	1506	
		PCB 156 (as categorical variable)	OR 1.35 (95% CI = 1.02 to 1.78) *	5	1202	
		PCB 170	OR 1.28 (95% CI = 0.89 to 1.86)	6	1334	
		PCB 170 (≥ 12.5 ng/g lipid)	OR 1.05 (95% CI = 0.84 to 1.32)	5	1274	
		PCB group 3 (phenobarbital, CYP1A and CYP2B inducers)				
		PCB 99	OR 1.36 (95% CI = 1.02 to 1.8) *	4	970	
		PCB 153	OR 1.04 (95% CI = 0.81 to 1.34)	11	2881	
		PCB 153 (high quality)	OR 0.95 (95% CI = 0.78 to 1.15)	10	2821	Newcastle-Ottawa Scale >5
		PCB 180	OR 1.02 (95% CI = 0.81 to 1.29)	11	2881	
		PCB 180 (excluding Japan)	OR 1.1 (95% CI = 0.93 to 1.32)	10	2476	Countries other than Japan
		PCB 183	OR 1.56 (95% CI = 1.25 to 1.95) *	6	1506	
		Congeners reported by only two studies				
		PCB 28	OR 2.39 (95% CI = 0.16 to 35.6)	2	135	
		PCB 52	OR 0.98 (95% CI = 0.78 to 1.23)	2	130	
		PCB 74	OR 0.94 (95% CI = 0.84 to 1.04)	2	334	
		PCB 77	OR 1.2 (95% CI = 0.39 to 3.73)	2	113	
		PCB 101	OR 1.02 (95% CI = 0.8 to 1.31)	2	130	
		PCB 105	OR 2.22 (95% CI = 1.18 to 4.17) *	2	287	
		PCB 126	OR 1.4 (95% CI = 0.78 to 2.5)	2	113	
		PCB 167	OR 0.87 (95% CI = 0.07 to 10.71)	2	142	
NON-HODGKIN'S LYMPHOMA (PCBs) - 3 reviews		**Range of effects (total PCBs):**	**OR 1.4 to 1.5 (95% CI = 1.10 to 1.71) ***	**6 to 11**	**2540 to 4422**	
children and adults; General population (measured in blood, serum and fat)	Zani et al. 2013 (2/11)	Total PCBs	OR 1.4 (95% CI = 1.14 to 1.71) *	11	4422	High vs low exposure
		Study type				
		Cohort studies	OR 1.34 (95% CI = 0.97 to 1.86)	6	unsp.	
		Case-control studies	OR 1.51 (95% CI = 1.17 to 1.96) *	4	unsp.	
	Catalani et al. 2019 (6/11)	Retrospective studies	RR 0.98 (95% CI = 0.58 to 1.38)	8	1106	
	Zani et al. 2017 (5/11)	Total PCBs	OR 1.5 (95% CI = 1.1 to 1.7) *	6	2540	High vs low exposure
		Total PCBs	OR 1.42 (95% CI = 1.1 to 1.83) *	5	2668	Serum PCB ≈ 1000 versus ≲ 500 ng/g lipid
		Congener or group				
	Catalani et al. 2019 (6/11)	PCB 118	RR 0.82 (95% CI = 0.53 to 1.1)	8	1571	High vs low exposure
	Zani et al. 2013 (2/11)	PCB 118	OR 1.2 (95% CI = 0.8 to 1.8)	7	unsp.	High vs low exposure
	Catalani et al. 2019 (6/11)	PCB 138	RR 0.93 (95% CI = 0.59 to 1.27)	8	1571	High vs low exposure
	Zani et al. 2013 (2/11)	PCB 138	OR 1.4 (95% CI = 1 to 1.8)	6	unsp.	High vs low exposure
	Catalani et al. 2019 (6/11)	PCB 153	RR 1.1 (95% CI = 0.68 to 1.53)	8	1571	High vs low exposure
	Zani et al. 2013 (2/11)	PCB 153	OR 1.5 (95% CI = 1.2 to 1.9) *	7	unsp.	High vs low exposure
	Catalani et al. 2019 (6/11)	PCB 180	RR 1.07 (95% CI = 0.67 to 1.47)	7	954	High vs low exposure

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
	Zani et al. 2013 (2/11)	PCB 180	OR 1.4 (95% CI = 1 to 2.1)	6	unsp.	High vs low exposure
	Catalani et al. 2019 (6/11)	PCB 170	RR 0.89 (95% CI = 0.58 to 1.21)	5	984	High vs low exposure
NON-HODGKIN'S LYMPHOMA - Chronic Lymphocytic Leukemia (CLL) (PCBs) - 1 review						
children and adults; General population (measured in blood, serum and fat)	Catalani et al. 2019 (6/11)	Total PCBs	RR 0.63 (95% CI = 0.39 to 0.87) *	4	573	High vs low exposure
NON-HODGKIN'S LYMPHOMA - Diffuse large B-cell lymphoma (DLBCL) (PCBs) - 1 review						
children and adults; General population (measured in blood, serum and fat)	Catalani et al. 2019 (6/11)	Total PCBs	RR 0.68 (95% CI = 0.24 to 1.12)	6	1049	High vs low exposure
NON-HODGKIN'S LYMPHOMA - Follicular Lymphoma (FL) (PCBs) - 1 review						
children and adults; General population (measured in blood, serum and fat)	Catalani et al. 2019 (6/11)	Total PCBs	RR 1.21 (95% CI = 0.79 to 1.64)	5	920	High vs low exposure
			Cancer-related mortality			
ALL CANCER MORTALITY (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Males	SMR 1.3 (95% CI = 1.1 to 1.6) *	2	1690	*Special PCB exposure (poisoning)*
		Females	SMR 0.8 (95% CI = 0.5 to 1.3)	2	1777	*Special PCB exposure (poisoning)*
BREAST CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Females	SMR 1.1 (95% CI = 0.4 to 2.9)	2	1777	*Special PCB exposure (poisoning)*
LEUKEAMIA (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Males	SMR 2 (95% CI = 0.6 to 6)	2	1690	*Special PCB exposure (poisoning)*
LIVER CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Females	SMR 2 (95% CI = 1.1 to 3.6) *	2	1777	*Special PCB exposure (poisoning)*
LUNG CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment:	Li et al. 2015 (4/11) [p]	Males and Females	SMR 1.5 (95% CI = 1.1 to 2.1) *	2	3467	*Special PCB exposure (poisoning)*
PCB contaminated food		Males	SMR 1.2 (95% CI = 1.2 to 2.3) *	2	1690	*Special PCB exposure (poisoning)*
(measure not specified but		Females	SMR 0.7 (95% CI = 0.3 to 1.9)	2	1777	*Special PCB exposure (poisoning)*

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
reference to PCB levels in blood of affected population)						
MALIGNANT MELANOMA (PCBs) - 1 review						
Adults; high-risk environment: occupationally exposed workers (measured in blood)	Zani et al. 2017 (5/11)	Main analysis	SMR 1.32 (95% CI = 1.05 to 1.64) *	8	214241	*Special PCB exposure (occupational)*
NON-HODGKIN'S LYMPHOMA (PCBs) - 1 review						
Adults; high-risk environment: occupationally exposed workers (measured in blood)	Zani et al. 2017 (5/11)	Main analysis	SMR 0.94 (95% CI = 0.73 to 1.23)	7	174207	*Special PCB exposure (occupational)*
PANCREATIC CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Females	SMR 1.1 (95% CI = 0.4 to 3.75)	2	1777	*Special PCB exposure (poisoning)*
RECTAL CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Females	SMR 1 (95% CI = 0.2 to 5.8)	2	1777	*Special PCB exposure (poisoning)*
STOMACH CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Females	SMR 0.3 (95% CI = 0.1 to 1.1)	2	1777	*Special PCB exposure (poisoning)*
UTERINE CANCER (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Females	SMR 1.1 (95% CI = 0.4 to 3.4)	2	1777	*Special PCB exposure (poisoning)*
			Mortality			
ALL-CAUSE MORTALITY (PCBs) - 1 pooled analysis						
Adults; high-risk environment: PCB contaminated food (measure not specified but reference to PCB levels in blood of affected population)	Li et al. 2015 (4/11) [p]	Males and Females	SMR 1.1 (95% CI = 1.1 to 1.2) *	2	3467	*Special PCB exposure (poisoning)*
		Males	SMR 1.2 (95% CI = 1.1 to 1.3) *	2	1690	*Special PCB exposure (poisoning)*
		Females	SMR 1.1 (95% CI = 0.9 to 1.2)	2	1777	*Special PCB exposure (poisoning)*

Table legend:

*[p] Indicates a pooled analysis, * indicates significant effect.*

Studies or participants unspecified (unsp.) indicates no data available from the reviews

Total PCBs: composite measure of PCB exposure which is the total concentration of all PCB congeners measured in the individual primary research study.

Special PCB exposure (poisoning): the main exposure to PCBs in this study or studies was attributable to PCB poisoning of a geographically-defined population through contaminated food products

Special PCB exposure (occupational): the main exposure to PCBs in this study or studies was attributable to the occupation (work) of the sample population.

Total PBDEs: a composite measure of PBDE exposure which is the total concentration of all PBDE congeners measured in the individual primary research study.

Descriptive summary of included reviews

Presentation of studies in this section is in alphabetical order to facilitate rapid reference. This section includes details of exposures investigated, number and type of studies and total sample size, number of meta-analyses presented and various outcomes reported (Full details are available in Appendix 8). AMSTAR scores are provided for each reference.

Cano-Sancho et al. (2019) - *Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis. No COIs declared, AMSTAR Score: 8/11.*

Cano-Sancho et al. (2019) explored the association between organochlorine chemicals exposure and endometriosis among women. The review included a total of 17 studies – including case control (n=16) and cohort (n=1), with a total of 32,743 participants. Nine studies with 31041 participants were included in the meta-analysis. An adapted version of the National Toxicology Program/ Office of Health Assessment and Translation (NTP/OHAT) Risk of Bias Rating Tool for Human and Animal Studies was used to assess the quality of all the cohort and case-control studies. Quality scores of studies were predominantly tier 1 or 2 indicating the presence of plausible bias. The exposure route and units were not reported, the exposure measure was blood serum, and the time period was not reported. Risk of endometriosis risk was the main outcome of interest. For PCB exposure, the authors concluded a significant positive association with endometriosis risk.

Catalani et al. (2019) - *Occupational and environmental exposure to polychlorinated biphenyls and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis of epidemiology studies. No COIs declared, AMSTAR Score: 6/11.*

Catalani et al. (2019) explored the association between polychlorinated biphenyls (PCB) exposure and non-Hodgkin's lymphoma. The review included a total of 30 studies – including cohort (n=12) and case control (n=18), with a total of 309,975 participants. All studies were included in the meta-analysis. The Newcastle-Ottawa Scale appraisal tool was used to assess the quality of all included studies. Authors did report an interpretation of the critical appraisal results. The exposure routes included occupational, ingestion (food contamination) or being residents in a polluted area, the exposure measure was not reported, period included 1920-2008. The outcome reported was non-Hodgkin's lymphoma risk. It should be noted that the combined analysis for the overall summary (general population) [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead. For PCB exposure, the authors concluded no significant association with non-Hodgkin's lymphoma risk.

Fu et al. (2020) - *The association between environmental endocrine disruptors and cardiovascular disease: A systematic review and meta-analysis. No COIs declared, AMSTAR Score: 6/11.*

Fu et al. (2020) explored the association between polychlorinated biphenyl (PCBs), any phthalate compound, BPA and the risk of cardiovascular disease among a general population in whom environmental exposure to endocrine disrupters could be determined. The review and meta-analyses included a total of 29 studies – (cross-sectional studies (n=17), retrospective cohort (n=7), prospective cohort (n=4), case control (n=1)), with a total of 41854 participants. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies. The quality scores of studies ranged from 7 to 9 (all considered to be of high quality).

For exposure to BPA there was a significant positive association with risk of cardiovascular disease (no subgroup analysis conducted).

For exposure to any phthalate, there was a significant positive association with risk of cardiovascular disease. When grouped based on phthalate compound, there was no association between exposure to MEP, MiBP, MBzP, MEHP, MEHHP, MEOHP or MEP.

PCB exposure was via an unspecified route, the measure and timing of this exposure was also unspecified by the authors. The only outcome reported was the risk of cardiovascular disease. For PCB exposure across populations, the authors concluded significant positive association with risk of cardiovascular disease. With subgroup analysis according to PCB subtype/congener, exposure to PCB 138 and PCB 153 were found to be positively associated with an increased risk of cardiovascular disease. There were no associations found for PCB 180 nor total PCBs.

It should be noted that the combined analyses for BPA were valid, however, for phthalates and PCBs, the overall summary (and other composite exposure findings) were invalid as data from individual studies were used repeatedly within these analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead.

The authors suggest that exposure to environmental endocrine disruptors is a risk factor for CVD. PCBs, BPA, OCPs and PAEs have a great impact on the development and progression of CVD. Except PCB180 and total PCBs, PCB138, PCB153, were all CVD risk factors. However, the findings from the invalid combined analyses should be interpreted with caution.

Gascon et al. (2014) - *Prenatal exposure to DDE and PCB 153 and respiratory health in early childhood: a meta-analysis. No COIs declared, AMSTAR Score: 3/11.*

Gascon et al. (2014) explored the association between prenatal polychlorinated biphenyl-153 (PCB 153) and Dichlorodiphenyldichloroethylene (DDE) (a pesticide) exposure and the occurrence of bronchitis and wheeze in young children from 10 European cohorts including a total of 4,608 mother-infant pairs. All cohorts were included in the meta-analysis. Critical appraisal was not performed. PCB 153 exposure was via maternal/prenatal exposure, measured in ng/L or ng/g lipid from maternal blood (whole or serum), cord plasma or serum or breast milk. The outcomes reported were bronchitis, wheeze or a combination of bronchitis and wheeze. For PCB 153 exposure in infants <18 months of age, the authors concluded no significant association with bronchitis, wheeze or bronchitis and wheeze combined. For infants > 18 months of age only wheeze was reported and there was no significant association with PCB 153 exposure.

Govarts et al. (2012) - *Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European birth cohorts. No COIs declared, AMSTAR Score: 3/11.*

Govarts et al. (2012) explored the association between persistent organochlorines including polychlorinated biphenyls (PCBs) and Dichlorodiphenyldichloroethylene (DDE) (a pesticide) exposure and birthweight from 12 European cohorts. The meta-analysis included a total of 12 cohorts, with a total of 7,762 mother-infant pairs. Critical appraisal was not undertaken. PCB exposure was via maternal/prenatal exposure, measured in ng/L or ng/g fat from maternal blood (whole or serum), cord plasma or serum or breast milk. The outcome reported was birthweight. The authors concluded a significant negative association with birth weight for prenatal exposure to PCBs. Authors concluded that low-level PCB exposure (or correlated exposures) impairs foetal growth by around 150g per 1µg/L increase in PCB 153 cord serum concentration.

Lam et al. (2017) - *Developmental PBDE exposure and IQ/ADHD in childhood: a systematic review and meta-analysis. No COIs declared, AMSTAR Score: 11/11.*

Lam et al. (2017) explored the association between polybrominated diphenyl ethers (PBDE) and IQ among mother-child pairs studied from late-pregnancy to children of 84 months. The review included a total of 15 studies – (cross sectional(n=1), prospective cohort (n=13), case control (n=1)), with a total of 2884 participants. The number of studies included in the meta-analysis was 4 with

595 participants. The authors designed their own critical appraisal tool to assess the quality of the included studies and state that the risk of bias for studies of IQ was generally "low" or "probably low" across studies and domains. PBDE exposure was via an unspecified route, however, detection was limited to maternal or umbilical cord serum, plasma or whole blood or maternal milk expressed in logarithmic units. The time of the exposure was unspecified but limited to prenatal exposure. The only outcome reported was IQ. For exposure to PBDE across populations, the authors found a negative association between PBDE exposure and intelligence as measured by IQ.

Leng et al. (2016) - *Polychlorinated biphenyls and breast cancer: A congener-specific meta-analysis. No COIs declared, AMSTAR score: 8/11*

Leng et al. (2016) explored the association between PCB congeners and breast cancer among females with a clear breast cancer diagnosis. The review included 16 studies –case control (n=11) and nested case control (n=5) with a total of 7,041 participants. The number of studies used in the meta-analyses was 13 with 6,615 participants. The Newcastle-Ottawa Scale appraisal tool was used to assess the quality of included studies. Quality scores for included studies were moderate to high. No description was provided regarding the exposure route; PCB was measured in serum and adipose tissue in ng/g. Outcome reported was incidence of breast cancer. For PCB 118, PCB 138, PCB 156 and PCB 180 exposure across populations, no associations were found with breast cancer. For PCB 187, PCB 99 and PCB 183 exposure, the authors concluded a significant positive association with breast cancer. A dose-response effect could not be properly evaluated, and that the mechanism of effect was suggested to be through the induction of the CYP2B family of cytochrome P450 enzymes.

Li et al. (2015) - *Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: A meta-analysis of two highly exposed cohorts. No COIs declared, AMSTAR score: 4/11.*

Li et al. (2015) explored the association between PCBs among workers from two separate contamination events ("Yusho" incident, Japan [1968] and "Yu-Cheng" incident, Taiwan [1979]). The review included two cohort studies with a total of 3,467 participants; all participants were included in the meta-analyses. No critical appraisal was undertaken. Exposure to PCBs was via indigestion during two separate contamination incidents: in Yusho, the oil contamination was estimated to be 1,000 to 3,000 ppm with an exposure time of one to two months, and in Yu-cheng, concentrations were 67 to 99 ppm over a period of nine to 10 months. Outcomes (ICD-9 cause of death codes) were measured using all-cause standardised mortality rates for: all causes; all cancers; stomach, rectum, liver, pancreas, lung, female breast and uterine cancer; leukemia; hypertension; heart disease; cerebrovascular disease; and hepatic disease. For PCB exposure across populations, the authors concluded a significant positive association with all-cause mortality, mortality due to lung cancer and mortality due to hepatic disease. When grouped by gender, the same associations were seen in males, but not females. Exposure to PCB across all populations was not undertaken for all cancer mortality and liver cancer mortality, due to heterogeneity of studies (> 50%). PCB exposure was found to be significantly positively associated with all cancer mortality in males, but not females and significantly positively associated with lung cancer mortality in females, but not males. For PCB exposure across populations, the authors concluded a significant positive association with mortality due to heart disease; no subgroup analyses were undertaken. No other significant associations were found. Meta-analyses of Yu-cheng and Yusho cohorts showed similar elevation from all cancer, lung cancer, heart disease and hepatic disease mortalities in exposed men.

Nieminen et al. (2013) - *Polychlorinated biphenyls (PCBs) in relation to secondary sex ratio –A systematic review of published studies. No COIs declared, AMSTAR Score: 3/11.*

Nieminen et al. (2013) explored the associations between PCBs and secondary sex ratio (proportions of males) through maternal and paternal exposure. The review included a total of 15 studies (no indication of study design), there was no information on the total sample size in this review. The methodological quality was assessed by the authors, but no formalised scale was

utilised, nor an assessment presented. PCB exposure was direct or indirect through various means (Indigenous people of the Russian Artic; Lake Michigan mothers who had eaten Lake Michigan fish); mothers who came to the hospital for delivery; female anglers; individuals who purchased food from contaminated farms, fish-eaters, residents of post codes that contain PCB waste sites, families in polluted JingHai country, individuals who ingested contaminated waste, women who had worked in three electrical capacitor plants), through a non-specific exposure time, measured through blood serum (µg/L or ng/g), cord serum (ng/mL), breast milk (mg/kg). High exposure group was taken as defined in the original papers: as the upper half (values above median), the highest quartile, quintile or 10th percentile group of the measured PCB distribution (however, no details were presented in the review). For direct PCB exposure, the authors concluded that there was a significant positive association with direct high maternal exposures and secondary sex ratio, but not with low maternal exposure. For PCB exposure, the authors concluded that for high paternal exposure that was no significant association, however, there was a significant difference in boys between low and high paternal exposure.

Park et al. (2016) - *Body burden of persistent organic pollutants on hypertension: a meta-analysis. No COIs declared, AMSTAR Score: 7/11.*

Park et al. (2016) explored the association between persistent organic pollutants including PCBs and DDE (a pesticide) exposure and hypertension risk in the general population. The review included 11 studies- including cross sectional (n=10) and cohort (n=1), with a total of 14,742 participants. All studies were included in the meta-analysis. The Newcastle-Ottawa Scale was used to assess the quality of all included studies. Authors decided to include all 11 studies based on quality, since the Newcastle-Ottawa scale scores of all studies were equal to or greater than 6 (moderate-high quality). PCB exposure route was not reported, but was measured in serum or adipose tissue as ng/g lipid, pg/g lipid, µg/L or µg/kg lipid. The outcome reported was hypertension. For exposure to PCBs (118, 153, non-dioxin like and dioxin like) across populations, the authors concluded no significant association with hypertension in the general population.

It should be noted that the combined analyses for the overall summary (and other composite exposure findings) were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; only relevant analysis of individual chemical exposures have been extracted.

Roy et al. (2015) – *Integrated bioinformatics, environmental epidemiologic and genomic approaches to identify environmental and molecular links between endometriosis and breast cancer. No COIs declared, AMSTAR Score: 3/11.*

Roy et al. (2015) explored the association between endocrine-disrupting chemicals including polychlorinated biphenyls (PCBs), bisphenol A (BPA) and phthalate exposure and risk of developing estrogen-dependent breast cancer and endometriosis. The review included 23 studies – including case control (n=20), cohort (n=2), and cross sectional (n=1), with a total of 9,781 participants. The number of studies used in the meta-analysis was 12 (n=6 breast cancer, n=6 endometriosis) with 3,435 participants. No critical appraisal was undertaken. Chemical exposure was not reported, but was measured in ng/g from serum or plasma, and the time period was not reported. The outcomes reported were breast cancer and endometriosis risk. The authors concluded an increased risk of breast cancer and endometriosis with PCB exposure. No meta-analysis was performed for BPA or phthalate exposure and breast cancer or endometriosis risk due to paucity of studies.

Song et al. (2016) - *Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. No COIs declared, AMSTAR Score: 7/11.*

Song et al. (2016) explored the association between endocrine-disrupting chemical exposure and risk of type 2 diabetes and diabetes-related metabolic traits. The review included a total of 49 studies- including cross sectional (n=41) and cohort (n=8), with a total of 55,774 participants. Thirty-two studies were included in the meta-analysis for polychlorinated biphenyls (PCBs; n=21),

phthalates (n=7) and bisphenol A (BPA; n=4). Critical appraisal was not undertaken. Exposure routes were not reported, but were measured in serum or urine as pg/ml, pg/g or ng/g lipid. The outcome reported was type 2 diabetes and it was analysed using a risk ratio as highest versus lowest exposure categories (no further details of the categories reported). For exposure to PCBs and BPA across populations, the authors concluded a significant positive association with type 2 diabetes risk. No association was found for phthalate exposure and type 2 diabetes risk. It should be noted that multiple subgroups from within a single study were included within an analysis of individual chemical exposures (BPA, phthalates and PCBs) and these data have been extracted and included, assuming these are mutually exclusive subgroups; however, this may underestimate true heterogeneity.

Wu et al. (2013) - *Persistent organic pollutants and Type 2 Diabetes: a prospective analysis in the nurses' health study and meta-analysis. No COIs declared, AMSTAR Score: 4/11.*

Wu et al. (2013) explored the association between polychlorinated biphenyls (PCBs) and the prevalence of diabetes. The study was a cohort study (NHS; Nurses health study; female only; two cohorts with breast cancer and non-Hodgkin's lymphoma) with that data combined with that of six other studies that included adult men and women from the general population in meta-analysis. The meta-analysis included seven studies – (prospective cohort (n=5, including NHS), case control (n=2)), with a total of 4,975 participants includingthe authors primary data in the analysis. No critical appraisal of the included studies was performed. PCB exposure was via an unspecified route, measured in the serum (units unspecified), for an unspecified period. The only outcome reported was the incidence of diabetes. For exposure to total PCBs, the authors concluded significant positive association with the incidence of diabetes. No association with diabetes was observed with exposure to PCB 118, PCB 138, PCB 153, PCB 180, DDE and DDT. However, for the exposure of hexachlorobenzene (HCB) an organochloride, there was a positive association with diabetes.

Zani et al. (2017) - *Do polychlorinated biphenyls cause cancer? A systematic review and meta-analysis of epidemiological studies on risk of cutaneous melanoma and non-Hodgkin lymphoma. No COIs declared, AMSTAR Score: 5/11.*

Zani et al. (2017) explored the association between PCB exposure and mortality due to melanoma and non-Hodgkin's lymphoma among workers (both men and women) in capacitor and transformer producing factories, in electrical power generation and the telecommunication industry. The review included a total of 11 studies– 10 cohort studies and one case-control study with 217,048 participants in total. The number of studies included in the meta-analysis was 10, with 214,241 participants. No critical appraisal was performed to assess the quality of the included studies. PCB exposure via an unspecified route but limited to occupational exposure, measured in ng/g lipid, for an unspecified period. Outcomes reported were mortality due to melanoma and mortality due to non-Hodgkin's lymphoma and analysed using standardised mortality ratios. For occupational exposure across populations, the authors concluded there was a significant positive association with mortality due to melanoma, but there was no association with mortality due to non-Hodgkin's lymphoma. No subgroup analyses were conducted. The authors conclude there is little strong evidence that PCB exposure can increase the risk of melanoma and non-Hodgkin's lymphoma in humans.

Zani et al. (2013) - *Polychlorinated biphenyls and cancer: an epidemiological assessment. No COIs declared, AMSTAR score: 2/11.*

Zani et al. (2013) explored the association between polychlorinated biphenyl (PCB) and cancer among workers from "Yusho" incident, Japan (1968) and "Yu-Cheng" incident, Taiwan (1979). The review included a total of 29 studies – cohort and case-control studies with no specific breakdown of the numbers, with a total of 16,067 participants. All studies were used in the meta-analyses. No critical appraisal of studies was undertaken. PCB exposure was via a single incident of ingestion, measured in lipid samples in ng/g. Outcomes reported were incidence of non-Hodgkin's lymphoma

and breast cancer, analysed quantiles of exposure – high/low. For PCB across population, the authors concluded a significant positive association with non-Hodgkin's lymphoma; no association between PCB serum levels and breast cancer was found. Evidence was found for a role of PCBs in the development of non-Hodgkin's lymphoma, but not of other cancers, although the inconsistent results of occupational cohort studies and of studies performed on highly polluted people did not allow a firm conclusion on PCB carcinogenicity to be drawn.

Zhang et al. (2015) - *Environmental polychlorinated biphenyl exposure and breast cancer risk: a meta-analysis of observational studies. No COIs declared, AMSTAR score: 8/11.*

Zhang et al. (2015) explored the association between PCB and breast cancer among females aged 18 years and over. The review included 25 studies -retrospective cohort (n=16) and prospective cohort (n=9), with a total of 12,866 participants. The Newcastle-Ottawa Scale was used to assess the quality of included studies. Quality scores of the 25 studies ranged from five (moderate) to nine (high). No descriptions were provided regarding the exposure route; PCB was measured in lipids in ng/g. Outcome was risk of breast cancer. The combined analyses for the overall summary [and other composite exposure findings] were valid, however, the results of analysis of individual chemical exposures were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore, these individual chemical exposures results have not been extracted for the review. For PBC across populations, the authors concluded no association between risk of breast cancer and total PCB exposure.

Zhao et al. (2017) - *Correlation between prenatal exposure to polybrominated diphenyl ethers (PBDEs) and infant birth outcomes: a meta-analysis and an experimental study. No COIs declared, AMSTAR score: 9/11.*

Zhao et al. (2017) explored the association between PBDEs (total), BDE 47, BDE 99, BDE 100 BDE 153 and infant birth outcomes among infants (at birth). The review included seven cross-sectional studies with a total of 1,332 participants. An unnamed cross-sectional assessment tool was used to assess the quality of included studies. Quality scores of the seven studies were high. Exposure to PBDEs was via the mother (prenatal exposure) measured in lipid samples in ng/g. Outcomes reported were birthweight (g), birth length (cm), and head circumference (cm). For prenatal exposure of total PBDEs across populations, the authors concluded a significant negative association with birth weight, but no association with birth length nor head circumference. When grouped by gender, the authors concluded a significant negative association with birth weight for males, but not females. No associations were found between the congeners (BDE 47, BDE 99, BDE 100, BDE 153) and birth weight, length nor head circumference. Overall, there was a gender difference in birth weight in the responses to prenatal exposure to PBDEs in the subgroup analysis of epidemiological studies.

Zhao et al. (2015) - *The correlation between polybrominated diphenyl ethers (PBDEs) and thyroid hormones in the general population: a meta-analysis. No COIs declared, AMSTAR score: 9/11.*

Zhao et al. (2015) explored the association between PBDEs and thyroid function among children (including infants and neonates) and adults. The review included 19 cross-sectional studies, with a total of 2,951 participants. The Agency for Healthcare Research and Quality (Rostom et al., 2004) was used to assess the quality of included studies. Quality scores of the 19 studies were 18 to 22 (n=4), 13 to 17 (n=7), 11 to 13 (n=5), 9 (n=1). Exposure of PBDEs was via the mother (prenatal exposure) measured in lipids in ng/g. Outcomes reported were thyroid stimulating hormone (TSH) and total thyroxine (TT4). When grouped by exposure level, the authors concluded a significant negative correlation with median PBDE levels < 35 ng/g lipid (ten studies, 1,034 participants) and median PBDE levels between 35 ng/g and 100 ng/g lipid (three studies, 466 participants), but not over 100 ng/g (the remaining eight studies, 1,451) and TT4. Authors concluded that effects of PBDEs on thyroid function may mainly depend on PBDEs exposure and their levels found in the

body. The relationship between PBDEs exposure and changes in thyroid function fit an approximate u-shaped curve.

Zou et al. (2019) - *Neonatal weight and prenatal exposure to polychlorinated biphenyls: a meta-analysis; no COIs declared, AMSTAR score: 4/11.*

Zou et al. (2019) explored the association between PCBs and birth outcomes (neonatal birth weight) among infants. The review included seven studies (study types were not reported) with a total of 8,054 participants. No critical appraisal of studies was undertaken. Exposure of PCB was via the mother (prenatal exposure); no detail was given on the exposure route or measure. Outcome reported was birth weight (g). For PCB exposure across populations, the authors concluded a significant negative association with infant birth weight; no subgroup analysis was undertaken. No further conclusions were drawn.

Critical appraisal of included reviews and pooled analyses

Methodological quality of the included 15 systematic reviews with meta-analyses and four pooled analyses assessed using the AMSTAR tool is presented in the following table.

Table 3.6: Critical appraisal of flame retardant reviews and pooled analyses

Author (Year)	Question											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Cano-Sancho et al. (2019)	Y	Y	CA	N	N	Y	Y	Y	Y	Y	Y	**8**	PubMed and Web of Science were searched but no supplementary search of the literature and no grey literature search were undertaken (Q3&4); No list of excluded studies provided (Q5); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Catalani et al. (2019)	Y	CA	Y	N	N	Y	Y	N	CA	Y	Y	**6**	Study selection done in duplicate; however, not clear if extraction was done in duplicate or if any strategy was undertaken to check the data extraction (Q2); No grey literatures search was undertaken (Q4); while a list of included studies was provided, there was no list of excluded studies provided (Q4 &Q5); authors undertook quality assessment using the Newcastle-Ottawa Scale, however, the results of this appraisal were not mentioned futher (Q8). Combined analyses for the overall summary (general population) [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Fu et al. (2020)	N	CA	Y	N	N	Y	Y	Y	CA	Y	Y	**6**	No *a priori* protocol (Q1); Study selection done in duplicate; however, not clear if extraction was done in duplicate or if any strategy was undertaken to check the data extraction (Q2); no grey literature search undertaken (Q4); no list of excluded studies available (Q5); table and narrative appear to be presented with relevant details. NB. an exclusion criterion in this study was to exclude those for which an OR could not be calculated (~33 studies) - this is acceptable practice for conduct of a meta-analysis, however, the SR is likely at risk of bias - evidence has been omitted on this basis (Q6). Combined analyses for BPA were valid, however, for phthalates and PCBs, the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (double counting), artificially increasing the sample size and constraining confidence limits; therefore, these results have not been extracted for the review. Where available, results of analysis of individual chemical exposures have been extracted instead (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Gascon et al. (2014)	N	N	N	N	N	Y	N	N	Y	N	Y	**3**	This was not a systematic review but rather a pooled analysis of data; therefore, no systematic methods relating to searching, screening, extraction and appraisal of the evidence were undertaken. However, meta-analyses of available data were undertaken (Q6 & Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Govarts et al. (2012)	N	N	N	N	N	Y	N	N	Y	N	Y	**3**	This was not a systematic review but rather a pooled analysis of data; therefore, no systematic methods relating to searching, screening, extraction and appraisal of the evidence were undertaken. However, meta-analyses of available data were undertaken and authors have applied a comprehensive range of regression analyses to explore effect modifiers (Q6 & Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).

Author (Year)	Question											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Lam et al. (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**	Conflict of interest in the individual review was discussed but not for all included articles (Q11).
Leng et al. (2016)	N	CA	Y	Y	Y	Y	Y	N	Y	Y	Y	**8**	Stated the use of PRISMA to guide the review but no mention of a protocol (Q1); Duplicate data extraction undertaken but no mention of duplicate screening (Q2); key words used but no systematic search provided (Q3); quality results were not used in the formulation of the recommendations (Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Li et al. (2015)	N	Y	N	N	Y	Y	N	N	Y	N	N	**4**	This was not a systematic review but rather a pooled analysis of data; therefore, no systematic methods relating to searching, screening, extraction and appraisal of the evidence were undertaken. However, meta-analyses of available data were undertaken (Q6 & Q9); no conflict of interest available in the individual review and all included articles (Q11).
Nieminen et al. (2013)	N	CA	Y	N	Y	Y	N	N	CA	N	N	**3**	No *a priori* protocol (Q1); no grey literature search undertaken (Q4); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8); unable to determine the type of meta-analysis which was conducted (Q9); no publication bias assessment undertaken (Q10); no conflict of interest available in the individual review and all included articles (Q11).
Park et al. (2016)	N	Y	Y	N	N	Y	Y	Y	CA	Y	Y	**7**	No *a priori* protocol (Q1); no grey literature search undertaken (Q4); no list of excluded studies provided (Q5); combined analyses for the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; only relevant analysis of individual chemical exposures have been extracted (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Roy et al. (2015)	N	N	N	N	N	Y	N	N	Y	N	Y	**3**	Search was undertaken only in MEDLINE as written in the published paper; however, in the PROSPERO version, both MEDLINE and Embase and reference list were searched (Q3); No search of grey literature (Q4); no list of excluded studies (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8). conflict of interest in the individual review was discussed but not for all included articles (Q11).
Song et al. (2016)	Y	Y	CA	N	N	Y	N	N	Y	Y	Y	**6**	Search was undertaken only in MEDLINE as written in the published paper; however, in the PROSPERO version, both MEDLINE and Embase and reference list were searched (Q3); No search of grey literature (Q4); no list of excluded studies (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8). Note: Multiple subgroups within a study were included within an analysis of individual chemical exposures (BPA, phthalates and PCBs) and these data have been extracted and included, assuming these are mutually exclusive subgroups; however, this may underestimate of true heterogeneity (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Wu et al. (2013)	N	Y	CA	N	N	Y	N	N	Y	N	Y	**4**	This study is not a systematic review. This is a prospective cohort study that has included its cohort in meta-analysis with other similar published data. As a pooled analysis, restricting to included cohorts is appropriate. However, it is difficult to determine what/where other cancer studies have been searched (breast and non-Hodgkin's lymphoma) (Q2&3); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Zani et al. (2017)	N	CA	Y	N	N	Y	N	N	Y	Y	Y	**5**	No *a priori* protocol (Q1); duplicate screening done but not clear about extraction and decisions in extracting data (Q2); no grey literature search undertaken (Q4); no list of excluded studies provided but list of included studies are available (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).

Author (Year)	Question											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
Zani et al. (2013)	N	N	N	N	N	Y	N	N	Y	N	N	**2**	No *a priori* protocol (Q1); No comprehensive search undertaken (Q2-Q4); no list of excluded studies (Q5); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8); no conflict of interest available in the individual review and all included articles (Q11).
Zhang et al. (2015)	N	Y	Y	Y	N	Y	Y	Y	CA	Y	Y	**8**	No *a priori* protocol (Q1); no list of excluded studies provided (Q5); consideration of quality is explored in the discussion (Q8); combined analyses for the overall summary [and other composite exposure findings] were valid, however, the results of analysis of individual chemical exposures were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore these individual chemical exposures results have not been extracted for the review (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Zhao et al. (2017)	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	**9**	No list of excluded studies provided (Q5); quality results were not used in the formulation of the recommendations (Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Zhao et al. (2015)	Y	Y	Y	CA	Y	Y	Y	Y	CA	Y	Y	**9**	No grey literature search undertaken (Q4); combined analyses for the overall summary [and other composite exposure findings] were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits for overall analysis and some subgroups based on median PDBE concentration in serum; only relevant analysis of individual chemical exposures have been extracted (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11).
Zou et al. (2019)	N	Y	Y	N	N	N	N	N	CA	Y	Y	**4**	No *a priori* protocol (Q1); no grey literature search was undertaken (Q4); no list of excluded studies provided (Q5); list of included studies in the table and in the meta-analysis were inconsistent (Q6 and Q9); no study quality assessment was undertaken and therefore no quality results were used in the formulation of the recommendations (Q7 & Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11).

*Legend: Y = Yes, N = No, CA = Can't Answer

Flame retardants and birth outcomes

Three systematic reviews with meta-analyses (Nieminen et al., 2013; Zhao et al., 2017; Zou et al., 2019) and one pooled analysis (Govarts et al., 2012) explored the association between prenatal exposure to flame retardants and birth outcomes; of these, three explored exposure to PCBs (Govarts et al., 2012; Nieminen et al., 2013; Zou et al., 2019), and one exposure to PBDEs (Zhao et al., 2017). Govarts et al. (2012) specifically reported on PCB 153 whilst Nieminen et al. (2013) and Zou et al (2019) reported on total PCBs. Zhao et al. (2017) reported on total PBDEs. Outcomes included were birth weight, birth length, head circumference and secondary sex ratio. Reviews had a mix of cohort studies and cross-sectional studies.

Quality of the systematic reviews informing birth outcomes was varied, with scores on the AMSTAR tool ranging from 3 to 9/11. Only one indicated there was an *a priori* protocol available to guide the conduct of the review and searched grey literature (Zhao et al., 2017). Only one of the reviews provided a list of excluded studies but had no declaration of conflict of interest (Nieminen et al., 2013). Only one conducted a quality assessment (Zhao et al., 2017).

Prenatal exposure to PCB 153, total PCBs and total PBDEs were associated with low birth weight in infants. However, specific PBDEs were not associated with any birth outcome.

Exposure to PCBs

Birth weight

Two reviews had pooled findings for birth weight and exposure to PCB 153 (Govarts et al., 2012) and total PCBs (Zou et al., 2019). Exposure to PCB 153 and total PCBs was found to be associated with reduced infant birth weight in both reviews; Govarts et al. (2012) (β -0.15 g, 95%CI: -0.24 to -0.05 g; 12 studies, 7,666 participants) and Zou et al. (2019) (β -0.59 g, 95%CI: -0.852 to -0.343 g; 7 studies, 8,054 participants).

Subgroup findings

Zou et al (2019) also reported negative associations between total PCB exposure and birth weight for period of pregnancy: first trimester exposure (β -0.39, 95% CI: -0.56 to -0.21; 3 studies, participants unspecified), second trimester exposure (β -0.49, 95% CI: -0.66 to -0.33; 2 studies, participants unspecified) and third trimester exposure (β -0.66, 95%CI: -0.91 to -0.41; 6 studies, participants unspecified). Associations were also found for studies conducted in different continents: Asia (β -0.40, 95%CI: -0.52 to -0.27; studies, 680 participants), studies conducted in Europe (β -0.60, 95%CI; -0.65 to -0.55; 3 studies; 5,618 participants), and studies conducted in America (β -0.88, 95%CI: -1.64 to -0.11; 2 studies; 1,756 participants). Associations with reduced birthweight were also found in the subgroup of cord serum measurements (β -0.83, 95%CI: -1.70 to -0.03; 2 studies, 1,004 participants), subgroup of maternal serum measurements (β -0.50, 95%CI: -0.79 to -0.22; 5 studies, 7,050 participants) and subgroup of prospective studies (β -0.63, 95%CI: -0.91 to -0.35; 6 studies; participants unspecified).

Secondary sex ratio

Nieminen et al. (2013) reported no association between total PCB exposure and any change in secondary sex ratio (ratio of male to female live births) for maternal exposure (ratio: 0.5, 95% CI: 0.45, 0.551, 8 studies, participants unspecified).

Exposure to PBDEs

Birth weight

Zhao et al. (2017) pooled findings for birth weight with exposure to total PBDEs investigated (BDE 47, BDE 99, BDE 100, and BDE 153). Overall, there was decreased birthweight in infants when their mothers had been exposed to total PBDEs (β -50.6 g, 95%CI: -95.91 to -5.28 g; 7 studies, 1,332 participants).

Total PBDE exposure was associated with a decreased birth weight in subgroup of male infants (β -121.456 g, 95% CI: -230.139 to -12.773 g; 2 studies, 296 participants) but not with female infants (β

37.766 g, 95% CI: -81.425 to 156.957 g; 2 studies, 265 participants) or if considering both males and females (β -54.388, 95% CI: -115.98 to 7.206; 3 studies, 771 participants).

No association was found with individual congeners of PBDE: BDE 47 (β -41.54, 95%CI: -90.35 to 7.28; 4 studies, 768 participants), BDE 99 (β -29.78, 95%CI: -95.09 to 35.53; 4 studies, 768 participants), BDE 100 (β -28.55, 95%CI: -91.19 to 34.10; 4 studies, 768 participants), nor BDE 153 (β -41.22, 95%CI: -102.73 to 20.29; 4 studies, 768 participants).

Birth length

Zhao et al. (2017) reported no change in birth length of infants when their mothers had been exposed to total PBDEs investigated (β -0.33 cm, 95%CI: -0.74 to 0.07 cm; 3 studies, 632 participants).

Head circumference

Zhao et al. (2017) presented pooled findings for head circumference with exposure to total PBDEs investigated (Zhao 2017). There was no evidence of change in head circumference in infants, when their mothers had been exposed to total PBDE (β -0.175 cm, 95%CI: -0.42 to 0.07 cm; 3 studies, 632 participants).

Flame retardants and women's reproductive health outcomes

Two reviews the association between exposure to the flame retardants (specifically total PCBs) and reproductive health outcomes explored (Cano-Sancho et al., 2019; Roy et al., 2015). These reviews included cohort, case-control, and cross-sectional studies among female populations. No reviews were found that included male reproductive health outcomes.

Exposure was measured using serum samples. Endometriosis was measured from reviews of women in the general population and women with breast cancer and healthy controls.

Quality of the two reviews was mixed. Cano-Sancho et al. (2019) was assessed to be of moderate quality, scoring 8 /11 on the AMSTAR tool, whilst Roy et al. (2015) scored 3/11. Cano-Sancho et al. (2019) indicated using an *a priori* protocol was available to guide the conduct of the review. Both reviews included a table of characteristics of included studies; however, neither reported the excluded studies. Roy et al. (2015) did not perform a comprehensive search, did not include grey literature, did not critically appraise the included studies and did not assess publication bias. Cano-Sancho et al. (2019) used an Adapted National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT) risk of bias rating tool for human and animal studies.

There is evidence of increased risk of developing endometriosis in women exposed to total PCBs.

Endometriosis

The two reviews reported increased odds of developing endometriosis from exposure to total PCBs (Cano-Sancho et al., 2019; Roy et al., 2015). Cano-Sancho et al. (2019) reported an OR of 1.70 (95%CI: 1.20 to 2.39; 9 studies, 31,041 participants) and Roy et al. (2015) reported an OR of 1.91 (95%CI: 1.05 to 5.54; 6 studies, 1,380 participants).

Subgroup findings

Cano-Sancho et al. (2019) reported an association between total PCBs and serum samples (OR 2.02, 95%CI; 1.20 to 3.40; 6 studies, 2,271 participants) but not with adipose samples (OR 1.42, 95%CI: 0.91 to 2.21; 3 studies, 28,770 participants). An association was found between total PCBs and studies in Europe (OR 2.35, 95%CI: 1.44 to 3.82; 4 studies, 385 participants) but not in studies in the United States (OR 1.08, 95%CI: 0.93 to 1.26; 5 studies, 30,656 participants). An association was found for case-control studies (OR 2.08, 95%CI: 1.40 to 3.08; 6 studies, participants unspecified) but not with population-based studies (OR 1.14, 95%CI: 0.88 to 1.48; 3 studies, participants unspecified). Total PCBs was associated with an increased risk in both types of endometriosis; deep endometriosis (OR 1.76, 95%CI: 1.35 to 2.28, 2 studies, participants unspecified) and total (without peritoneal form) endometriosis (OR 1.73, 95%CI: 1.08 to 2.76; 7 studies, participants unspecified).

In subgroup of studies by exposure contrast procedures, an association was found for categorical contrast exposure (OR 1.86, 95%CI: 1.21 to 2.86; 5 studies, participants unspecified) but not with continuous contrast (OR 1.51, 95%CI: 0.89 to 2.57; 4 studies, participants unspecified). When studies were grouped according to risk of bias (no basis for information provided by authors), both tier 1 (OR 1.78, 95%CI: 1.02 to 3.12; 5 studies, participants unspecified) and tier 2 (OR 1.57, 95%CI: 1.18 to 2.09; 4 studies, participants unspecified) studies were associated with endometriosis. Similarly, when studies were grouped by having laparoscopy (OR 1.78, 95%CI: 1.02 to 3.13; 5 studies, participants unspecified) or no laparoscopy (OR 1.57, 95%CI: 1.18 to 2.09; 4 studies, participants unspecified), both subgroups were found to be associated with endometriosis.

Flame retardants and endocrine and metabolic outcomes

Two reviews (Song et al., 2016; Zhao et al., 2015) and two pooled analyses (Li et al., 2015; Wu et al., 2013) explored the association between exposure to flame retardants and metabolic or endocrine health outcomes. Li et al. (2015), Song et al. (2016), and Wu et al. (2013) investigated PCBs, whilst Zhao et al. (2015) investigated PBDEs. Li et al. (2015) specifically reported on special PCB exposure by poisoning whilst Song et al. (2016), and Wu et al. (2013) reported on total PCBs. Wu et al. (2013) also investigated PCB 118, 138, 153 and 180. The outcomes included were type 2 diabetes mellitus, fasting glucose, 2 hr glucose, fasting insulin, 2 hr insulin, HOMA- IR, hepatic disease mortality and thyroid function. Reviews had a mix of cohort, case-control and cross-sectional studies. Wu et al. (2013) and Zhao et al. (2015)reported on participants from the general population, whilst Li et al. (2015) reported on adults in high-risk environment (contaminated areas) and Song et al. (2016) reported on a mix of general population and people in high-risk environment.

Quality of the reviews informing metabolic and endocrine outcomes was low to high. Two of the reviews had an *a priori* protocol available to guide the conduct of the review (Song et al., 2016; Zhao et al., 2015). Conduct of all reviews included duplicate screening and extraction but not grey literature searching. Song et al. (2016) and Wu et al. (2013) did not provide a list of excluded studies. Only Zhao et al. (2015) assessed the quality of included studies. Song et al. (2016) had multiple subgroups within a study that were included within an analysis of individual chemical exposures and these data have been extracted and included, assuming these are mutually exclusive subgroups. The combined analyses for the overall summary and other composite exposure findings for subgroups based on median serum PDBE (ng/g lipid) by Zhao et al. (2015) were invalid as data from studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; only relevant analysis of individual chemical exposures have been extracted.

Overall, there was an association found between total PCB exposure (but not for any specific PCBs) and risk for T2D and increase in fasting glucose. Risk for T2D was greater among females and all races. No associations were found between total PCBs and 2 hr glucose, fasting insulin, 2 hr insulin and HOMA- IR. No associations were found between special PCB exposure by poisoning and hepatic disease mortality. Exposure to PBDEs was associated with increased TT4 levels.

Exposure to PCBs

Type 2 diabetes

Overall findings across populations

One review (Song et al., 2016) and one pooled analysis (Wu et al., 2013) explored the association between exposure to total PCBs and type 2 diabetes. Exposure to total PCBs (118, 138, 153, 180) was consistently found to be associated with type 2 diabetes in the general and high-risk populations. Wu et al. (2013) reported an OR 1.70 (95%CI:1.28 to 2.27; 7 studies, 3,508 participants) and Song et al. (2016) reported an overall RR 2.39 (95%CI: 1.86 to 3.08; 21 studies, 21,530 participants) based on highest (>104 to >1348 ng/g lipid) and lowest (≤60 to ≤455 ng/g lipid) PCB 153 concentrations. Song et al. (2016) also provided analyses by type of study design: there was a positive association between PCBs and type 2 diabetes in both cross-sectional studies (RR 2.90, 95%CI: 2.14 to3.92; 13 studies,

13,419 participants) and prospective cohort studies (RR 1.63, 95%CI: 1.15 to 2.33; 8 studies, 4,681 participants).

Wu et al. (2013) found no association between exposure to PCB 118 (OR 1.20, 95%CI: 0.73 to 1.96; 4 studies, 2,471 participants), PCB 138 (OR 1.36, 95%CI: 0.69 to 2.68; 2 studies, 1,820 participants), PCB 153 (OR 1.06, 95%CI: 0.79 to 1.42; 4 studies, 2,472 participants) and PCB 180 (OR 1.46, 95%CI: 0.77 to 2.77; 3 studies, 2,000 participants) and incidence of T2D.

Subgroup findings

Song et al. (2016) found that exposure to total PCBs was associated with a greater risk in women (RR 2.65, 95%CI: 1.57 to 4.48; studies and participants unspecified) but not in men (RR 1.73, 95%CI: 0.80 to 3.75; studies and participants unspecified). Song et al. (2016) also found an increase in risk in both groups of white people (RR 1.94, 95%CI: 1.43 to 2.62; studies and participants unspecified) and non-white people (RR 2.91, 95%CI: 1.60 to 5.30; studies and participants unspecified).

Fasting glucose

Song et al. (2016) reported that exposure to total PCBs was associated with an increase in fasting glucose in the general and high-risk populations (MD 3.27, 95%CI: 1.87 to 4.67; 3 studies, 2,882 participants) using the highest (>104 to >1348 ng/g lipid) vs lowest (≤60 to ≤455 ng/g lipid) PCB 153 concentrations.

2hr glucose

Song et al. (2016) reported that there was no association between exposure to total PCBs and 2 hr glucose in the general and high-risk populations (MD 0.72, 95%CI: −7.44 to 8.87; 2 studies, 836 participants) using the highest (>104 to >1348 ng/g lipid) vs lowest (≤60 to ≤455 ng/g lipid) PCB 153 concentrations.

Fasting insulin

Song et al. (2016) found that there was no association between exposure to total PCBs and fasting insulin in the general and high-risk populations (MD −0.48, 95%CI: −2.06 to 1.09; 3 studies, 2,882 participants) using the highest (>104 to >1348 ng/g lipid) vs lowest (≤60 to ≤455 ng/g lipid) PCB 153 concentrations.

2 hr insulin

Song et al. (2016) found that there was no association between exposure to total PCBs and 2 hr insulin in the general and high-risk populations (MD −17.56, 95%CI; −59.06 to 23.93; 2 studies; 836 participants) using the highest (>104 to >1348 ng/g lipid) vs lowest (≤60 to ≤455 ng/g lipid) PCB 153 concentrations.

HOMA- IR

Song et al. (2016) found that there was no association between exposure to total PCBs and HOMA-IR in the general and high-risk populations (MD −2.05, 95%CI: −4.65 to 0.56; 3 studies, 933 participants) using the highest (>104 to >1348 ng/g lipid) vs lowest (≤60 to ≤455 ng/g lipid) PCB 153 concentrations.

Hepatic disease death

Li et al. (2015) reported a significant association between special PCB exposure by poisoning and death due to hepatic disease among adults in high-risk environment (SMR 1.5, 95%CI: 1.0 to 2.4; 2 studies, 3,467 participants).

Subgroup findings

Li et al. (2015) found an association between special PCB exposure by poisoning and hepatic disease mortality among males (SMR 1.9, 95%CI: 1.3 to 2.8; 2 studies, 1,690 participants) but not with females (SMR 1.0, 95%CI: 0.5 to 1.9; 2 studies, 1,777 participants).

Exposure to PBDEs

Thyroid function

Zhao et al. (2015) reported measures of thyroid function by level of exposure (serum) to total PBDE in children (including infants and neonates) and adults. When comparing by PBDE level in serum sample (<30 ng/g; low exposure), no association was found with total PBDE exposure and TSH (z -0.07, 95%CI -0.14 to 0.00; 10 studies, 1,065 participants). However, exposure to total PBDE levels between 35-100 ng/g lipid (high exposure) was found to be positively associated with TT4 levels (z 0.15, 95%CI: 0.06 to 0.24; 3 studies, 466 participants).

Flame retardants and child neurodevelopment

One review explored the association between flame retardants (PBDEs) and child neurodevelopment outcomes (Lam et al., 2017). This review included cohort, case-control and cross-sectional studies evaluating prenatal or postnatal PBDE exposure and child intelligence quotient (IQ). The review scored 11/11 with the AMSTAR tool.

Overall prenatal exposure to BDE 47 was associated with a reduced IQ in children aged 4-7 years.

Intelligence quotient (IQ)

Lam et al. (2017) reported IQ in children prenatally exposed to PBDE. Prenatal exposure to PBDE congener 47 was found to be associated with lower IQ in children aged 4-7 years (β -3.7 points per 10-fold increase in lipid-adjusted PBDE concentration (BDE 47 concentration range: <limits of detection –761 ng/g lipid), 95% CI: -6.56 to -0.83 points; 4 studies; 595 participants).

Flame retardants and circulatory outcomes

Two reviews (Fu et al., 2020; Park et al., 2016) and one pooled analysis (Li et al., 2015) explored the association between PCB exposure and circulatory outcomes. Fu et al. (2020) and Park et al. (2016) 2016 reported on total PCBs, whilst Li et al. (2015) reported on special PCB exposure by poisoning. The outcomes included were hypertension and hypertension mortality, cardiovascular disease and cardiovascular disease mortality and cerebrovascular disease mortality. Reviews had a mix of prospective and retrospective cohort studies, case-control and cross-sectional studies.

Quality of the two reviews informing circulatory outcomes was low to moderate, with scores on the AMSTAR tool ranging from 4 to 7/11. Neither of the reviews indicated there was an *a priori* protocol available to guide the conduct of the review, nor reported searching the grey literature. Both reviews provided a list of included studies; however, no list of excluded studies were provided. In addition, both reviews conducted combined analyses for the overall summary (and other composite exposure findings) that were invalid as data from individual studies were used repeatedly in the analyses (multiple counting), artificially increasing the sample size and constraining confidence limits; therefore, only relevant analyses of individual chemical exposures have been extracted. As Li et al. (2015) was a published meta-analysis rather than a systematic review it scored poorly on the AMSTAR tool (4/11).

There is an association between PCB congeners 138 and 153 and risk of cardiovascular disease in the general population and special PCB exposure by poisoning and cardiovascular disease mortality. An association was also observed for dioxin-like PCBs and PCB 118 and risk of hypertension. No associations were found between total PCBs and PCB 180 and cardiovascular disease; special PCB exposure by poisoning and cerebrovascular disease mortality and hypertension mortality; and PCB congener 153, and non-dioxin-like PCBs and hypertension.

Cardiovascular disease

Fu et al. (2020) did not find any association between total PCB exposure (PCB 138, PCB 153, PCB 180 and total PCBs) and incidence of cardiovascular disease (OR 1.32, 95%CI: 0.97 to 1.78; 4 studies, 8,826 participants).

PCB congeners

Fu et al. (2020) also reported cardiovascular outcomes according to exposure to PCB congener types, including PCB 138, PCB 153, and PCB 180. Cardiovascular disease incidence was found to be positively associated with exposure to PCB 138 (OR 1.35, 95%CI: 1.10 to 1.66; 7 studies, 13,409 participants) and PCB 153 (OR 1.35, 95%CI: 1.13 to 1.62; 10 studies, 49,326 participants), but not PCB 180 (OR 1.19, 95%CI: 0.98 to 1.45; 9 studies, 14,735 participants).

Cardiovascular disease mortality

Li et al. (2015) reported cardiovascular disease mortality in adult men and women with special PCB exposure by poisoning. Special PCB exposure by poisoning was found to be associated with an increased cardiovascular disease mortality (SMR 1.3, 95%CI: 1.0 to 1.7; 2 studies, 3,467 participants).

Cerebrovascular disease mortality

Overall findings across populations

Li et al. (2015) reported no association between special PCB exposure by poisoning and cerebrovascular disease mortality (SMR 1.0, 95%CI: 0.8 to 1.29; 2 studies, 3,467 participants).

Subgroup findings

Similarly, no association between special PCB exposure by poisoning and cerebrovascular disease mortality was found among males (SMR 0.9, 95%CI: 0.6 to 1.2; 2 studies, 1,690 participants) and females (SMR 1.1, 95%CI: 0.8 to 1.5; 2 studies, 1,777 participants).

Hypertension and hypertension-related mortality

One review (Park et al., 2016) and a pooled analysis (Li et al., 2015) reported hypertension in the general population and hypertension-related mortality in two cohorts exposed via incident poisoning with PCBs respectively. Park et al. (2016) reported an association between hypertension and PCB 118 (OR 1.26, 95%CI: 1.00 to 1.58; 5 studies, 9,134 participants) and dioxin-like PCBs (OR 1.45 95%CI: 1.00 to 2.12; 5 studies, 8,793 participants). No significant association was reported with exposure to PCB 153 (OR 1.09, 95%CI: 0.97 to 1.23; 6 studies, 9,431 participants), and non-dioxin-like PCBs (OR 1.00, 95%CI: 0.89 to 1.12; 3 studies, 2,048 participants). Li 2015 did not find any association between special PCB exposure by poisoning and hypertension-related mortality (SMR 1.6, 95%CI: 0.9 to 2.9; 2 studies, 3,467 participants).

Subgroup findings

Li et al. (2015) reported no association between special PCB exposure by poisoning and hypertension-related mortality in males (SMR 1.5, 95%CI: 0.7 to 3.4; 2 studies, 1,690 participants) or females (SMR 1.4, 95%CI: 0.3 to 5.6; 2 studies, 1,777 participants).

FLAME RETARDANTS AND RESPIRATORY OUTCOMES

One pooled analysis (Gascon et al., 2014) explored the association between prenatal flame retardants (PCB 153) exposure and respiratory outcomes in infants and children in cohort studies. The outcomes included were bronchitis, wheeze and/or both.

The pooled analysis scored poorly on the AMSTAR tool (3/11) because there was no systematic searching, screening and critical appraisal of the included studies.

There was an association between increasing PCB 153 exposure and bronchitis in infants, but no association was found for bronchitis and/or wheeze and wheeze.

Bronchitis

Gascon et al. (2014) reported a pooled analysis of PCB 153 exposure and the presence of bronchitis and/or wheeze in infants <18 months of age. Bronchitis increased with doubling of exposure to PCB 153 (RR 1.06, 95%CI: 1.01 to 1.12; 7 studies, 2,990 participants). However, when medium vs lowest tertiles (RR 1.13, 95%CI: 0.98 to 1.31; 7 studies, 2,990 participants) and highest vs lowest tertiles (RR

1.17, 95%CI: 0.97 to 1.41; 7 studies, 2,990 participants) were used in the analysis, no significant changes were reported.

Bronchitis and/or wheeze

There was no association between PCB 153 and the presence of bronchitis and/or wheeze in infants <18 months of age with doubling of exposure to PCB 153 (RR 1.02, 95%CI: 0.96 to 1.08; 9 studies, 4,394 participants) and when analysing medium vs lowest tertiles (RR 1.04, 95%CI: 0.92 to 1.18; 9 studies, 4,394 participants) and highest vs lowest tertiles (RR 0.95, 95%CI: 0.75 to 1.21; 9 studies, 4,394 participants).

Wheeze

Gascon et al. (2014) reported on exposure to PCB 153 and wheeze in children (< 18 months and 18-49 months of age). There was no association between PCB 153 exposure and presence of wheeze with doubling exposure to PCB 153 (RR 1.01, 95%CI: 0.94 to 1.09; 8 studies, 3,675 participants) and when analysing medium vs lowest tertiles (RR 1.06, 95%CI: 0.89 to 1.25; 8 studies, 3,675 participants) and highest vs lowest tertiles (RR 0.92, 95%CI: 0.68 to 1.25; 8 studies, 3,675 participants) in infants <18 months of age. There was also no association found for presence of wheeze in children aged 18 to 49 months with doubling exposure to PCB 153 (RR 1.06, 95%CI: 0.98 to 1.15; 6 studies, 1,754 participants) and when analysing medium vs lowest tertiles (RR 1.02, 95%CI: 0.87 to 1.19; 6 studies, 1,754 participants) and highest vs lowest tertiles (RR 1.12, 95%CI: 0.95 to 1.32; 6 studies, 1,754 participants).

Flame retardants and cancer

Six reviews (Catalani et al., 2019; Leng et al., 2016; Roy et al., 2015; Zani et al., 2017, 2013; Zhang et al., 2015) and one pooled analysis (Li et al., 2015) explored the association between PCB exposure and cancer in the general population. Five reviews reported findings based on total PCBs (Catalani et al., 2019; Roy et al., 2015; Zani et al., 2017, 2013; Zhang et al., 2015), and three reviews reported on specific PCB congeners (Catalani et al., 2019; Leng et al., 2016; Zani et al., 2013). One review (Leng et al., 2016) used Wolff and Toniolo's PCB congener grouping (Wolff and Toniolo, 1995) to report their findings. One review (Zani et al., 2017) considered special PCB exposure by occupation and one pooled analysis (Li et al., 2015) considered special PCB exposure by poisoning. Outcomes included were risk of developing breast cancer, and non-Hodgkin's lymphoma including its subtypes and cancer-related mortality. Reviews included a mix of study designs that were cohort, cross sectional, case-control and a proportionate mortality study.

Quality of the majority of reviews informing cancer outcomes were generally poor (n=3) to moderate (n=3) quality, with scores on the AMSTAR tool ranging from 2 to 8/11. One pooled analysis (not systematic review) also informed this section (Li et al., 2015). Only one indicated that there was an *a priori* protocol to guide the conduct of the review (Catalani et al., 2019). Two of the reviews did not complete either study screening, data extraction or both in duplicate (Roy et al., 2015; Zani et al., 2013). A total of 4/7 reviews had a comprehensive literature search (Catalani et al., 2019; Leng et al., 2016; Zani et al., 2017; Zhang et al., 2015); however, only two reviews searched for grey literature (Leng et al., 2016; Zhang et al., 2015) and only two reviews provided a list of excluded studies (Leng et al., 2016; Zani et al., 2017). Three reviews assessed the quality of included studies (Catalani et al., 2019; Leng et al., 2016; Zhang et al., 2015), with only one of these used the findings to inform their conclusions and recommendations (Zhang et al., 2015).

There was no association between exposure to total PCBs and cancer. However, PCB congeners 187, 99, 183, were associated with an increased risk of developing breast cancer in women. Total PCB exposure was found to have an increased risk of developing non-Hodgkin's lymphoma in children and adults; no associations were found for subtypes of non-Hodgkin's lymphoma except for chronic lymphocytic leukemia where a decreased risk was found. PCB exposure due to poisoning was found to be associated with all cancer mortality and lung cancer mortality and especially in males and liver cancer mortality in females. No further associations were found for special PCB exposure by poisoning

and other cancer-related mortality. Special PCB exposure by occupation was associated with melanoma mortality but not with non-Hodgkin's lymphoma mortality.

Breast cancer

Four reviews reported risk of breast cancer in women with PCB exposure (Leng et al., 2016; Roy et al., 2015; Zani et al., 2013; Zhang et al., 2015). Three reviews reported on total PCBs (Roy et al., 2015; Zani et al., 2013; Zhang et al., 2015) and one review reported on different PCB congeners and organised the findings using the PCB congener grouping I to III by Wolff and Toniolo (Leng et al., 2016; 1995).

Total PCBs

Three reviews reported no association between total PCBs and breast cancer: Zani et al. (2013) (OR 1.15, 95%CI: 0.92 to 1.43; 18 studies, 11,645 participants), Zhang et al. (2015) (OR 1.09, 95%CI: 0.97 to 1.22; 25 studies, 12,866 participants) and Roy et al. (2015) (OR 1.33, 95%CI: 0.72 to 2.65; 6 studies, 2,458 participants).

Zani et al. (2013) reported PCB exposure subgroup findings based on the design of studies used in the analysis and found no associations with breast cancer: cohort studies (OR 1.01, 95%CI: 0.78 to 1.31; 6 studies, participants unspecified) and case-control studies (OR 1.19, 95%CI: 0.92 to 1.43; 12 studies, participants unspecified). Zhang et al. (2015) also reported PCB exposure subgroup findings based on the design of studies but slightly different to that of Zani et al. (2013) and found no associations with breast cancer: prospective studies (OR 1.02, 95%CI: 0.85 to 1,23; 9 studies, participants unspecified) and retrospective studies (OR 1.12, 95%CI: 0.96 to 1.30; 16 studies, participants unspecified).

Zhang et al. (2015) conducted a sensitivity and subgroup analyses in their review. A sensitivity analyses excluding three retrospective studies with divergent ORs revealed an OR 1.06, 95% CI 0.98 to 1.15; 22 studies, 11,729 participants. There were no associations in subgroup analyses by study design (prospective studies, OR 1.02, 95%CI: 0.85 to 1,23; 9 studies, participants unspecified, retrospective studies, OR 1.12, 95%CI: 0.96 to 1.30; 16 studies, participants unspecified), nor retrospective studies looking at studies by specimen type for serum/plasma specimen (OR 1.12, 95%CI 0.95 to 1.32; 14 studies, 7,556 participants), adipose tissue (OR 1.06. 95%CI 0.70 to 1.60; 2 studies, 985 participants) nor geographical locations for, studies in Asia (OR 1.91, 95%CI 0.34 to 10.68; 3 reviews, participants unspecified), except for studies in North America where significant associations were found (OR 1.08, 95%CI 1.01 to 1.16; 12 reviews, participants unspecified).

PCB congener groups (by Wolff and Toniolo 1995)

PCB group I (potentially oestrogenic)

Leng et al. (2016) reported on PCB 187 and found that it was associated with increased breast cancer risk (OR 1.18, 95%CI: 1.01 to 1.39; 7 studies, 1,456 participants).

PCB group II (potentially antiestrogenic dioxin like)

Leng et al. (2016) reported on PCB 118, 138, 156, 170. No associations were observed between PCB 118 (OR 1.32, 95%CI: 0.98 to 1.78; 9 studies, 2,446 participants), PCB 138 (OR 1.08, 95%CI: 0.99 to 1.17; 11 studies, 2,911 participants), PCB 156 (OR 1.19, 95%CI: 0.85 to 1.67; 6 studies, 1,506 participants) and PCB 170 (OR 1.28, 95%CI: 0.89 to 1.86; 6 studies, 1,334 participants) and breast cancer risk. For PCB 118, there was an association found with breast cancer risk in subgroups of less than 100 cases (OR 3.72, 95%CI: 2.16 to 6.42; 2 studies, 100 participants) but not with more than 100 cases (OR 1.07, 95%CI: 0.87 to 1.32; 7 studies, 2,346 participants). For PCB 156, an association was found in subgroups of studies which used PCB as categorical variable (OR 1.35, 95%CI: 1.02 to 1.78; 5 studies, 1,202 participants) For PCB 170, no association was found for levels ≥12.5 ng/g lipid (OR 1.05, 95%CI: 0.84 to 1.32; 5 studies, 1,274 participants).

PCB group III (phenobarbital, CYP1A and CYP2B inducers)

Leng et al. (2016) reported on PCB 99, 153, 180, 183. Associations between PCB 99 and increased breast cancer risk (OR 1.36, 95%CI: 1.02 to 1.80; 4 studies, 970 participants) and PCB 183 (OR 1.56, 95%CI: 1.25 to 1.95; 6 studies, 1506 participants) were reported, but not with PCB 153 (OR 1.04,

95%CI: 0.81 to 1.34; 11 studies, 5836 participants) and PCB 180 (OR 1.02, 95%CI: 0.81 to 1.29; 11 studies, 2,881 participants). When PCB 153 studies were grouped by study quality, no association was found in studies of higher quality based on the Newcastle-Ottawa Scale (NOS) (NOS >5) (OR 0.95, 95%CI: 0.78 to 1.15; 10 studies, 2,821participants) When PCB 180 was grouped according to country, no associations were found with studies from other countries other than Japan (OR 1.10, 0.93 to1.32; 10 studies, 2,476 participants).

Leng et al. (2016) also reported findings for PCB congeners informed by only two studies each (PCB 28, 52, 74, 77, 101, 105, 126, 167). PCB 105 was associated with an increased risk of breast cancer (OR 2.22, 95%CI: 1.18 to 4.17; 2 studies, participants unspecified) but not PCB 28 (OR 2.39, 95%CI: 0.16 to 35.60; 2 studies, 135 participants), PCB 52 (OR 0.98, 95%CI: 0.78 to 1.23; 2 studies, 130 participants), PCB 74 (OR 0.94, 95%CI: 0.84 to 1.04; 2 studies, 334 participants), PCB 77 (OR 1.20, 95%CI: 0.39 to 3.73; 2 studies, 113 participants), PCB 101 (OR 1.02, 95%CI: 0.80 to 1.31; 2 studies, 130 participants), PCB 126 (OR 1.40, 95%CI: 0.78 to 2.50; 2 studies, 113 participants) and PCB 167 (OR 0.87, 95%CI: 0.07 to 10.71; 2 studies, 142 participants).

Non-Hodgkin's lymphoma

Three reviews reported risk of non-Hodgkin's lymphoma (incidence) in general population of children and adults with exposure to total PCBs (Catalani et al., 2019; Zani et al., 2017, 2013). Zani et al. (2017, 2013) found an association between exposure to total PCBs and risk of non-Hodgkin's lymphoma (Zani et al. (2013), OR 1.40, 95%CI: 1.14 to 1.71; 11 studies, 4,422 participants; Zani et al. (2017) OR 1.5, 95%CI: 1.1 to 1.7; 6 studies, 2,540 participants). Zani 2017 also reported a dose response for PCB serum levels around 1000 ng/g lipid (OR 1.42, 95%CI: 1.10 to 1.83; 5 studies, 2,668 participants). Catalani et al. (2019) findings were only relevant to specific study types and specific PCB congeners.

Study types

Two reviews reported on subgroups based on study types. Catalani et al. (2019) found no associations between total PCBs and risk of non-Hodgkin's lymphoma in retrospective studies (RR 0.98, 95%CI: 0.58 to 1.38; 8 studies, 1,106 participants). Zani et al. (2013) found an association between total PCBs and risk of non-Hodgkin's lymphoma in case-control studies (OR 1.51, 95%CI: 1.17 to 1.96; 4 studies, participants unspecified) but not in cohort studies (OR 1.34, 95%CI: 0.97 to 1.86; 6 studies, participants unspecified).

PCB 118

Two reviews reported no association between PCB 118 and risk of non-Hodgkin's lymphoma; Catalani et al. (2019) (RR 0.82, 95%CI: 0.53 to 1.10; 8 studies, 1,571 participants), Zani et al. (2013) (OR 1.2, 95%CI: 0.8 to 1.8; 7 studies, participants unspecified).

PCB 138

Two reviews reported no association between PCB 138 and risk of non-Hodgkin's lymphoma; Catalani et al. (2019) (RR 0.93, 95%CI: 0.59 to 1.27; 8 studies, 1,571 participants), Zani et al. (2013)(OR 1.4, 95%CI: 1.0 to 1.8; 6 studies, participants unspecified).

PCB 153

Two reviews reported on PCB 153. Zani et al. (2013) found an association between PCB 153 and and risk of non-Hodgkin's lymphoma (OR 1.5, 95%CI: 1.2 to 1.9; 7 studies, participants unspecified) whilst Catalani et al. (2019) found no association (RR 1.10 95%CI: 0.68 to 1.53; 8 studies, 1,571 participants)

PCB 180

Two reviews found no association between PCB 180 and risk of non-Hodgkin's lymphoma; Catalani et al. (2019) (RR 1.07, 95%CI: 0.67 to 1.47; 7 studies, 954 participants), Zani et al. (2013)(OR 1.4, 95%CI: 1.0 to 2.1; 6 studies, participants unspecified).

PCB 170

Catalani et al. (2019) reported no association between PCB 170 and risk of non-Hodgkin's lymphoma (RR 0.89, 95%CI: 0.58 to 1.21: 5 studies, 984 participants).

Non-Hodgkin's lymphoma subtypes

Catalani et al. (2019) reported on total PCB exposure and subtypes of non-Hodgkin's lymphoma in general population of children and adults.

Chronic Lymphocytic leukemia

Catalani et al. (2019) found an association between total PCBs and decreased risk of chronic lymphocytic leukemia (RR 0.63, 95% CI: 0.39 to 0.87; 4 studies, 573 participants).

Diffuse large B-cell lymphoma

Catalani et al. (2019) found no association between total PCBs and risk of diffuse large B-cell lymphoma (RR 0.68, 95% CI: 0.24 to 1.12; 6 studies, 1,049 participants).

Follicular lymphoma

Catalani et al. (2019) found no association between total PCBs and risk of follicular lymphoma (RR 1.21, 95% CI: 0.79 to 1.64; 5 studies, 920 participants).

Cancer-related mortality

Mortality outcomes were reported as standardised mortality ratio (SMR) which is the ratio of the observed number of deaths in a study population and the number of deaths that would be expected, based on the age- and sex-specific rates in a standard population and the population size of the study population by the same age/sex groups.

One review (Zani et al., 2017) and one pooled analysis (Li et al., 2015) reported cancer-related mortality in adult men and women with special PCB exposure. Zani et al. (2017) reported on special PCB exposure by occupation, whilst Li et al. (2015) reported on special PCB exposure by poisoning. Special PCB exposure by poisoning was found to be significantly associated with lung cancer mortality rate as reported by Li et al. (2015) (SMR 1.5, 95%CI: 1.1 to 2.1; 2 studies, 3,467 participants) and special PCB exposure by occupation was found to be significantly associated with melanoma mortality, Zani et al. (2017) (SMR 1.32, 95%CI: 1.05 to 1.64; 8 studies, 214,241 participants). Special PCB exposure by occupation was not found to be associated with non-Hodgkin's lymphoma mortality Zani et al. (2017) (SMR 0.94, 95%CI: 0.73 to 1.23; 7 studies, 174,207 participants).

Subgroup findings

Sex

Only one pooled synthesis (Li et al., 2015) reported some subgroup analyses by sex. Special PCB exposure by poisoning was found to be associated with all cancer mortality in males (SMR 1.3, 95%CI: 1.1 to 1.6; 2 studies, 1,690 participants), liver cancer mortality in females (SMR 2.0, 95%CI: 1.1 to 3.6; 2 studies, 1,777 participants) and lung cancer mortality in males (SMR 1.2, 95%CI: 1.2 to 2.3; 2 studies, 1,690 participants). In males there was no association between special PCB exposure by poisoning and leukaemia mortality (SMR 2.0, 95%CI: 0.6 to, 6.0; 2 studies, 1,690 participants). In females there was no association between special PCB exposure by poisoning and all cancer mortality (SMR 0.8, 95%CI: 0.5 to 1.3; 2 studies, 1,777 participants), breast cancer mortality (SMR 1.1, 95%CI: 0.4, 2.9; 2 studies, 1,777 participants), lung cancer mortality (SMR 0.7, 95%CI: 0.3 to 1.9; 2 studies, 1,777 participants), pancreatic cancer mortality (SMR 1.1, 95%CI: 0.4 to 3.75.8; 2 studies, 1,777 participants), rectal cancer mortality (SMR 1.0, 95%CI: 0.2 to 5.8; 2 studies, 1,777 participants), stomach cancer mortality (SMR 0.3, 95%CI: 0.1 to 1.1; 2 studies, 1,777 participants), or uterine cancer mortality (SMR1.1, 95%CI: 0.4, 3.4; 2 studies, 1,777 participants).

FLAME RETARDANTS AND MORTALITY

One pooled analysis (Li et al., 2015) explored the association between special PCB exposure by poisoning and mortality in adult men and women exposed to food contaminated PCBs from the "Yusho" incident in Japan (1968) and "Yu-Cheng" incident in Taiwan (1979). Mortality was reported using all-cause mortality which reflects all deaths that occur in a population regardless of the cause.

Quality of the pooled analysis was low (4/11) because it didn't comply with most of the methods of a proper systematic review with meta-analysis. There was no *a priori* protocol and searching, screening and appraisal were not undertaken. There was also no declaration of conflict of interest available for the review.

Special PCB exposure by poisoning was associated with an increase in all-cause mortality in the population cohorts (SMR 1.1, 95%CI: 1.1 to 1.2; 2 studies, 3467 participants) and in the subgroup of males only (SMR 1.2, 95%CI: 1.1 to 1.3; 2 studies, 1,690 participants) but not in females (SMR 1.1, 95%CI: 0.9, 1.2; 2 studies, 1,777 participants).

PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS)

There were six systematic reviews (Johnson et al., 2014; Kim et al., 2018; Liu et al., 2018; Luo et al., 2020; Negri et al., 2017; Steenland et al., 2018) and one pooled analysis (Forns et al., 2020), that together include 240 meta-analyses and for outcomes related to PFAS, including PFOS, PFOA, and PFHxS and perfluorononanoic acid (PFNA). Outcomes for which pooled analyses were available were categorised into overarching health conditions based on ICD-11 (World Health Organization, 2020):

- Birth – Birth weight, birth length, head circumference, ponderal index
- Child neurodevelopment – Attention deficit hyperactivity disorder (ADHD)
- Metabolic – Thyroid function
- Nutritional – Childhood obesity/overweight, BMI z score
- Respiratory – Asthma, allergic rhinitis, wheeze
- Skin-related – Atopic dermatitis/ eczema

Abbreviations

PFOA	Perfluorooctanoic acid	**PFHxS**	Perfluorohexane sulfonate
PFAS	Per- and Polyfluoroalkyl Substances	**PFNA**	Perfluorononanoic acid
PFOS	Perfluorooctane sulfonate		
ADHD	Attention deficit hyperactive disorder	**BMI**	Body Mass Index

Exposure description and measures

Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic, highly stable compounds widely used in protective coatings for food (food packaging), textiles, furniture and non-stick cookware (Forns et al., 2020; Liu et al., 2018). The most frequently detected PFAS in humans are *perfluorooctane sulfonate (PFOS),* perfluorooctanoic acid (*PFOA*) and perfluorohexane sulfonate (PFHxS). Exposure to PFAS is through ingestion (e.g. contaminated drinking water or food, particularly fish) and inhalation (dust and indoor air) (Forns et al., 2020). For additional details on PFAS, see Appendix 1.

Exposure to PFAS can be from a variety of sources in the environment. Specific exposure routes (e.g. inhalation or ingestion) were rarely reported in the included reviews and pooled analysis. Levels were commonly measured in ng/g, ng/mL, µg/L, µg/kg or mmol/L, in blood (whole, serum or plasma), cord serum or plasma and breast milk.

Overall findings

Prenatal exposure to PFAS, particularly PFOA, resulted in decreased birthweight in infants; this reduction was also observed in subgroups of studies in Asia, and in the second and third trimester of pregnancy. In subgroups of studies using maternal blood for sample collection, prenatal PFOA exposure was associated with decreased birthweight in infants, particularly in the third trimester. Inconsistent findings were found in the subgroup of cord samples analysed. PFOA exposure also resulted in decreased birth length, but no change in head circumference and ponderal index. Prenatal PFOS exposure was also associated with decreased birthweight in infants based on studies using transformed data, particularly in subgroups of studies in Asia and America, and those using blood (third trimester) and cord samples.

PFOA and PFOS exposure were found to have a negative association with TT4 levels in adults after a sensitivity analysis was conducted (due to removal of a study with significantly older population). In addition, PFOS exposure was associated with lower T3 levels. PFOA exposure was positively correlated with fT4 levels and in subgroups with intermediate PFOS concentration levels and in a non-pregnant population. No associations were found between PFHxS exposure and any of the thyroid function measures and subgroups reported. No associations were found in subgroups of girls and boys.

PFOA exposure was not found to be associated with ADHD at different time periods up to two years using a prediction model. However, in a subgroup of girls, PFOA exposure was associated with an increased risk of having ADHD at birth and at 3 months but not for 6, 12 and 24 months. No associations were found in the subgroup of boys at all time periods up to two years.

PFOA exposure increased the risk of childhood obesity/overweight and higher BMI z-scores. PFOA, PFOS, PFHxS and PFNA exposure was not found to be associated with the risk of having asthma in children, except in subgroups of studies in Asia where PFOS, PFHxS and PFNA exposures were found to increase the risk of asthma. PFOA exposure increased the risk of having allergic rhinitis and no associations were found for PFOS, PFHxS and PFNA exposure and allergic rhinitis and wheeze. PFOS and PFNA exposure were associated with increased risk in atopic dermatitis and decreased risk in eczema, respectively.

Table 3.7: Summary of health outcomes related to per- and polyfluorinated alkyl substances (PFAS) exposure

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
			Birth outcomes			
BIRTH WEIGHT (PFOA) - 3 reviews		**Range of effects:**	**β -18.9 to -10.5g (95% CI = -29.8 to -2.38g) ***	**9 to 24**	**4149 to 19173**	
Infants; prenatal	Johnson et al. 2014 (10/11)	Untransformed	β -18.9g (95% CI = -29.8 to -7.9g) *	9	4149	per 1-ng/mL increase in serum or plasma PFOA
		Sensitivity analysis	β -15.4g (95% CI = -26.5 to -4.3g) *	10	8501	additional study with high risk of bias
	Negri et al. 2017 (8/11)	*Untransformed*				
		Main analysis	β -12.8g (95% CI = -23.21 to -2.38g) *	12	6501	per 1 ng/mL increase in untransformed PFOA
		America	β -11.8g (95% CI = -32.1 to 8.6g)	4	unsp.	
		Asia	β -12.2g (95% CI = -27.3 to 3g)	3	unsp.	
		Europe	β -15.5g (95% CI = -35.4 to 4.4g)	5	unsp.	
		Cord blood	β -35.3g (95% CI = -101 to 30.7g)	4	unsp.	
		Maternal blood; 1st to 2nd trimester	β -10.5g (95% CI = -23.6 to 2.6g)	6	unsp.	
		Maternal blood; 3rd trimester	β -20g (95% CI = -52.1 to 12.1g)	2	unsp.	
		Transformed				
		Main analysis	β -27.12g (95% CI = -50.64 to -3.6g) *	9	3844	per 1 $\log_e$ ng/mL PFOA
		America	β -28.2g (95% CI = -64.5 to 8.1g)	6	unsp.	
		Asia	β -31.9g (95% CI = -63.6 to -0.2g) *	4	unsp.	
		Cord blood	β -24.4g (95% CI = -66.3 to 18.2g)	3	unsp.	
		Maternal blood; 1st to 2nd trimester	β -10.6g (95% CI = -43.2 to 22g)	4	unsp.	
		Maternal blood; 3rd trimester	β -51g (95% CI = -86.6 to -15.5g) *	3	unsp.	
	Steenland et al. 2018 (4/11)	*Untransformed*				
		Main analysis	β -10.5g (95% CI = -16.7 to -4.4g) *	24	19173	approximately a decrease of 0.3% in weight per unit of serum PFOA, assuming a mean birthweight of about 3,500 g
		First trimester	β -3.3g (95% CI = -9.6 to 3g)	7	5393	
		Second and third trimester	β -17.8g (95% CI = -25 to -10.6g) *	17	7563	
		Maternal Blood	β -9.2g (95% CI = -15.6 to -2.8g) *	15	unsp.	
		Cord blood	β -13.3g (95% CI = -24.7 to -1.8g) *	9	unsp.	
BIRTH WEIGHT (PFOS) - 1 review						
Infants; prenatal	Negri et al. 2017 (8/11)	*Untransformed*				
		Main analysis	β -0.92g (95% CI = -8.92 to 1.6g)	8	5465	per 1 ng/mL increase in untransformed PFOS
		America	β -1.6g (95% CI = -4.9 to 8.1g)	2	unsp.	
		Asia	β -11.2g (95% CI = -16.7 to -5.8g) *	2	unsp.	
		Europe	β -0.5g (95% CI = -1.6 to 2.7g)	4	unsp.	
		First to second trimester	β 0.6g (95% CI = -1.4 to 2.5g)	5	unsp.	
		Third trimester	β -4g (95% CI = -16.3 to 8.2g)	2	unsp.	
		Transformed				
		Main analysis	β -46.09g (95% CI = -80.33 to -11.85g) *	8	3677	per 1 $\log_e$ ng/mL PFOS
		America	β -25.4g (95% CI = -66 to -15.2g) *	6	unsp.	
		Asia	β -85.7g (95% CI = -135 to -36.3g) *	3	unsp.	
		Maternal blood; 1st to 2nd trimester	β -4g (95% CI = -62.3 to 54.3g)	4	unsp.	
		Maternal blood; 3rd trimester	β -65.1g (95% CI = -127 to -3.2g) *	2	unsp.	
		cord blood	β -93.2g (95% CI = -149 to -37.8g) *	3	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
BIRTH LENGTH (PFOA) - 1 review						
Infants; prenatal	Johnson et al. 2014 (10/11)	Main analysis	β -0.06cm (95% CI = -0.09 to -0.02cm) *	5	2853	
HEAD CIRCUMFERENCE (PFOA) - 1 review						
Infants; prenatal	Johnson et al. 2014 (10/11)	Main analysis	β -0.03cm (95% CI = -0.08 to 0.01cm)	4	2497	
PONDERAL INDEX (PFOA) - 1 review						
Infants; prenatal	Johnson et al. 2014 (10/11)	Main analysis	β -0.01cm (95% CI = -0.03 to 0.01cm)	4	1510	
Child reproductive outcomes – No data						
Adult reproductive outcomes – No data						
Metabolic and endocrine outcomes						
THYROID FUNCTION (TT4) (PFOA) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z -0.01 (95% CI = -0.07 to 0.05)	8	4487	
		Fixed-effects model	z -0.05 (95% CI = -0.08 to -0.02) *	8	4487	
		Sensitivity analysis	z -0.06 (95% CI = -0.08 to -0.03) *	7	4400	
		Intermediate concentration (2-3ng/mL)				
		Random effects model	z -0 (95% CI = -0.08 to 0.07)	5	2552	
		Fixed-effects model	z -0.04 (95% CI = -0.08 to 0)	5	2552	
		High concentration (>3ng/mL)				
		Random effects model	z -0 (95% CI = -0.016 to 0.16)	3	1935	
		Fixed-effects model	z -0.06 (95% CI = -0.1 to -0.01) *	3	1935	
		Pregnancy status				
		Pregnant women	z 0.04 (95% CI = -0.06 to 0.13)	2	unsp.	
		Non-pregnant population	z -0.03 (95% CI = -0.09 to 0.04)	6	unsp.	
THYROID FUNCTION (TSH) (PFOA) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z 0.00 (95% CI = -0.03 to 0.04)	11	5823	
		Fixed-effects model	z 0 (95% CI = -0.02 to 0.03)	11	5823	
		Low concentration (<2ng/mL)				
		Fixed and random effects model	z 0.04 (95% CI = -0.06 to 0.13)	2	423	
		Intermediate concentration (2-3ng/mL)				
		Random effects model	z -0.01 (95% CI = -0.06 to 0.04)	6	3466	
		Fixed-effects model	z 0 (95% CI = -0.04 to 0.03)	6	3466	
		High concentration (>3ng/mL)				
		Random effects model	z 0.03 (95% CI = -0.06 to 0.12)	3	1934	
		Fixed-effects model	z 0 (95% CI = -0.04 to 0.05)	3	1934	
		Pregnancy status				
		Pregnant women	z 0 (95% CI = -0.05 to 0.04)	4	unsp.	
		Non-pregnant population	z 0 (95% CI = -0.03 to 0.04)	6	unsp.	
THYROID FUNCTION (fT4) (PFOA) - 1 review						
Adults	Kim et al. 2018 (7/11)	Fixed and random effects model	z 0.01 (95% CI = -0.02 to 0.04)	8	4120	
		Low concentration (<2ng/mL)				
		Fixed and random effects model	z 0.02 (95% CI = -0.08 to 0.12)	2	423	
		Intermediate concentration (2-3ng/mL)				
		Fixed and random effects model	z 0.02 (95% CI = -0.03 to 0.06)	4	2008	
		High concentration (>3ng/mL)				

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Random effects model	z 0.05 (95% CI = -0.12 to 0.21)	2	1689	
		Fixed-effects model	z 0 (95% CI = -0.05 to 0.05)	2	1689	
		Pregnancy status				
		Pregnant women	z 0.00 (95% CI = -0.07 to 0.06)	3	unsp.	
		Non-pregnant population	z 0.01 (95% CI = -0.02 to 0.05)	5	unsp.	
THYROID FUNCTION (T3) (PFOA) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z 0.05 (95% CI = 0 to 0.1)	7	3933	
		Fixed-effects model	z 0.03 (95% CI = 0 to 0.06)	7	3933	
		Intermediate concentration (2-3ng/mL)				
		Random effects model	z 0.05 (95% CI = -0.03 to 0.14)	4	1998	
		Fixed-effects model	z 0.02 (95% CI = -0.02 to 0.06)	4	1998	
		High concentration (>3ng/mL)				
		Random effects model	z 0.06 (95% CI = -0.02 to 0.14)	3	1935	
		Fixed-effects model	z 0.04 (95% CI = 0 to 0.08)	3	1935	
		Pregnancy status				
		Pregnant women	z 0.04 (95% CI = -0.05 to 0.14)	2	unsp.	
		Non-pregnant population	z 0.05 (95% CI = -0.01 to 0.11)	5	unsp.	
THYROID FUNCTION (TT4) (PFOS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z 0.01 (95% CI = -0.05 to 0.07)	8	4489	
		Fixed-effects model	z -0.3 (95% CI = -0.6 to 0)	8	4489	
		Sensitivity analysis	z -0.04 (95% CI = -0.07 to -0.01) *	7	4402	
		Low concentration (<8ng/mL)				
		Fixed and random effects model	z -0.02 (95% CI = -0.1 to 0.6)	2	713	
		Intermediate concentration (8-16ng/mL)				
		Random effects model	z -0.01 (95% CI = -0.11 to 0.09)	3	1839	
		Fixed-effects model	z -0.04 (95% CI = -0.09 to 0)	3	1839	
		High concentration (>16ng/mL)				
		Random effects model	z 0.09 (95% CI = -0.11 to 0.28)	3	1937	
		Fixed-effects model	z -0.02 (95% CI = -0.06 to 0.02)	3	1937	
		Pregnancy status				
		Pregnant women	z 0.06 (95% CI = -0.03 to 0.15)	2	unsp.	
		Non-pregnant population	z 0 (95% CI = -0.07 to 0.07)	6	unsp.	
THYROID FUNCTION (TSH) (PFOS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z -0.02 (95% CI = -0.07 to 0.03)	12	6445	
		Fixed-effects model	z -0.01 (95% CI = -0.04 to 0.01)	12	6445	
		Sensitivity analysis	z 0.01 (95% CI = -0.02 to 0.03)	10	5896	
		Low concentration (<8ng/mL)				
		Random effects model	z -0.14 (95% CI = -0.28 to 0.01)	3	1105	
		Fixed-effects model	z -0.1 (95% CI = -0.16 to -0.05) *	3	1105	
		Intermediate concentration (8-16ng/mL)				
		Fixed and random effects model	z 0.03 (95% CI = 0 to 0.07)	4	2753	
		High concentration (>16ng/mL)				
		Random effects model	z -0.01 (95% CI = -0.08 to 0.07)	5	2578	
		Fixed-effects model	z -0.02 (95% CI = -0.06 to 0.02)	5	2578	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Pregnancy status				
		Pregnant women	z -0.08 (95% CI = -0.12 to 0.08)	4	unsp.	
		Non-pregnant population	z -0.01 (95% CI = -0.04 to 0.02)	8	unsp.	
THYROID FUNCTION (fT4) (PFOS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Fixed and random effects model	z 0.05 (95% CI = 0.03 to 0.08) *	9	4741	
		Low concentration (<8ng/mL)				
		Random effects model	z 0.04 (95% CI = -0.09 to 0.16)	2	548	
		Fixed-effects model	z 0.05 (95% CI = -0.03 to 0.13)	2	548	
		Intermediate concentration (8-16ng/mL)				
		Fixed and random effects model	z 0.07 (95% CI = 0.02 to 0.11) *	3	1852	
		High concentration (>16ng/mL)				
		Random effects model	z 0.06 (95% CI = -0.01 to 0.13)	4	2341	
		Fixed-effects model	z 0.05 (95% CI = 0.01 to 0.09) *	4	2341	
		Pregnancy status				
		Pregnant women	z 0.05 (95% CI = -0.02 to 0.11)	3	unsp.	
		Non-pregnant population	z 0.06 (95% CI = 0.02 to 0.09) *	6	unsp.	
THYROID FUNCTION (T3) (PFOS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z -0.02 (95% CI = -0.07 to 0.04)	8	4555	
		Fixed-effects model	z -0.05 (95% CI = -0.08 to -0.02) *	8	4555	
		Sensitivity analysis (from supplementary)	z -0.06 (95% CI = -0.09 to -0.03) *	7	4309	
		Sensitivity analysis (from text)	z -0.04 (95% CI = -0.06 to -0.01) *	7	4309	
		Intermediate concentration 8-16ng/mL				
		Random effects model	z -0.03 (95% CI = -0.11 to 0.06)	3	1843	
		Fixed-effects model	z -0.05 (95% CI = -0.1 to -0.01) *	3	1843	
		High concentration >16ng/mL				
		Random effects model	z 0.01 (95% CI = -0.1 to 0.11)	4	2557	
		Fixed-effects model	z -0.05 (95% CI = -0.09 to -0.02) *	4	2557	
		Pregnancy status				
		Pregnant women	z -0.01 (95% CI = -0.1 to 0.09)	2	unsp.	
		Non-pregnant population	z -0.01 (95% CI = -0.08 to 0.06)	6	unsp.	
THYROID FUNCTION (TT4) (PFHxS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z -0.04 (95% CI = -0.08 to 0.01)	6	4154	
		Fixed-effects model	z -0.04 (95% CI = -0.07 to -0.01) *	6	4154	
		Low concentration (<0.8ng/mL)				
		Fixed and random effects model	z -0.04 (95% CI = -0.11 to 0.02)	3	929	
		High concentration (>0.8ng/mL)				
		Random effects model	z -0.02 (95% CI = -0.09 to 0.04)	3	3225	
		Fixed-effects model	z -0.04 (95% CI = -0.07 to 0)	3	3225	
		Pregnancy status				
		Pregnant women	z 0.01 (95% CI = -0.18 to 0.2)	2	unsp.	
		Non-pregnant population	z -0.04 (95% CI = -0.07 to -0.01) *	4	unsp.	
THYROID FUNCTION (TSH) (PFHxS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Random effects model	z 0 (95% CI = -0.03 to 0.04)	8	5099	
		Fixed-effects model	z 0 (95% CI = -0.03 to 0.03)	8	5099	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Low concentration (<0.8ng/mL)				
		Random effects model	z 0.02 (95% CI = -0.04 to 0.7)	5	1872	
		Fixed-effects model	z 0.01 (95% CI = -0.03 to 0.06)	5	1872	
		High concentration (>0.8ng/mL)				
		Random effects model	z -0.01 (95% CI = -0.07 to 0.04)	3	3227	
		Fixed-effects model	z 0 (95% CI = -0.04 to 0.03)	3	3227	
		Pregnancy status				
		Pregnant women	z 0 (95% CI = -0.12 to 0.13)	3	unsp.	
		Non-pregnant population	z 0 (95% CI = -0.04 to 0.03)	5	unsp.	
THYROID FUNCTION (fT4) (PFHxS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Fixed and random effects model	z 0.02 (95% CI = -0.01 to 0.05)	6	3641	
		Low concentration (<0.8ng/mL)				
		Fixed and random effects model	z 0 (95% CI = -0.1 to 0.09)	3	415	
		High concentration (>0.8ng/mL)				
		Fixed and random effects model	z 0.02 (95% CI = -0.01 to 0.06)	3	3226	
		Pregnancy status				
		Pregnant women	z 0.01 (95% CI = -0.01 to 0.05)	2	unsp.	
		Non-pregnant population	z 0.02 (95% CI = -0.01 to 0.05)	4	unsp.	
THYROID FUNCTION (T3) (PFHxS) - 1 review						
Adults	Kim et al. 2018 (7/11)	Fixed and random effects model	z 0 (95% CI = -0.03 to 0.04)	5	3600	
		Low concentration (<0.8ng/mL)				
		Random effects model	z 0 (95% CI = -0.19 to 0.19)	2	375	
		Fixed-effects model	z -0.03 (95% CI = -0.13 to 0.07)	2	375	
		High concentration (>0.8ng/mL)				
		Fixed and random effects model	z 0.01 (95% CI = -0.03 to 0.04)	3	3225	
		Pregnancy status				
		Pregnant women	z -0.01 (95% CI = -0.16 to 0.14)	2	unsp.	
		Non-pregnant population	z 0.01 (95% CI = -0.03 to 0.04)	3	unsp.	
Child neurodevelopmental outcomes						
ATTENTION DEFICIT HYPERACTIVE DISORDER (ADHD) (PFOA) - 1 pooled analysis						
Children; Prenatal (measured in serum/plasma and breast milk)	Forns et al. 2020 (3/11) [p]	*Boys and Girls*				
		Maternal PFOA levels modelled at birth	OR 1.01 (95% CI = 0.93 to 1.11)	9	4826	
		Maternal PFOA levels at 3 months	OR 1.02 (95% CI = 0.93 to 1.11)	9	4826	
		Maternal PFOA levels at 6 months	OR 1.01 (95% CI = 0.91 to 1.12)	9	4826	
		Maternal PFOA levels at 12 months	OR 1 (95% CI = 0.89 to 1.12)	9	4826	
		Maternal PFOA levels at 24 months	OR 0.99 (95% CI = 0.88 to 1.12)	9	4826	
		Girls				
		Maternal PFOA levels modelled at birth	OR 1.28 (95% CI = 1.03 to 1.59) *	9	1356	
		Maternal PFOA levels at 3 months	OR 1.28 (95% CI = 1.01 to 1.62) *	9	1356	
		Maternal PFOA levels at 6 months	OR 1.29 (95% CI = 1 to 1.66)	9	1356	
		Maternal PFOA levels at 12 months	OR 1.24 (95% CI = 0.96 to 1.61)	9	1356	
		Maternal PFOA levels at 24 months	OR 1.3 (95% CI = 0.98 to 1.73)	9	1356	
		Boys				
		Maternal PFOA levels modelled at birth	OR 0.98 (95% CI = 0.87 to 1.09)	9	2639	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Maternal PFOA levels at 3 months	OR 1 (95% CI = 0.89 to 1.11)	9	2639	
		Maternal PFOA levels at 6 months	OR 1.02 (95% CI = 0.86 to 1.22)	9	2639	
		Maternal PFOA levels at 12 months	OR 1.03 (95% CI = 0.85 to 1.25)	9	2639	
		Maternal PFOA levels at 24 months	OR 0.97 (95% CI = 0.83 to 1.14)	9	2639	
ATTENTION DEFICIT HYPERACTIVE DISORDER (ADHD) (PFOS) - 1 pooled analysis						
Children; Prenatal (measured in serum/plasma and breast milk)	Forns et al. 2020 (3/11) [p]	*Boys and Girls*				
		Maternal PFOS levels modelled at birth	OR 0.99 (95% CI = 0.92 to 1.07)	9	4826	
		Maternal PFOS levels at 3 months	OR 0.99 (95% CI = 0.92 to 1.06)	9	4826	
		Maternal PFOS levels at 6 months	OR 0.98 (95% CI = 0.9 to 1.06)	9	4826	
		Maternal PFOS levels at 12 months	OR 0.96 (95% CI = 0.87 to 1.06)	9	4826	
		Maternal PFOS levels at 24 months	OR 0.97 (95% CI = 0.88 to 1.07)	9	4826	
		Girls				
		Maternal PFOS levels modelled at birth	OR 1.14 (95% CI = 0.91 to 1.34)	9	1356	
		Maternal PFOS levels at 3 months	OR 1.12 (95% CI = 0.94 to 1.34)	9	1356	
		Maternal PFOS levels at 6 months	OR 1.13 (95% CI = 0.93 to 1.36)	9	1356	
		Maternal PFOS levels at 12 months	OR 1.19 (95% CI = 0.92 to 1.53)	9	1356	
		Maternal PFOS levels at 24 months	OR 1.26 (95% CI = 0.93 to 1.72)	9	1356	
		Boys				
		Maternal PFOS levels modelled at birth	OR 0.96 (95% CI = 0.88 to 1.05)	9	2639	
		Maternal PFOS levels at 3 months	OR 0.96 (95% CI = 0.89 to 1.05)	9	2639	
		Maternal PFOS levels at 6 months	OR 0.95 (95% CI = 0.86 to 1.05)	9	2639	
		Maternal PFOS levels at 12 months	OR 0.93 (95% CI = 0.83 to 1.04)	9	2639	
		Maternal PFOS levels at 24 months	OR 0.92 (95% CI = 0.81 to 1.03)	9	2639	
Nutritional outcomes						
CHILDHOOD OBESITY/OVERWEIGHT (PFOA) - 1 review						
Children; Pre- and postnatal exposure (measured in maternal serum or plasma)	Liu et al. 2018 (7/11)	Effect size	ES 1.25 (95% CI = 1.04 to 1.5) *	8	5457	
		Risk estimate				
		Relative risk	RR 1.26 (95% CI = 1.01 to 1.56) *	6	4224	
		Odds ratio	OR 1.39 (95% CI = 0.85 to 2.28)	2	1223	
BMI (z-score) (PFOA) - 1 review						
Children; Pre- and postnatal exposure (measured in maternal serum or plasma)	Liu et al. 2018 (7/11)	Main analysis	β 0.1 (95% CI = 0.03 to 0.17) *	9	5411	
		Sensitivity analysis	β 0.07 (95% CI = 0.01 to 0.14) *	5	3825	
		Timing of exposure				
		Prenatal	β 0.09 (95% CI = 0.02 to 0.17) *	unsp.	5505	
		Postnatal	β 0.16 (95% CI = 0.01 to 0.3) *	unsp.	571	
		Sex				
		Girls	β 0.06 (95% CI = -0.01 to 0.13)	unsp.	1549	
		Boys	β -0.01 (95% CI = -0.1 to 0.08)	unsp.	1628	
		Geographically				
		Europe	β 0.1 (95% CI = 0.02 to 0.17) *	7	3545	
		North America	β 0.19 (95% CI = -0.05 to 0.42)	3	2102	
		Maternal parity				
		Adjusted for maternal parity	β 0.13 (95% CI = 0.02 to 0.24) *	unsp.	3949	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Not adjusted for maternal parity	β 0.07 (95% CI = -0.01 to 0.15)	unsp.	2127	
		Other				
		Not adjusted for birthweight	β 0.1 (95% CI = 0.03 to 0.17) *	unsp.	5704	
Circulatory outcomes – No data						
Respiratory outcomes						
ASTHMA (PFOA) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 1.11 (95% CI = 0.85 to 1.24)	8	7050	
		Timing of exposure				
		Prenatal	OR 0.92 (95% CI = 0.79 to 1.07)	6	unsp.	
		Postnatal	OR 2.05 (95% CI = 0.58 to 7.27)	2	unsp.	
		Geographically				
		Asia	OR 2.37 (95% CI = 0.62 to 9.13)	2	unsp.	
		Europe	OR 0.92 (95% CI = 0.78 to 1.07)	5	unsp.	
ASTHMA (PFOS) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 1.11 (95% CI = 0.88 to 1.4)	8	7050	
		Timing of exposure				
		Prenatal	OR 0.99 (95% CI = 0.8 to 1.22)	6	unsp.	
		Postnatal	OR 1.57 (95% CI = 0.62 to 4)	2	unsp.	
		Geographically				
		Asia	OR 2.47 (95% CI = 1.43 to 4.25) *	2	unsp.	
		Europe	OR 0.98 (95% CI = 0.78 to 1.23)	5	unsp.	
ASTHMA (PFHxS) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 1.02 (95% CI = 0.85 to 1.24)	8	7050	
		Timing of exposure				
		Prenatal	OR 0.94 (95% CI = 0.84 to 1.05)	6	unsp.	
		Postnatal	OR 1.83 (95% CI = 0.45 to 7.38)	2	unsp.	
		Geographically				
		Asia	OR 3.66 (95% CI = 2.06 to 6.49) *	2	unsp.	
		Europe	OR 0.94 (95% CI = 0.84 to 1.04)	5	unsp.	
ASTHMA (PFNA) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 0.99 (95% CI = 0.81 to 1.21)	8	7050	
		Timing of exposure				
		Prenatal	OR 0.9 (95% CI = 0.74 to 1.06)	6	unsp.	
		Postnatal	OR 1.52 (95% CI = 0.6 to 3.85)	2	unsp.	
		Geographically				
		Asia	OR 2.37 (95% CI = 1.34 to 4.2) *	2	unsp.	
		Europe	OR 0.9 (95% CI = 0.73 to 1.09)	5	unsp.	
ALLERGIC RHINITIS (PFOA) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 1.32 (95% CI = 1.13 to 1.55) *	4	3396	
		Timing of exposure				
		Prenatal	OR 1.29 (95% CI = 1 to 1.66)	3	unsp.	
		Geographically				
		Europe	OR 1.29 (95% CI = 0.98 to 1.69)	2	unsp.	

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
ALLERGIC RHINITIS (PFOS) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 1.07 (95% CI = 0.89 to 1.29)	4	3396	
		Timing of exposure				
		Prenatal	OR 0.97 (95% CI = 0.74 to 1.29)	3	unsp.	
		Geographically				
		Europe	OR 1.03 (95% CI = 0.75 to 1.41)	2	unsp.	
ALLERGIC RHINITIS (PFHxS) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 0.94 (95% CI = 0.79 to 1.13)	4	3396	
		Timing of exposure				
		Prenatal	OR 0.99 (95% CI = 0.84 to 1.16)	3	unsp.	
		Geographically				
		Europe	OR 1.01 (95% CI = 0.86 to 1.2)	2	unsp.	
ALLERGIC RHINITIS (PFNA) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 0.99 (95% CI = 0.71 to 1.37)	4	3396	
		Timing of exposure				
		Prenatal	OR 0.83 (95% CI = 0.47 to 1.46)	3	unsp.	
		Geographically				
		Europe	OR 1.11 (95% CI = 0.79 to 1.54)	2	unsp.	
WHEEZE (PFOA) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 1.03 (95% CI = 0.93 to 1.15)	6	6672	
		Timing of exposure				
		Prenatal	OR 1.03 (95% CI = 0.9 to 1.17)	5	unsp.	
		Geographically				
		Asia	OR 0.98 (95% CI = 0.6 to 1.6)	2	unsp.	
		Europe	OR 1.04 (95% CI = 0.88 to 1.23)	3	unsp.	
WHEEZE (PFOS) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 0.9 (95% CI = 0.78 to 1.04)	6	6672	
		Timing of exposure				
		Prenatal	OR 0.91 (95% CI = 0.76 to 1.09)	5	unsp.	
		Geographically				
		Asia	OR 0.79 (95% CI = 0.55 to 1.13)	2	unsp.	
		Europe	OR 0.95 (95% CI = 0.74 to 1.22)	3	unsp.	
WHEEZE (PFHxS) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 0.97 (95% CI = 0.87 to 1.08)	6	6672	
		Timing of exposure				
		Prenatal	OR 1 (95% CI = 0.89 to 1.13)	5	unsp.	
		Geographically				
		Asia	OR 0.73 (95% CI = 0.5 to 1.05)	2	unsp.	
		Europe	OR 1.04 (95% CI = 0.93 to 1.16)	3	unsp.	
WHEEZE (PFNA) - 1 review						
Children; Pre- and postnatal exposure (measured in serum, cord blood)	Luo et al. 2020 (7/11)	Main analysis	OR 0.98 (95% CI = 0.88 to 1.08)	6	6672	
		Timing of exposure				
		Prenatal	OR 0.99 (95% CI = 0.86 to 1.13)	5	unsp.	
		Geographically				

Outcomes Population; Exposure (matrix)	Citation (AMSTAR score)	Analysis	Effect size (95% CI) * Indicates significant effect	Studies	Participants	Notes
		Asia	OR 0.96 (95% CI = 0.49 to 1.87)	2	unsp.	
		Europe	OR 0.98 (95% CI = 0.84 to 1.15)	3	unsp.	
Skin-related outcomes						
SKIN: ATOPIC DERMATITIS & ECZEMA (PFOA) - 1 review						
Children;	Luo et al. 2020 (7/11)	*Atopic dermatitis analysis*				
Pre- and postnatal		Main analysis	OR 1.39 (95% CI = 0.89 to 2.18)	4	2650	
exposure (measured		Asia	OR 1.49 (95% CI = 0.73 to 3.06)	3	unsp.	
in serum, cord blood)		*Eczema analysis*				
		Main analysis	OR 0.99 (95% CI = 0.88 to 1.1)	5	5276	
		Europe	OR 1 (95% CI = 0.89 to 1.12)	4	unsp.	
SKIN: ATOPIC DERMATITIS & ECZEMA (PFOS) - 1 review						
Children;	Luo et al. 2020 (7/11)	*Atopic dermatitis analysis*				
Pre- and postnatal		Main analysis	OR 1.26 (95% CI = 1.01 to 1.58) *	4	2650	
exposure (measured		Asia	OR 1.54 (95% CI = 1.03 to 2.31) *	3	unsp.	
in serum, cord blood)		*Eczema analysis*				
		Main analysis	OR 0.91 (95% CI = 0.81 to 1.02)	5	5276	
		Europe	OR 0.92 (95% CI = 0.81 to 1.04)	4	unsp.	
SKIN: ATOPIC DERMATITIS & ECZEMA (PFHxS) - 1 review						
Children;	Luo et al. 2020 (7/11)	*Atopic dermatitis analysis*				
Pre- and postnatal		Main analysis	OR 1.08 (95% CI = 0.92 to 1.27)	4	2650	
exposure (measured		Asia	OR 1.2 (95% CI = 0.77 to 1.88)	2	unsp.	
in serum, cord blood)		*Eczema analysis*				
		Main analysis	OR 1.07 (95% CI = 0.96 to 1.2)	5	5276	
		Europe	OR 1.09 (95% CI = 0.97 to 1.23)	4	unsp.	
SKIN: ATOPIC DERMATITIS & ECZEMA (PFNA) - 1 review						
Children;	Luo et al. 2020 (7/11)	*Atopic dermatitis analysis*				
Pre- and postnatal		Main analysis	OR 0.96 (95% CI = 0.65 to 1.43)	4	2650	
exposure (measured		Asia	OR 1 (95% CI = 0.66 to 1.53)	3	unsp.	
in serum, cord blood))		*Eczema analysis*				
		Main analysis	OR 0.89 (95% CI = 0.8 to 0.99) *	5	5276	
		Europe	OR 0.9 (95% CI = 0.81 to 1)	4	unsp.	
Cancer outcomes – No data						

Table legend:

*p Indicates a pooled analysis, * indicates significant effect.*

Studies or participants unspecified (unsp.) indicates no data available from the reviews

Descriptive summary of included reviews

Presentation of studies in this section is in alphabetical order to facilitate rapid reference. This section includes details of exposures investigated, number and type of studies and total sample size, number of meta-analyses presented and various outcomes reported (Full details are available in Appendix 9). AMSTAR scores are provided for reference.

Forns et al. (2020) - *Early-life exposure to perfluoroalkyl substances (PFAS) and ADHD: a meta-analysis of nine European population-based studies. No COIs declared, AMSTAR Score: 3/11.*

Forns et al. (2020) explored the association between perfluoroalkyl substances (PFAS) exposure and attention deficit hyperactivity disorder (ADHD). The study included a total of 9 European cohorts with a total of 4,826 mother-child pairs. All cohorts were included in the meta-analysis. A validated pharmacokinetic model was used to harmonise the measures of exposure across studies and generate estimates of postnatal PFOS and PFOA levels in the children at each month from birth until 24 months of age; this approach was validated against longitudinal measurements from published literature. The exposure routes included prenatal exposure or breast milk, measured in ng/ml from maternal serum, plasma or breast milk, in the first 24 months of life using different time points (at birth, 3 months, 6 months, 12 months and 24 months). Critical appraisal was not undertaken. The outcome reported was ADHD. For perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) exposure, the authors concluded no significant association with ADHD in children at any time point. Subgroup analysis also found no association when stratified by sex.

Johnson et al. (2014) - *The Navigation Guide - Evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on foetal growth. No COIs declared, AMSTAR Score: 10/11.*

Johnson et al. (2014) explored the association between perfluorooctanoic acid (PFOA) and birth-related outcomes among children born to pregnant mothers studied during the reproductive / developmental time period (before and / or during pregnancy). The review included a total of 19 studies – (cross sectional (n=13), prospective cohort (n=2), retrospective cohort (n=3), case control (n=1)), with a total of 32,565 participants. The number of studies included in the meta-analysis was 9 with 4149 participants. The authors developed their own critical appraisal instrument to assess the quality of the included studies. The authors simply state that there was generally low risk of bias across the 19 studies. PFOA exposure was measured prenatally in mothers exposed to PFOA or its salts during the time before pregnancy and/or during pregnancy for females or directly to foetuses. This was reported as median PFOA (ng/mL). The period of exposure was unspecified. Outcomes reported were birth weight, birth length, head circumference and ponderal index. Authors concluded that there was sufficient evidence of a decrease in birth weight and birth length with PFOA exposure, but there was no evidence of an association between PFOA exposure and head circumference or ponderal index.

Kim et al. (2018) – *Association between perfluoroalkyl substances exposure and thyroid function in adults: A meta-analysis. No COIs declared, AMSTAR Score: 7/11*

Kim et al. (2018) explored the association between PFASs - PFOS, PFHxS, PFOA, and thyroid function among the general population, pregnant women and women attempting to conceive. The review included 12 studies (cross sectional) with a total of 6,123 participants. A modified cross-sectional assessment provided by the Agency for Healthcare Research was used to assess the quality of the included studies. Quality scores ranged from 6-8. PFAS exposure was through various means (such as populations close to polluted areas, Inuit, sport anglers), for a non-specific exposure time, measured in blood ng/mL (< 8 ng/mL, (low), 8- 16 ng/mL (intermediate), and > 16 ng/mL (high)). Outcomes reported were thyroid function (measured through free T4, T3 and TSH).

For PFOS (no levels), the authors concluded that there was a significant positive association with free T4 in adults. Exposure to mean PFOS (<8ng/mL) was significant negatively associated with TSH in the total population. For PFOS and levels of 8-16ng/mL and >16ng/mL, the authors concluded a

significant positive relationship with free T4, a significant negative relationship with total T3. A significant negative association between PFOA levels of >3ng/mL and total T4 was found.

Liu et al. (2018) - *Perfluorooctanoic acid (PFOA) Exposure in early life increases risk of childhood adiposity: a meta-analysis of prospective cohort studies. No COIs declared, AMSTAR Score: 7/11.*

Liu et al. (2018) explored the association between early-life exposure to PFOA and childhood adiposity. The review included 10 studies (prospective) with a total of 6077 participants. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. Quality scores ranged from 7-8. PFOA exposure was maternal exposure, during pregnancy, however, the study was non-specific about when the PFOA entered the mother's blood stream, measured in maternal serum, plasma, or cord blood (measurement not listed). Outcomes reported were childhood obesity and increase in childhood BMI. For PFOA (no levels noted), the authors concluded that there was a significantly increased risk of childhood obesity and increased BMI among males and females. Sensitivity analysis for childhood obesity used differing effect measures (OR and RR) revealed an increased relative risk (RR) of children being overweight when exposed to early-life PFOA, while the odds ratio (OR) group did not have a significant risk for childhood overweight.

Subanalysis of childhood BMI scores was performed across geographic locations (Europe, Northern America, and Asia), and considering the sex of child. For PFOA exposure, the authors concluded that there was a significant positive association with studies from Europe, but not for Northern America or Asia. Exposure to PFOA was not associated with childhood BMI in either girls or boys.

Luo et al. (2020) - *Exposure to perfluoroalkyl substances and allergic outcomes in children: A systematic review and meta-analysis. No COIs declared, AMSTAR Score: 7/11.*

Luo et al. (2020) explored the association between perfluoroalkyl substances (PFAS) including PFOS and PFOA, PFHxS, PFNA and allergic outcomes among children. The review included 13 studies – cohort (n=10), cross sectional (n= 2), case control (n=1), with a total of 11,255 participants. Newcastle-Ottawa Scale was used to assess the quality of the included studies. Quality scores of 13 studies ranged from moderate (n=2) to high quality (n=11). PFAS exposure was via prenatal exposure in all but three studies, details of the route of exposure for postnatal exposure was not reported, exposure was measured in cord blood or plasma, serum, maternal serum or plasma, measurement units and exposure time were not reported. Outcomes reported were asthma, wheeze, eczema, dermatitis and allergic rhinitis. For PFAS across populations, the authors concluded significant positive associations with eczema, atopic dermatitis and allergic rhinitis, but not asthma or wheeze. When grouped by region, PFAS exposure was associated with asthma in the Asian region (PFOS, PFHxS and PFNA) but not for the other regions.

Negri et al. (2017) - *Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data. No COIs declared, AMSTAR Score: 8/11.*

Negri et al. (2017) explored the association between PFOA and PFOS and birth weight among children born to pregnant mothers studied during the reproductive/developmental time period (before and/or during pregnancy). The review included 16 studies – (prospective cohort (n=9), case control (n=3), cross sectional (n=4)) with a total of 8,335 participants. Nine studies were included in meta-analysis with 5465 participants. The authors reported separate meta-analyses for studies reporting on untransformed and transformed data. A modified version of the Newcastle-Ottawa Scale was used to assess the quality of the included studies. Quality scores of the included studies ranged from 3/7 to 7/7. PFOA exposure was via maternal or umbilical cord serum, plasma or whole blood or maternal milk, for an unspecified period of time. The only outcome reported was birth weight. For PFOA exposure across populations, the authors concluded significant negative association with birthweight. For PFOS exposure across populations in different regions, PFOA and PFOS were associated with reduced birthweight mostly in the Asian region.

Steenland et al. (2018) - *Serum perfluorooctanoic acid and birthweight. An updated meta-analysis with bias analysis. No COIs declared,* AMSTAR Score: 4/11.

Steenland et al. (2018) explored the association between PFOA and birthweight among newborns. The review included 24 studies (no information about study type provided), with a total of 19173 participants. No critical appraisal appears to have been conducted. PFOA exposure was maternal, during pregnancy, measured in ng/ml of maternal or cord blood untransformed PFOA. Outcomes reported were birthweight and analysed using summary coefficients (95%CI), with an assumed birthweight mean of 3500grams. For PFOA exposure there was a significant negative association between a change of birthweight of 10.5 grams for every ng/ml of PFOA exposure. Subanalyses were performed for the timing of blood sampling (early: First trimester a mixture of first and second, or mostly/all preconception, or late: either second or third trimester, or a mixture of second/third trimester), and method of collecting PFOA levels (maternal blood, cord blood studies). For PFOA, the authors concluded that there was no association with early blood sampling, but there was a significant reduction in birthweight with late blood sampling. For PFOA, a significant negative association was found with birth weight.

Critical appraisal of included reviews and pooled analyses

The methodological quality of the six systematic reviews with meta-analyses and one pooled analysis included assessed with the AMSTAR tool are presented in the following table.

Table 3.8: Critical appraisal of per- and polyfluorinated alkyl substances (PFAS) reviews and pooled analysis

Author (Year)	Question*											Score	Notes
	1	2	3	4	5	6	7	8	9	10	11		
***Forns et al.* (2020)**	N	N	N	N	N	Y	N	N	Y	N	Y	**3**	This is not a systematic review but rather a pooled analysis of data; therefore. no systematic methods relating to searching, screening, extraction and appraisal of the evidence were undertaken. A validated pharmacokinetic model was used to harmonise the measures of exposure across studies and generate estimates of postnatal PFOS and PFOA levels in the children at each month from birth until 24 months of age; this approach was validated against longitudinal measurements from published literature; this allowed the statistical pooling of data (Q9); conflict of interest in the individual review was discussed but not for all included articles (Q11)
***Johnson et al.* (2014)**	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	**10**	No list of excluded studies was presented (Q5). Noteworthy that while authors did perform rigorous and transparent risk of bias assessment, they did not use a standardised instrument for this review, instead designing their own. Authors have presented many sensitivity analyses based on study quality to ensure conclusions are robust and performed a GRADE assessment on the certainty of the evidence (Q7, Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11)
***Kim et al.* (2018)**	N	CA	Y	N	N	Y	Y	Y	Y	Y	Y	**7**	No *a priori* protocol (Q1); Duplicate screening undertaken but not data extraction (Q2); No supplementary and grey literature searches undertaken (Q3, Q4); conflict of interest in the individual review was discussed but not for all included articles (Q11)
***Liu et al.* (2018)**	N	Y	Y	N	N	Y	Y	N	Y	Y	Y	**7**	No *a priori* protocol provided (Q1); no grey literature search undertaken (Q4); No list of excluded studies was provided (Q5); The NOS was used to assess quality; however, the results of the assessment were not considered in the analysis nor formulation of conclusions (Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11)
***Luo et al.* (2020)**	N	Y	Y	N	N	Y	Y	N	Y	Y	Y	**7**	No *a priori* protocol provided (Q1); no grey literature search undertaken (Q4); No list of excluded studies was provided (Q5); limited information in the table of included studies - no findings available (Q6); The NOS was used to assess quality; however, the results of the assessment were not considered in the analysis nor formulation of conclusions (Q8); conflict of interest in the individual review was discussed but not for all included articles (Q11)
***Negri et al.* (2017)**	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	**8**	No *a priori* protocol provided (Q1); no grey literature search undertaken (Q4); No details nor identifying information was provided for excluded studies, simply the number excluded (Q5); authors made their declarations based on their employment, however, not for individual studies included (Q11)
***Steenland et al.* (2018)**	N	CA	N	N	N	Y	N	N	Y	Y	Y	**4**	No *a priori* protocol provided (Q1); It is unclear if screening and extraction were done in duplicate as authors used 'we' but did not state what processes were undertaken by at least two reviewers (Q2); only PubMed was searched and no supplemental search undertaken; No grey literatures search undertaken (Q4); No list of excluded studies was provided (Q5); No study quality appraisal was undertaken and no study quality findings could be used to inform the recommendations and conclusions (Q7, 8); Authors declared no conflict of interest in their review, but not for individual studies included (Q11)

*Legend: Y = Yes, N = No, CA = Can't Answer

PFAS and birth outcomes

Three systematic reviews with meta-analyses (Johnson et al., 2014; Negri et al., 2017; Steenland et al., 2018) explored the association between prenatal exposure to PFAS and birth outcomes; all three explored exposure to PFOAs, one additionally included exposure to PFOS (Negri et al., 2017). Outcomes included were birth weight, birth length, head circumference and ponderal index. Reviews had a mix of case-control, cross-sectional, and both prospective and retrospective cohort studies.

Quality of the systematic reviews informing birth outcomes was varied, with scores on the AMSTAR tool ranging from 4 to 10/11. Only one review (Johnson et al., 2014) indicated that there was an *a priori* protocol available to guide the conduct of the review. Only one of the reviews provided a list of excluded studies (Negri et al., 2017) and one did not perform a thorough search, screen nor did the authors assess the quality of included studies (Steenland et al., 2018). Negri et al. (2017) specifically reported separate pooled findings for untransformed and transformed data because some of the studies used untransformed PFOA/PFOS levels in the regression model, while the others used log-transformed values.

Overall, there was evidence that prenatal exposure to PFOA and PFOS was associated with adverse birth outcomes (predominately decreased birth weight) in infants.

Birth weight

Three reviews (Johnson et al., 2014; Negri et al., 2017; Steenland et al., 2018) investigated prenatal exposure to PFAS and birth weight. Overall, there was evidence of risk of decreased birthweight in infants when their mothers had been exposed to PFOA and PFOS.

Exposure to PFOA

Prenatal PFOA exposure was associated with decreased in birthweight in infants reported in all reviews: Johnson et al. (2014) (β -18.9 g, 95%CI: -29.8 to -7.9; 9 studies, 4,149 participants); Negri et al. (2017) (untransformed group β -12.8 g, 95%CI: -23.21 to -2.38; 12 studies, 6,501 participants - estimated linear regression coefficient range -213 to 154 g for an increase of 1 log ng/mL PFOA; transformed group β -27.12 g, 95%CI: -50.64 to -3.60; 9 studies; 3,844 participants - estimated linear regression coefficient -142 to 5 g for an increase of 1 log ng/mL PFOA) Steenland et al. (2018) (β -10.5 g, 95%CI: -16.7 to -4.4; 24 studies, 19,173 participants; a decrease of approximately 0.3% in weight per unit of serum PFOA).

Subgroup findings

Two reviews presented subgroup analyses (Negri et al., 2017; Steenland et al., 2018). Both reviews reported subgroup findings based on method of sample collection (maternal vs cord). Negri et al. (2017) also reported subgroup findings based on regions and specific subgroup findings for method of sample collection by phases of pregnancy. Steenland 2018 reported subgroup findings by phases of pregnancy independent of the method of sample collection.

Region

In studies using untransformed data, Negri et al. (2017) found no association between prenatal PFOA exposure and birthweight in infants, in America (β -11.8 g, 95%CI: -32.1 to 8.6; 4 studies, participants unspecified), Asia (β -12.2 g, 95%CI: -27.3 to 3.0; 3 studies, participants unspecified) and Europe (β -15.5 g, 95%CI: -35.4 to 4.4; 5 studies, participants unspecified). However, in studies using transformed data, prenatal PFOA exposure was associated with decreased birthweight in infants in studies in Asia (β -31.9 g, 95%CI: -63.6 to -0.2; 4 studies, participants unspecified) but not in America (β -28.2 g, 95%CI: -64.5 to 8.1; 6 studies, participants unspecified).

Phases of pregnancy

Steenland et al. (2018) found no association between prenatal PFOA exposure and birthweight in infants in the first trimester of pregnancy (β -3.3 g, 95%CI: -9.6 to 3.0; 7 studies, 5,393 participants), however, found an association between prenatal PFOA exposure and decreased birthweight in the second and third trimesters (β -17.8 g, 95%CI: -25.0 to -10.6; 17 studies, 7,563 participants).

Method of sample collection

Maternal blood samples

Steenland et al. (2018) found that prenatal PFOA exposure was associated with decreased birthweight in infants (β -9.2 g, 95%CI: -15.6 to -2.8; 15 studies, participants unspecified) using maternal blood samples.

In studies using untransformed data, Negri 2017 found no association between prenatal PFOA exposure and birthweight in infants in the first and second trimesters (β -10.5 g, 95%CI: -23.6 to 2.6; 6 studies, participants unspecified) and third trimester (β -20.0 g; 95%CI: -52.1 to 12.1; 2 studies, participants unspecified) using maternal blood samples. However, in studies using transformed data, prenatal PFOA exposure was associated with decreased birthweight in infants in the third trimester (β -51.0 g, 95%CI: -86.6 to -15.5; 3 studies; participants unspecified) but not in the first and second trimesters (β -10.6 g, 95%CI: -43.2 to 22.0; 4 studies, participants unspecified).

Cord blood samples

Steenland et al. (2018) found that prenatal PFOA exposure was associated with decreased birthweight in infants (β -13.3 g, 95%CI: - 24.7 to -1.8; 9 studies, participants unspecified) using cord blood samples.

Negri et al. (2017) found no associations between prenatal PFOA exposure and birthweight in infants using cord blood samples in studies using untransformed data (β -35.3 g, 95%CI: -101.0 to 30.7; 4 studies, participants unspecified) and transformed data (β -24.4 g, 95%CI: -66.3 to 18.2; 3 studies, participants unspecified).

<u>Exposure to PFOS</u>

Only one review reported on PFOS exposure and birth outcomes (Negri et al., 2017).

Negri et al. (2017) reported an association between PFOS exposure and reduced birth weight in infants among studies which used and reported transformed data (β -46.09 g, 95%CI: -80.33 to -11.85; 8 studies; 3,677 participants. However, no association was found for studies which used and reported untransformed data (β -0.92 g, 95%CI: -3.43 to 1.60; 8 studies; 5,465 participants).

Subgroup findings

Negri et al. (2017) reported subgroup findings based on regions and method of sample collection (maternal vs cord). Negri 2017 also reported specific subgroup findings for method of sample collection by phases of pregnancy.

Region

In studies using untransformed data, Negri et al. (2017) found that prenatal PFOS exposure was associated with decreased birthweight in infants in studies in Asia (β -11.2 g, 95%CI: -16.7 to -5.8: 2 studies, participants unspecified) but not in America (β -1.6 g, 95%CI: -4.9 to 8.1; 2 studies, participants unspecified) and Europe (β -0.5 g, 95%CI: -1.6 to 2.7; 4 studies, participants unspecified). In studies using transformed data, prenatal PFOA exposure was associated with decreased birthweight in infants in studies in America (β -25.4 g, 95%CI: -66.0 to -15.2; 6 studies, participants unspecified) and Asia (β -85.7 g, 95%CI: -135 to -36.3; 3 studies, participants unspecified).

Method of sample collection

Maternal blood samples

In studies using untransformed data, Negri et al. (2017) found no association between prenatal PFOS exposure and birthweight in infants in the first and second trimesters (β 0.6 g, 95%CI: -1.4 to 2.5; 5 studies, participants unspecified) and third trimester (β -4.0 g, 95%CI: -16.3 to 8.2; 2 studies, participants unspecified) using maternal blood samples. However, in studies using transformed data, prenatal PFOA exposure was associated with decreased birthweight in infants in the third trimester (β -65.1 g, 95%CI: -127.0 to -3.2; 2 studies, participants unspecified) but not in the first and second trimesters (β -4.0 g, 95%CI: -62.3 to 54.3; 4 studies, participants unspecified).

Cord blood samples

In studies using transformed data, Negri et al. (2017) found that prenatal PFOS exposure was associated with decrease in birthweight in infants, using cord blood samples (β -93.2 g, 95%CI: -149 to -37.8; 3 studies, participants unspecified).

Birth length

One review (Johnson et al., 2014) reported an association between prenatal PFOA exposure and decreased birth length in infants (β -0.06 cm, 95% CI: -0.09 to -0.02; 5 studies, 2,853 participants).

Head circumference

Johnson et al. (2014) found no association with prenatal exposure to PFOA and change in head circumference in infants (β -0.03 cm, 95%CI: -0.08 to 0.01; 4 studies, 2,497 participants).

Ponderal index

The same review (Johnson et al., 2014) also presented pooled findings for ponderal index (or corpulence index; a measure of leanness, similar to BMI) with prenatal exposure to PFOA. There was no evidence of association between prenatal PFOA exposure and change in ponderal index in infants (β -0.01 cm, 95% CI: -0.03 to 0.01; 4 studies, 1,510 participants).

PFAS and endocrine and metabolic outcomes

One review explored the association between exposure to PFAS (PFOA, PFOS, PFHxS) determined from measures of these chemicals in the blood and metabolic or endocrine outcomes (Kim et al., 2018). The outcomes included were various measures of thyroid function reported for various statistical models used and subgroups of pregnant and non-pregnant populations. The review had a mix of population groups from cross-sectional studies of PFAS exposure and thyroid function.

The review scored 7/11 on the AMSTAR tool. The review did not have *a priori* protocol available to guide the conduct of the review and did not provide a list of excluded studies. It did include a comprehensive search and characteristics of the included studies, and critically appraised those included studies using a modified cross-sectional assessment provided by the Agency for Healthcare Research (Rostom et al., 2004). The review reported using both fixed and random effects for all analyses of z transformed correlation coefficients (pooled z values reported below). Significant heterogeneity was a common finding and therefore, in this report, the findings from the random effect model analyses have been reported preferentially. Sensitivity analyses were conducted to explore outlier studies and their influence and impact on estimates and heterogeneity in analyses were also reported.

PFOA exposure was found to have a negative association with TT4 levels after a sensitivity analysis (removal of elderly population from analysis) was conducted. No other evidence of association was found for PFOA and thyroid function measures.

PFOS exposure was also found to have a negative association with TT4 and T3 levels after a sensitivity analysis was conducted (removal of elderly population from analysis). However, PFOS exposure was positively correlated with free T4 and in subgroups of intermediate PFOS concentration levels and non-pregnant population.

No associations were found between PFHxS exposure and any of the thyroid function measures and subgroups reported.

Exposure to PFOA

Thyroid function

TT4

PFOA exposure was not associated with TT4 levels (z -0.01, 95%CI: -0.07 to 0.05; 8 studies 4,487 participants) in adults. However, after a sensitivity analysis (removing an outlier study with

significantly older population than the other included studies; 28-41 years) was conducted, PFOA exposure was found to be negatively associated with TT4 (z -0.06, 95%C: -0.08 to -0.03; 7 studies, 4,400 participants).

Subgroup findings

Considering PFOA concentration measured in blood, no associations were noted between mean PFOA concentration and TT4: intermediate concentration (2-3ng/mL) (z -0.00, 95%CI: -0.08 to 0.07; 5 studies, 2,552 participants) and high concentration (>3ng/mL) (z -0.00, 95%CI: -0.016 to 0.16; 3 studies, 1,935 participants).

When grouped by population, no associations were found between PFOA exposure and TT4 among pregnant women (z 0.04, 95%CI: -0.06 to 0.13; 2 studies; participants unspecified) and non-pregnant population (z -0.03, 95%CI: -0.09 to 0.04; 6 studies, participants unspecified).

TSH

No associations were found between PFOA exposure and TSH (z 0.00, 95%CI: -0.03 to 0.04; 11 studies 5,823 participants) in adults.

Subgroup findings

When grouped by PFOA concentration, no associations were found between mean blood PFOA concentration and TSH: low concentration (<2ng/mL) (z 0.04, 95%CI: -0.06 to 0.13; 2 studies, 423 participants), intermediate concentration (2-3ng/mL) (z -0.01, 95%CI: -0.06 to 0.04; 6 studies, 3,466 participants) and high concentration (>3ng/mL) (z 0.03, 95%CI: -0.06 to 0.12; 3 studies, 1,934 participants).

When grouped by population, no associations were found between PFOA exposure and TSH among pregnant women (z 0.00, 95%CI: -0.05 to 0.04; 4 studies, participants unspecified) and non-pregnant population (z 0.00, 95%CI: -0.03 to 0.04; 6 studies, participants unspecified).

fT4

No association was found between PFOA exposure and fT4 (z 0.01, 95%CI: -0.02 to 0.04; 8 studies, 4,120 participants) in adults.

Subgroup findings

When grouped by PFOA concentration, no associations were found between mean blood PFOA concentration and fT4: low concentration (<2ng/mL) (z 0.02, 95%CI: -0.08 to 0.12; 2 studies, 423 participants), intermediate concentration (2-3ng/mL) (z 0.02, 95%CI: -0.03 to 0.06; 4 studies, 2,008 participants), high concentration (>3ng/mL) (z 0.05, 95%CI: -0.12 to 0.21; 2 studies, 1,689 participants)

When grouped by population, no associations were found between PFOA exposure and fT4 among pregnant women (z 0.00, 95%CI: -0.07 to 0.06; 3 studies, participants unspecified) and non-pregnant population (z 0.01, 95%CI: -0.02 to 0.05; 5 studies, participants unspecified).

T3

No associations were found between PFOA exposure and T3 (z 0.05, 95%CI: 0.00 to 0.10; 7 studies 3,933 participants) in adults.

Subgroup findings

When grouped by PFOA concentration, no associations were found between mean blood PFOA concentration and T3: intermediate concentration (2-3ng/mL) (z 0.05, 95%CI: -0.03 to 0.14; 4 studies, 1,998 participants), high concentration (>3ng/mL) (z 0.06, 95%CI; -0.02 to 0.14; 3 studies, 1,935 participants).

When grouped by population, no associations were found between PFOA exposure and T3 among pregnant women (z 0.04, 95%CI; -0.05 to 0.14; 2 studies, participants unspecified) and non-pregnant population (z 0.05, -0.01 to 0.11; 5 studies, participants unspecified).

<u>Exposure to PFOS</u>

TT4

PFOS exposure was not found to be associated with TT4 levels (z 0.01, 95%CI: -0.05 to 0.07; 8 studies, 4,489 participants) in adults. However, after a sensitivity analysis (removing an outlier study with significantly older population) was conducted, a negative association was found between PFOS exposure and TT4 (z -0.04, 95%CI: -0.07 to -0.01; 7 studies, 4,402 participants).

Subgroup findings

When grouped by PFOS concentration in the blood, no associations were found between mean blood PFOS concentration and TT4: low concentration (<8ng/mL) (z -0.02, 95%CI: -0.10 to 0.6; 2 studies, 713 participants), intermediate concentration (8-16ng/mL) (z -0.01, -0.11 to 0.09; 3 studies, 1,839 participants), high concentration (>16ng/mL) (z 0.09, 95%CI: -0.11 to 0.28; 3 studies, 1,937 participants).

When grouped by population, no associations were found between PFOS exposure and TT4 among pregnant women (z 0.06, 95%CI: -0.03 to 0.15; 2 studies, participants unspecified) and non-pregnant population (z 0.00, 95%CI: -0.07 to 0.07; 6 studies, participants unspecified).

TSH

PFOS exposure was not found to be associated with TSH levels (z -0.02, 95%CI: -0.07 to 0.03; 12 studies, 6,445 participants) in adults, even after a sensitivity analysis (no reason provided) was undertaken (z 0.01, 95%CI: -0.02 to 0.03; 10 studies, 5,896 participants).

Subgroup findings

When grouped by PFOS concentration, no associations were found between mean blood PFOS concentration and TSH: low concentration (<8ng/mL) (z -0.14, 95%CI: -0.28 to 0.01; 3 studies, 1,105 participants), intermediate concentration (8-16ng/mL) (z 0.03, 95%CI: 0.00 to 0.07; 4 studies, 2,753 participants), high concentration (>16ng/mL) (z -0.01, 95%CI: -0.8 to 0.07; 5 studies, 2,578 participants).

When grouped by population, no associations were found between PFOS exposure and TSH among pregnant women (z -0.08, 95%CI: -0.12 to 0.08; 4 studies, participants unspecified) and non-pregnant population (z -0.01, 95%CI: -0.04 to 0.02; 8 studies, participants unspecified).

fT4

PFOS exposure was associated with fT4 levels (z 0.05, 95%CI: 0.03 to 0.08; 9 studies, 4,741 participants) in adults.

Subgroup findings

When grouped by mean blood PFOS concentration, intermediate concentration (8-16ng/mL) was found to be positively associated with fT4 (z 0.07, 95%CI: 0.02 to 0.11; 3 studies, 1,852 participants) but not low (<8ng/mL) (z 0.04, 95%CI: -0.09 to 0.16; 2 studies, 548 participants) and high concentration (>16ng/mL) levels (z 0.06, 95%CI: -0.01 to 0.13; 4 studies, 2,341 participants).

When grouped by population, PFOS exposure was found to be positively associated with fT4 in the non-pregnant population (z 0.06, 95% CI: 0.02 to 0.09: 6 studies, participants unspecified) but not among pregnant women (z 0.05, 95% CI: -0.02 to 0.11: 3 studies, participants unspecified).

T3

PFOS exposure was not found to be associated with T3 levels (z -0.02, 95%CI: -0.07 to 0.04; 8 studies, 4,555 participants) in adults. However, after a sensitivity analysis (removing an outlier study with significantly older population) was conducted, a negative association was found between PFOS exposure and T3 (z -0.04, 95%CI: -0.06 to -0.01; 7 studies, 4,309 participants).

Subgroup findings

When grouped by mean blood PFOS concentration, no associations were found between different PFOS concentration and T3: intermediate concentration (8-16ng/mL) (z -0.03, 95%CI: -0.11 to 0.06; 3

studies, 1,843 participants), high concentration (>16ng/mL) (z 0.01, 95%CI: -0.10 to 0.11; 4 studies, 2,557 participants).

When grouped by population, no associations were found between PFOS exposure and T3 among pregnant women (z -0.01, 95%CI: -0.10 to 0.09; 2 studies, participants unspecified) and non-pregnant population (z -0.01, 95%CI: -0.08 to 0.06; 6 studies, participants unspecified).

Exposure to PFHxS

TT4

No association was found between PFHxS exposure and TT4 (z -0.04, 95%CI: -0.08 to 0.01; 6 studies, 4,154 participants) in adults.

Subgroup findings

When grouped by mean PFHxS concentration in the blood, no associations were found between different PFHxS concentration and TT4: low concentration (<0.8ng/mL) (z -0.04, 95%CI: -0.11 to 0.02; 3 studies, 929 participants), high concentration (>0.8ng/mL) (z -0.02, 95%CI: -0.09 to 0.04; 3 studies, 3,225 participants).

When grouped by population, PFHxS was associated with T4 in non-pregnant population (z -0.04, 95%CI: -0.07 to -0.01; 4 studies, participants unspecified) but not among pregnant women (z 0.01, 95%CI: -0.18 to 0.20; 2 studies, participants unspecified)

TSH

No association was found between PFHxS exposure and TSH (z 0.00, 95%CI: -0.3 to 0.04; 8 studies, 5,099 participants) in adults.

Subgroup findings

When grouped by mean blood PFHxS concentration, no associations were found between different PFHxS concentrations and TSH: low concentration (<0.8ng/mL) (z 0.02, 95%CI: -0.04 to 0.7; 5 studies, 1,872 participants), high concentration (>0.8ng/mL) (z -0.01, 95%CI: -0.07 to 0.04; 3 studies, 3,227 participants)

When grouped by population, no associations were found between PFHxS exposure and TSH among pregnant women (z 0.00, 95%CI: -0.12 to 0.13; 3 studies, participants unspecified) and non-pregnant population (z 0.00, 95%CI: -0.04 to 0.03; 5 studies, participants unspecified).

fT4

No association was found between PFHxS exposure and fT4 (z 0.02, 95%CI: -0.01 to 0.05; 6 studies, 3,641 participants) in adults.

Subgroup findings

When grouped by mean PFHxS concentration, no associations were found between different PFHxS concentration in the blood and fT4: low concentration (<0.8ng/mL) (z 0.00, 95%CI: -0.10 to 0.09; 3 studies, 415 participants), high concentration (>0.8ng/mL) (z 0.02, 95%CI: -0.01 to 0.06; 3 studies, 3,226 participants).

When grouped by population, no associations were found between PFHxS exposure and fT4 among pregnant women (z 0.01, 95%CI: -0.01 to 0.05; 2 studies, participants unspecified) and non-pregnant population (z 0.02, 95%CI: -0.01 to 0.05; 4 studies, participants unspecified).

T3

No association was found between PFHxS exposure and T3 (z 0.00, 95%CI: -0.03 to 0.04; 5 studies, 3,600 participants) in adults.

Subgroup findings

When grouped by mean PFHxS concentration in the blood, no associations were found between different PFHxS concentration and T3: low concentration (<0.8ng/mL) (z 0.00, 95%CI: -0.19 to 0.19; 2

studies, 375 participants), high concentration (>0. 8ng/mL) (z 0.01, 95%CI: -0.03 to 0.04; 3 studies, 3,225 participants).

When grouped by population, no associations were found between PFHxS exposure and fT4 among pregnant women (z -0.01, 95%CI: -0.16 to 0.14; 2 studies, participants unspecified) and non-pregnant population (z 0.01, 95%CI: -0.03 to 0.04; 3 studies, participants unspecified).

PFAS and child neurodevelopmental outcomes

One pooled analysis explored the association between PFAS (PFOA and PFOS) and child neurodevelopmental outcomes (Forns et al., 2020). The pooled analysis included European cohorts studying timing to which maternal PFAS levels were assessed during pregnancy and estimated for the first 24 months of life, and subsequent attention deficit hyperactivity disorder (ADHD), including a subgroup analysis by sex.

The pooled analysis scored poorly on the AMSTAR tool (3/11) because there were no systematic methods relating to searching, screening, extraction and appraisal of the evidence undertaken. The authors used a validated pharmacokinetic model to harmonise the measures of exposure across studies and generate estimates of postnatal PFOS and PFOA levels in the children at birth, 3, 6, 12 and 24 months.

Definitions/diagnosis of ADHD in the included cohorts was either clinical diagnosis (registries) or through questionnaires including the Attention Syndrome Scale of the Child Behaviour Checklist (CBCL-ADHD), the Hyperactivity/Inattention Problems subscale of the Strengths and Difficulties Questionnaire (SDQ-Hyperactivity/Inattention) or a list of ADHD criteria from the DSM-IV. Questionnaires were completed by either parents or teachers.

Exposure to PFOA

Using the model, PFOA exposure was not associated with increased prevalence of ADHD in children at birth (OR, 1.01, 95%CI: 0.93 to 1.11; 9 studies, 4,826 participants), 3 months (OR 1.02, 95%CI: 0.93 to 1.11; 9 studies, 4,826 participants), 6 months (OR 1.01, 95%CI: 0.91 to 1.12; 9 studies, 4,826 participants), 12 months (OR 1.00, 95%CI: 0.89 to 1.12; 9 studies, 4,826 participants) or 24 months (OR 0.99, 95%CI: 0.88 to 1.12; 9 studies, 4,826 participants).

Subgroup findings

In the subgroup of girls, PFOA exposure was found to be associated with an increased ADHD risk at birth (OR 1.28, 95%CI: 1.03 to 1.59; 9 studies, 1,356 participants) and at three months (OR, 1.28, 95%CI: 1.01 to 1.62; 9 studies, 1,356 participants) but not at 6 months (OR 1.29, 95%CI: 1.00 to 1.66; 9 studies, 1,356 participants), 12 months (OR 1.24, 95%CI: 0.96 to 1.61; 9 studies, 1,356 participants) and 24 months (OR 1.30, 95%CI: 0.98 to 1.73; 9 studies, 1,356 participants). No association was found in boys at any time period: at birth (OR 0.98, 95%CI: 0.87 to 1.09; 9 studies, 2,639 participants), 3 months (OR 1.00, 95%CI: 0.89 to 1.11; 9 studies, 2,639 participants), 6 months (OR 1.02, 95%CI: 0.86 to 1.22; 9 studies, 2,639 participants), 12 months (OR 1.03, 95%CI: 0.85 to 1.25; 9 studies, 2,639 participants) and 24 months (OR 0.97, 95%CI: 0.83 to 1.14; 9 studies, 2,639 participants).

Exposure to PFOS

PFOS exposure was not found to be associated with increased prevalence of ADHD in children at birth (OR 0.99, 95%CI: 0.92 to 1.07; 9 studies; 4,826 participants), 3 months (OR 0.99, 95%CI: 0.92 to 1.06; 9 studies, 4,826 participants), 6 months (OR 0.98, 95%CI: 0.90 to 1.06; 9 studies; 4,826 participants), 12 months (OR 0.96, 95%CI: 0.87 to 1.06; 9 studies; 4,826 participants) or 24 months (OR 0.97, 95%CI: 0.88 to 1.07; 9 studies; 4,826 participants).

Subgroup findings

PFOS exposure was not found to be associated with an increased ADHD risk among girls, at birth (OR 1.14, 95%CI: 0.91 to 1.34; 9 studies, 1,356 participants), 3 months (OR 1.12, 95%CI :0.94 to 1.34; 9

studies, 1,356 participants), 6 months (OR 1.13 95%CI: 0.93 to 1.36; 9 studies, 1,356 participants), 12 months (OR 1.19, 95%CI: 0.92 to 1.53; 9 studies, 1,356 participants) or 24 months (OR 1.26, 95%CI: 0.93 to 1.72; 9 studies, 1,356 participants). Similarly, no association was found in boys at birth (OR 0.96, 95%CI: 0.88 to 1.05; 9 studies, 2,639 participants), 3 months (OR 0.96, 95%CI: 0.89 to 1.05; 9 studies, 2,639 participants), 6 months (OR 0.95, 95%CI: 0.86 to 1.05; 9 studies, 2,639 participants), 12 months (OR 0.93, 95%CI: 0.83 to 1.04; 9 studies, 2,639 participants) or 24 months (OR 0.92, 95%CI: 0.81 to 1.03; 9 studies, 2,639 participants).

PFAS and nutritional outcomes (obesity & anthropometrics)

One review explored the association between PFAS and nutritional outcomes (Liu et al., 2018). Outcomes of interest were childhood obesity and/or BMI. The review included cohort and cross-sectional studies. Only PFOA was investigated.

The quality of the review was moderate, with a score of 7/11 in the AMSTAR tool. The review did not indicate that there was an *a priori* protocol, nor provided a list of excluded studies. Other concerns included omission of grey literature in the search and results of the study quality assessment were not considered in the analysis nor formulation of conclusions.

Overall PFOA exposure was associated with an increase in risk of childhood obesity and overweight using BMI levels and BMI z-scores. Both prenatal and postnatal PFOA exposures were found to be associated with higher BMI z scores. No associations were found in subgroups of girls and boys. PFOA exposure was associated with an increase in BMI z-score in studies conducted in Europe but not in Northern America.

Childhood obesity/overweight

Liu et al. (2018) did not provide a definition of obesity or cut-offs used. However, as the WHO provides a standard definition of obesity, it has been assumed that reviews have used the standard definition. Childhood obesity is defined differently depending on age (WHO, 2021). Prenatal exposure to PFOA was found to be associated with childhood overweight (ES 1.25, 95% CI: 1.04 to 1.50, 8 studies, 5,457 participants).

Subgroup findings

Prenatal PFOA exposure was found to be associated with childhood overweight in the subgroup of studies which used risk ratio (RR 1.26, 95% CI: 1.01 to 1.56; 6 studies, 4,224 participants), but not for the studies which used odds ratio (OR 1.39, 95% CI: 0.85 to 2.28; 2 studies, 1,223 participants).

Body mass index (BMI)

There was no clear definition in the review about what was considered high BMI as the studies used different definitions.

PFOA exposure was associated with increase in BMI z-scores in children (β 0.10, 95% CI: 0.03 to 17; 9 studies, 5,411 participants). After a sensitivity analysis was conducted to omit the studies with small sample sizes, PFOA exposure was still associated with increase in BMI z-scores in children (β 0.07, 95% CI: 0.01 to 0.14; 5 studies, 3,825 participants).

Subgroup findings

PFOA exposure was associated with an increase in BMI z-score for both prenatal exposure (β 0.09, 95%CI: 0.02 to 0.17; studies unspecified, 5,505 participants) and postnatal exposure (β 0.16, 95%CI: 0.01 to 0.30; studies unspecified, 571 participants).

PFOA exposure was not associated with BMI z-score in girls (β 0.06, 95%CI: −0.01 to 0.13; studies unspecified, 1,549 participants) and boys (β= −0.01, 95%CI: −0.10, 0.08; studies unspecified, 1,628 participants).

PFOA exposure was associated with an increase in BMI z-score studies conducted in Europe (β 0.10 95%CI: 0.02 to 0.17; 7 studies, 3,545 participants), but not in Northern America (β 0.19, 95%CI: −0.05 to 0.42; 3 studies, 2,102 participants).

PFOA exposure was associated with an increase in BMI z-score when study data were adjusted for maternal parity (β 0.13, 95%CI: 0.02 to 0.24; studies unspecified, 3,949 participants) and when no adjustments were conducted for birthweight (β 0.10, 95%CI: 0.03 to 0.17; studies unspecified, 5,704 participants), but not when no adjustments were conducted for parity (β 0.07, 95%CI: -0.01 to 0.15; studies unspecified, 2,127 participants). No association was found when).

PFAS and respiratory outcomes

One review explored the association between flame retardants PFAS and respiratory outcomes in children and included a mix of cohort, cross-sectional and case-control studies (Luo et al., 2020). The outcomes included were asthma, wheeze and allergic rhinitis.

Quality of the review was moderate (AMSTAR score 7/11). It did not include an *a priori* protocol, and there were concerns regarding the search strategy and publication bias assessment.

Overall PFAS exposure was not associated with increased risk of having asthma in children. However, in subgroup of studies in Asia, PFOS, PFHxS and PFNA exposure were associated with moderate to high increased risk in asthma. PFOA exposure was associated with an increased risk in having allergic rhinitis but not PFOS, PFHxS and PFNA. No associations were found for any PFAS exposure and wheeze.

Asthma

Exposure to PFOA

Luo et al. (2020) reported no association between PFOA and childhood asthma (OR 1.11, 95% CI: 0.85 to 1.24; 8 studies, 7,050 participants).

Subgroup findings

When grouped by exposure, no associations were found for both prenatal (OR 0.92, 95%CI: 0.79 to 1.07; 6 studies, participants unspecified) and postnatal (OR 2.05, 95%CI: 0.58 to 7.27; 2 studies, participants unspecified) exposure and childhood asthma.

When grouped by region, no associations were found for studies in Asia (OR 2.37, 95%CI: 0.62 to 9.13; 2 studies, participants unspecified) or Europe (OR 0.92, 95%CI: 0.78 to 1.07; 5 studies, participants unspecified).

Exposure to PFOS

No association was found between PFOS and childhood asthma (OR 1.11, 95%CI: 0.88 to 1.40; 8 studies, 7,050 participants).

Subgroup findings

When grouped by exposure, no associations were found for both prenatal (OR 0.99, 95%CI: 0.80 to 1.22; 6 studies, participants unspecified) or postnatal (OR 1.57, 95%CI: 0.62 to 4.00; 2 studies, participants unspecified) exposure and childhood asthma.

When grouped by region, PFOS exposure was found to be associated with an increased risk in asthma in studies conducted in Asia (OR 2.47, 95%CI: 1.43 to 4.25; 2 studies, participants unspecified) but not in studies in Europe (OR 0.98, 95%CI: 0.78 to 1.23; 5 studies, participants unspecified).

Exposure to PFHxS

No association was found between PFHxS and childhood asthma (OR 1.02, 95%CI: 0.85 to 1.24; 8 studies, 7,050 participants).

Subgroup findings

When grouped by exposure, no associations were found for both prenatal (OR 0.94, 95%CI: 0.84 to 1.05; 6 studies, participants unspecified) and postnatal (OR 1.83, 95%CI: 0.45 to 7.38; 2 studies, participants unspecified) exposure and childhood asthma.

When grouped by region, PFHxS exposure was found to be associated with an increased risk in asthma in studies conducted in Asia (OR 3.66, 95%CI: 2.06 to 6.49; 2 studies, participants unspecified) but not in studies in Europe (OR 0.94, 95%CI: 0.84 to 1.04; 5 studies, participants unspecified).

Exposure to PFNA

No association was found between PFNA and childhood asthma (OR 0.99, 95%CI: 0.81 to 1.21; 8 studies, 7,050 participants).

Subgroup findings

When grouped by exposure, no associations were found for both prenatal (OR 0.90, 95%CI: 0.74 to 1.06; 6 studies, participants unspecified) and postnatal (OR 1.52, 95%CI: 0.60 to 3.85; 2 studies, participants unspecified) exposures and childhood asthma.

When grouped by region, PFNA exposure was found to be associated with an increased risk in asthma in studies conducted in Asia (OR 2.37, 95%CI: 1.34 to 4.20; 2 studies, participants unspecified) but not in studies in Europe (OR 0.90, 95%CI: 0.73 to 1.09; 5 studies, participants unspecified).

Allergic rhinitis

Exposure to PFOA

PFOA exposure was associated with an increased risk of having allergic rhinitis in children (OR 1.32, 95%CI: 1.13 to 1.55; 4 studies, 3,396 participants).

Subgroup findings

No association was found between prenatal PFOA exposure and allergic rhinitis in children (OR 1.29, 95%CI: 1.00 to 1.66; 3 studies, participants unspecified).

When grouped by region, no association was found between PFOA exposure and allergic rhinitis in children in studies in Europe (OR 1.29, 95%CI: 0.98 to 1.69; 2 studies, participants unspecified).

Exposure to PFOS

No association was found between PFOS and allergic rhinitis in children (OR 1.07, 95%CI: 0.89 to 1.29; 4 studies, 3,396 participants).

Subgroup findings

No association was found between prenatal PFOS exposure and allergic rhinitis in children (OR 0.97, 95%CI: 0.74 to 1.29; 3 studies, participants unspecified).

When grouped by region, no association was found between PFOS exposure and allergic rhinitis in children in studies in Europe (OR 1.03, 95%CI: 0.75 to 1.41; 2 studies, participants unspecified).

Exposure to PFHxS

No association was found between PFHxS and allergic rhinitis in children (OR 0.94, 95%CI: 0.79 to 1.13; 4 studies, 3,396 participants).

Subgroup findings

No association was found between prenatal PFHxS exposure and allergic rhinitis in children (OR 0.99, 95%CI: 0.84 to 1.16; 3 studies, participants unspecified).

When grouped by region, no association was found between PFHxS exposure and allergic rhinitis in children in studies in Europe (OR 1.01, 95%CI: 0.86 to 1.20; 2 studies, participants unspecified).

Exposure to PFNA

No association was found between PFNA and allergic rhinitis in children (OR 0.99, 95%CI: 0.71 to 1.37; 4 studies, 3,396 participants).

Subgroup findings

When grouped by exposure, no association was found between prenatal PFNA exposure and allergic rhinitis in children (OR 0.83, 95%CI: 0.47 to 1.46; 3 studies, participants unspecified).

When grouped by region, no association was found between PFNA exposure and allergic rhinitis in children in studies in Europe (OR 1.11, 95%CI: 0.79 to 1.54; 2 studies, participants unspecified).

Wheeze

Exposure to PFOA

No association was found between PFOA and wheeze in children (OR 1.03, 95%CI: 0.93 to 1.15; 6 studies, 6,672 participants).

Subgroup findings

No association was found between prenatal PFOA exposure and wheeze in children (OR 1.03, 95%CI: 0.90 to 1.17; 5 studies, participants unspecified).

When grouped by region, no association was found between PFOA exposure and wheeze in children in studies in Asia (OR 0.98, 95%CI: 0.60 to 1.60; 2 studies, participants unspecified) or studies in Europe (OR 1.04, 95%CI: 0.88 to 1.23; 3 studies, participants unspecified).

Exposure to PFOS

No association was found between PFOS and wheeze in children (OR 0.90, 95%CI: 0.78 to 1.04; 6 studies, 6,672 participants).

Subgroup findings

No association was found between prenatal PFOS exposure and wheeze in children (OR 0.91, 95%CI: 0.76 to 1.09; 5 studies, participants unspecified).

When grouped by region, no association was found between PFOS exposure and wheeze in children in studies in Asia (OR 0.79, 95%CI: 0.55 to 1.13; 2 studies, participants unspecified) and studies in Europe (OR 0.95, 95%CI: 0.74 to 1.22; 3 studies, participants unspecified).

Exposure to PFHxS

No association was found between PFHxS and wheeze in children (OR 0.97, 95%CI: 0.87 to 1.08; 6 studies, 6,672 participants).

Subgroup findings

No association was found between prenatal PFHxS exposure and wheeze in children (OR 1.00, 95%CI: 0.89 to 1.13; 5 studies, participants unspecified).

When grouped by region, no association was found between PFHxS exposure and wheeze in children in studies in Asia (OR 0.73, 95%CI: 0.50 to 1.05; 2 studies, participants unspecified) and studies in Europe (OR 1.04, 95%CI: 0.93 to 1.16; 3 studies, participants unspecified).

Exposure to PFNA

No association was found between PFNA and wheeze in children (OR 0.98, 95%CI: 0.88 to 1.08; 6 studies, 6,672 participants).

Subgroup findings

No association was found between prenatal PFNA exposure and wheeze in children (OR 0.99, 95%CI: 0.86 to 1.13; 5 studies, participants unspecified).

When grouped by region, no association was found between PFNA exposure and wheeze in children in studies in Asia (OR 0.96, 95%CI: 0.49 to 1.87; 2 studies, participants unspecified) or studies in Europe (OR 0.98, 95%CI: 0.84 to 1.15; 3 studies, participants unspecified).

PFAS and skin-related outcomes

Only one review investigated the association between PFAS and skin-related outcomes in children Luo et al. (2020). The review evaluated the association with atopic dermatitis and eczema separately. The authors did not state how or why studies related to eczema and atopic dermatitis were distinguished, but it was interesting to note that there was no overlap in the studies considered under these two outcomes. The review did not report on a combined outcome of eczema or atopic dermatitis. The review included a mix of cohort, case-control and cross-sectional studies.

The quality of the review on the AMSTAR tool was moderate with a score of 6/11. The review did not include an *a priori* protocol, and there were concerns regarding the search strategy and publication bias assessment. As above, it also did not give details of how or why studies with eczema as an outcome were distinguished from those with atopic dermatitis as an outcome.

PFOS exposure was associated with an increased risk in developing atopic dermatitis in children, and specifically in studies in Asia. Other PFAS (PFOA, PFHxS and PFNA) were not found to be associated with atopic dermatitis or eczema.

Exposure to PFOA

Atopic dermatitis

No association was found between PFOA and atopic dermatitis in children (OR 1.39, 95%CI: 0.89 to 2.18; 4 studies, 2,650 participants).

When grouped by region, no association was found between PFOA exposure and atopic dermatitis in children in studies in Asia (OR 1.49, 0.73 to 3.06); 3 studies; participants unspecified).

Eczema

No association was found between PFOA and eczema in children (OR 0.99, 95%CI: 0.88 to 1.10; 5 studies, 5276 participants).

When grouped by region, no association was found between PFOA exposure and eczema in children in studies in Europe (OR 1.00, 95%CI: 0.89 to 1.12; 4 studies; participants unspecified).

Exposure to PFOS

Atopic dermatitis

PFOS exposure was associated with an increased risk of atopic dermatitis in children (OR 1.26, 95%CI: 1.01 to 1.58; 4 studies, 2,650 participants).

When grouped by region, PFOS was also associated with an increased risk of atopic dermatitis in children in studies in Asia (OR 1.54, 95%CI: 1.03 to 2.31; 3 studies; participants unspecified).

Eczema

No association was found between PFOS and eczema in children (OR 0.91, 95%CI: 0.81 to 1.02; 5 studies, 5,276 participants).

When grouped by region, no association was found between PFOS exposure and eczema in children in studies in Europe (OR 0.92, 95%CI: 0.81 to 1.04; 4 studies, participants unspecified).

Exposure to PFHxS

Atopic dermatitis

No association was found between PFHxS and atopic dermatitis in children (OR 1.08, 95%CI: 0.92 to 1.27; 4 studies, 2,650 participants).

When grouped by region, no association was found between PFHxS exposure and atopic dermatitis in children in studies in Asia (OR 1.20, 95%CI: 0.77 to 1.88; 2 studies, participants unspecified).

Eczema

No association was found between PFHxS and eczema in children (OR 1.07, 95%CI: 0.96 to 1.20; 5 studies, 5,276 participants).

When grouped by region, no association was found between PFHxS exposure and eczema in children in studies in Europe (OR 1.09, 95%CI: 0.97 to 1.23; 4 studies, participants unspecified).

Exposure to PFNA

Atopic dermatitis

No association was found between PFNA and atopic dermatitis in children (OR 0.96, 95%CI: 0.65 to 1.43; 4 studies, 2,650 participants).

When grouped by region, no association was found between PFNA exposure and atopic dermatitis in children in studies in Asia (OR 1.00, 95%CI: 0.66 to 1.53; 3 studies, participants unspecified).

Eczema

PFNA exposure was inversely associated with eczema in children (OR 0.89, 95%CI: 0.80 to 0.99; 5 studies, 5,276 participants).

When grouped by region, no association was found between PFNA exposure and eczema in children in studies in Europe (OR 0.90, 95%CI: 0.81 to 1.00; 4 studies, participants unspecified)

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GLOSSARY

Definitions for terms used in the Umbrella Review.

CHEMICALS

Bisphenols Chemical compounds used primarily in the manufacture of plastics.

Bisphenol A A synthetic monomer used to make polycarbonates and epoxy resins, including plastics used for food and beverage containers or their linings; they are also used as stabilisers. Bisphenol A (BPA) has attracted the most research.

Congener In relation to PCBs and PBDEs, a congener is a variant defined as any single, unique chemical compound. For PCBs, the congener specifies both the total number of chlorine substituents, and the position of each chlorine. For PBDEs, the congener specifies both the number of bromine substituents and the position of each bromine.

https://www.epa.gov/pcbs/learn-about-polychlorinated-biphenyls-pcbs

https://www.epa.gov/sites/default/files/2015-09/documents/pbdes_ap_2009_1230_final.pdf

Flame retardants Halogenated flame retardants that have been used in plastics include the polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs).

Monomers Chemical 'building-blocks' that when linked chemically form a polymer matrix. As well as bisphenol A, other monomers used to make plastic polymers include ethylene, propylene, styrene, and vinyl chloride.

Per- and polyfluoroalkyl substances (PFAS)

Best known for use in firefighting foams and protective coatings for food packaging, textiles and furniture. Applications in plastics include the manufacture of fluoropolymer plastics used for non-stick cookware and waterproof fabrics. They may also form from surface fluorination of plastic products, a chemical process to make plastic packaging more resilient.

Phthalates Are the main group of chemicals used as plasticisers which increase the flexibility of plastics. Also called ortho-phthalate diesters.

Phthalate metabolites Phthalates are rapidly metabolized to their respective monoesters, which - depending on the phthalate - can be further metabolized to their oxidative products. The metabolites may be also by further metabolised by conjugation (glucuronidated) prior to excretion in the urine (and to a small degree in faeces)

https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/phthte_g_met.pdf

See Table A1.

Plastic Can be broadly classified into seven different types based on their polymer composition: polyethylene terephthalate (PET); high density polyethylene (HD-PE); polyvinyl chloride (PVC); low density polyethylene (LD-PE); polypropylene (PP); polystyrene (PS) and other resins including polyurethane (PUR).

Plastic polymers Long chains of identical monomers that are synthesized during the manufacture of plastic.

QUANTITATIVE ASSESSMENTS / STATISTICS

For details, see Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2022)

Effect size	A quantitative measure of the magnitude of the effect. In this instance, the larger the effect size, the stronger the relationship between the exposure to a plastic-associated chemical/s and a health outcome.
β-coefficient	The degree of change in the outcome variable for every 1-unit of change in the predictor variable, in this case, the plastic-associated chemical.
z-transformed β-coefficient	Transformation of the sampling distribution of the correlation coefficient so that it becomes normally distributed**.**
Fixed effects model	Fixed effects model assumes that the true effect observed is the same in every study and any differences are solely due to random sampling error (chance) within each study. The results can be considered a typical effect.
Random effects model	Random effects model assumes that observed effects follow a distribution (usually normal) and differences are due to both random sampling error (chance) within studies and also variation between studies. The result can be considered an average effect.
Fixed variables	Variables that can be measured without error. It is assumed that a fixed variable in one study will have the same value as a fixed variable in another study (e.g. spontaneous pregnancy loss).
General population	A study sample or population that is representative of general population exposure to the chemical of interest (c.f. a special exposure group or a special risk group for exposure). Including both adults and children unless otherwise specified.
Meta-analysis	A statistical technique used to combine the numerical results of 2 or more separate studies of the same research question, in order to derive a single overall estimate.
Odds ratio	A quantitative measure of association between an exposure and an outcome, in this instance a health outcome. The odds ratio represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Odds ratios are most commonly used in case-control studies; however, they can also be used in cross-sectional and cohort study designs. Odds ratios > 1 indicate that an exposure is harmful; < 1 indicates a protective effect.
Pooled analysis	A statistical technique for combining individual data (c.f. results) from 2 or more studies and re-analysing as a whole.
Risk ratio	A quantitative measure of association comparing the risk of a health outcome among one group with the risk among another group in this instance the groups being differentiated by exposure to plastic-associated chemicals. Calculated by dividing the risk in one group by the risk in the comparison group. A risk ratio of 1 indicated identical risk in both groups. A risk ratio > 1 indicates and increased risk, usually in the more highly exposed group; a risk ratio <1 indicates a decreased risk.
Systematic review	Review of a clearly formulated question using systematic and reproducible methods to identify, select and critically appraise all relevant research, and collect and analyse data from eligible studies. (Curtin University Library Services 2022b)

ABBREVIATIONS

Abbreviations for the Umbrella Review are provided here.

CHEMICALS

BISPHENOLS

BPA	Bisphenol A

PHTHALATES AND METABOLITES

For full table of parent phthalate compounds and their metabolites, see Appendix 10

ΣDEHP	Sum of all measured DEHP metabolites
BBP	Butyl benzyl phthalate
DEP	Diethyl phthalate
DEHP	Di (2-ethylhexyl) phthalate
DEHP met.	Di (2-ethylhexyl) phthalate metabolites
DiBP	Diisobutyl phthalate
DMP	Dimethyl phthalate
DnBP	Di-n-butyl phthalate
MBzP	Monobenzyl phthalate
MCCP	Mono (3-carboxypropyl) phthalate
MCNP	Mono (carboxynonyl) phthalate
MCOP	Mono (carboxy-isooctyl) phthalate
MECPP	Mono (2-ethyl-5-carboxypentyl) phthalate
MEHP	Mono (2-ethylhexyl) phthalate
MEHHP	Mono (2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	Mono (2-ethyl-5-oxohexyl) phthalate
MEP	Monoethyl phthalate
MiBP	Monoisobutyl phthalate
MMP	Monomethyl phthalate
MnBP	Mono-n-butyl phthalate

FLAME RETARDANTS

PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls (and individual PCB congeners, e.g. PCB 99, PCB 105, PCB 183, PCB 187)
PCB classes I, II, III	Functional classes of PCBs based on structural and biological considerations (Wolff et al. 1997)

PER- AND POLYFLUOROALKYL SUBSTANCES

PFAS	Per- and Polyfluoroalkyl Substances

PFHxS	Perfluorohexane sulfonate
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	*Perfluorooctane sulfonate*

POLYMERS

PTFE	Polytetrafluoroethylene

QUANTITATIVE ASSESSMENTS / STATISTICS

AMSTAR	Assessment MeaSurement Tool for the Analysis of Systematic Reviews
ES	Effect Size
ICD	International Classification of Diseases
OR	Odds Ratio
RR	Risk Ratio

HEALTH OUTCOMES

ADHD	*Attention Deficit Hyperactive Disorder*
BMI	Body Mass Index
HDL	High Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IQ	Intelligence Quotient
LDL	Low Density Lipoprotein
NHL	Non-Hodgkin's Lymphoma
PCOS	Polycystic Ovary Syndrome
T2DM	Type 2 Diabetes Mellitus
TC	Total cholesterol
TG	Triglycerides
Yu-Cheng	PCB poisoning incident in Taiwan
Yu-Sho	PCB poisoning incident in Japan

APPENDICES

APPENDIX 1 – BACKGROUND INFORMATION ON INCLUDED PLASTIC-ASSOCIATED CHEMICALS

The following describes the included plastic-associated chemicals, their production volumes, when they were discovered or first made, their properties, applications and occurrence in the environment, and therefore the sources for human exposure, as well as how the chemicals are measured in humans.

Bisphenol A (BPA) is synthesised by condensation of phenol with acetone in the presence of a catalyst. It was first synthesised in 1891 (Eladak et al., 2015). Commercial BPA production began in the United States in 1957 and then in Europe a year later (Corrales et al., 2015). In 2021, the estimated production volume was 6 Mt (million tonnes) with a compound annual growth rate of 6%, with the Asia-Pacific regions dominating (Mordor Intelligence, 2022).

BPA is a monomer that is mainly used to make polycarbonate and epoxy resins, which can be used in food contact applications (Geens et al., 2011). Polycarbonate is a durable type of thermoplastic polymer, which is used to make e.g. water bottles, baby bottles, food storage containers, tableware, and microwave ovenware (Geens et al., 2011). Epoxy resins are used to coat metal food and beverage containers for corrosion protection (Geens et al., 2011). However, use of polycarbonates and epoxy resins is predominantly in non-food contact applications such as construction materials, electronics, safety equipment, and medical devices (Geens et al., 2011).

In addition to polycarbonate and epoxy resins, BPA is used to make many other types of thermoplastic with specific properties and therefore applications (Geens et al., 2011). These include polysulfone (highly transparent, heat resistant, sterilisable: applications in medical health care, hot water fittings); polyetherimide (high temperature resistance and mechanical stiffness: applications in medical, electronic, automotive, aircraft). The monomer BPA can also be used as an additive, for example as a phenolic developer in thermal paper, and as an antioxidant in soft PVC, hydraulic brake fluid and tyre production (Geens et al., 2011).

Residual monomers of BPA remain in the final products after incomplete polymerisation and can leach out. This has been shown in for example dental products (Hampe et al., 2022), plastic containers (Sajiki and Yonekubo, 2003), construction materials and automotive supplies (Lamprea et al., 2018), as well as epoxy-resin pavement materials (Sakamoto et al., 2007). Release via chemical degradation of the polymerized BPA less common, as extended time at elevated temperatures are required for hydrolysis (Geens et al., 2012). When used as an additive, BPA is generally not covalently bonded with the polymer matrix, allowing it to readily leach out (Geens et al., 2011).

BPA is moderately water soluble and has low volatility. Rapid photooxidation in the environment explains a low half-life of 0.2 days (Corrales et al., 2015) and it is considered to be moderately bioaccumulative (Staples et al., 1998). Despite its low half-life, BPA has been detected extensively in the environment with specific sources being the health care sector, meat and dairy processing plants as well as paint and pharmaceutical manufacturers (Česen et al., 2018) resulting in a wide range of exposure routes. Globally, BPA is detected in surface waters, effluents, biosolids, sediments, soil and air (Corrales et al., 2015).

In humans, BPA does not undergo significant Phase I biotransformation, a metabolic process that increases polarity and therefore solubility amongst other properties (Koch et al., 2012). Rather, it undergoes Phase II biotransformation with glucuronides and is excreted in urine as a BPA-glucuronide conjugate which has a half-life of 6h. Urinary BPA-glucuronide is widely used to quantify human exposure to BPA (Koch et al., 2012) and has the advantage of confirming internal exposure (i.e. it has been metabolised). Measurement of unconjugated BPA can provide a measure of exposure to the toxicologically active compound provided external contamination is strictly controlled.

Phthalates represent a major class of plasticiser used in the production of plastic. They are synthesized through the esterification of ortho-phthalic anhydrite (1,2-benzenedicarboxylic acid) with various alcohols, producing (diester) phthalates. Depending on which alcohols are used, different phthalates are synthesized, each with different chemical properties (Katsikantami et al., 2016). Phthalates were first produced in the 1920s, with large-scale commercial production starting in the 1930s when PVC was developed using phthalates as a plasticiser to soften an otherwise brittle plastic (Graham, 1973; Holland, 2018). The production volume of phthalates was around 5.5 Mt in 2018 (Holland, 2018).

Phthalates are typically classified into two groups based on their molecular weight (Zhang et al., 2021). Low molecular weight (LMW) phthalates, such as diethyl phthalate (DEP), butyl benzyl phthalate (BBP) diisobutyl phthalate (DiBP), are generally used in finishing coatings such as varnishes, sealants and welds. as solvents in cosmetics, and personal care products, in medical plastics such as tubing and blood storage bags as well as in candles, adhesives and paint. High molecular weight (HMW) phthalates such as diethyl hexyl phthalate (DEHP) tend to be used more in heavy-duty PVC products such as flooring, automotive parts, electronics, and electric cable jackets, but are also found in consumer general purpose PVC products (Zhang et al., 2021). Phthalates are not covalently bound to the polymer and readily leach and migrate out of the final product (Katsikantami et al., 2016; Rahman and Brazel, 2004; Zhang et al., 2021). This property, combined with their widespread use, results in phthalates being ubiquitous environmental contaminants (Zarean et al., 2019).

Human exposure to phthalates can occur via ingestion, inhalation or contact via the skin (Cai et al., 2015; Dorman et al., 2018; Zarean et al., 2019). While phthalates can be measured in human biospecimens (e.g. blood, urine, seminal and amniotic fluid, and breast milk) as the unaltered diester "parent" compound used in the plastic (e.g. diethylhexyl phthalate (DEHP)), these are often rapidly metabolised into monoester metabolites, which can serve as biomarker for short term exposure burden (Zhang et al., 2021). It is possible that more than one metabolite of a parent phthalate is measured reflecting different stages or pathways of metabolism, e.g. DEHP is metabolised to a range of monoester metabolites in the human body such as mono(2-ethylhexyl) phthalate (MEHP), the further oxidized mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and others (Appendix 10, Table A10.1).

Flame retardants - Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). As "flame retardant" suggests, these compounds added to plastics, which are otherwise flammable, to inhibit or delay combustion.

PCBs were first described in 1881 and were developed for industrial use in the 1930 as non-flammable oils in electrical transformers and paint (Cairns and Siegmund, 1981). The cumulative production of PCBs was approximately 1.3 Mt (Breivik et al., 2002), before being listed in the Stockholm Convention (United Nations Environment Programme (UNEP), 2019). As one of the 12 original persistent organic pollutants (POPs) to be listed, PCBs production was prohibited (Porta and Zumeta, 2002).

PCBs are produced through the chlorination of biphenyl parent moieties, resulting in a unique chemically and thermally stable product (Cairns and Siegmund, 1981). There are 209 different combinations of level of chlorination and location of chlorine atom on the PCB molecule, which are known as congeners. By mixing congeners with different properties, the industrial product with the exact desired thermal and chemical characteristics is achieved (Cairns and Siegmund, 1981).

Uncontrolled use of PCBs resulted in widespread environmental contamination (Cairns and Siegmund, 1981). Industrial accidents in both Japan ("Yu-sho", 1968) and Taiwan ("Yu-cheng", 1979), whereby rice bran oil was contaminated with PCBs that leaked from heat exchangers during processing, lead to realisation that these chemicals severely impacted human health (Ikeda, 1996). Despite tight regulation, PCBs are still unintentionally released by industries such as cement, steel, coking and e-waste (Cui et al., 2013). PCBs have a long half-life, potentially persisting for over 100 years, spreading and bioaccumulating in the environment

(United Nations Environment Programme (UNEP), 2017). Despite not being in production anymore, more than 80% of produced PCBs still need to be eliminated (United Nations Environment Programme (UNEP), 2017).

PCBs are measured in blood, breast milk, or fat tissue in humans. Due to their lipophilic nature and persistence, PCBs accumulate in fat tissue in the body. The different properties of PCB congeners are also reflected in how they affect the human body. PCBs can be classified into classes I, II and III according to biological properties related to the human endocrine and metabolic systems (Moysich et al., 1999; Wolff et al., 1997). Furthermore, 12 PCB congeners have chemical and toxicological properties similar to dioxins and furans (highly toxic chemical compounds known to negatively affect hormones, reproduction, development and the immune system in humans) and are therefore referred to as dioxin-like PCBs (Boffetta et al., 2018; Catalani et al., 2019).

PBDEs have been used since the 1960s (Siddiqi et al., 2003) and are characterised by a thermally labile carbon-bromine bond which, upon heating, releases bromine radicals that intercept carbon radicals thereby reducing heat, flames and the release of carbon monoxide (Schmitt et al., 2021).There are 209 possible synthetic PBDE congeners classified into 10 congener groups from mono- to deca-BDE, and are commercially available in three types of mixtures termed penta-, octa-, and deca-brominated diphenyl ethers (Schmitt et al., 2021). PBDEs are used as flame retardants in a wide range of consumer products including electrical equipment, construction materials, coatings, textiles and polyurethane foam in upholstered furniture both household and transport (Siddiqi et al., 2003). Annual production is estimated at 67,000 metric tons (Siddiqi et al., 2003). Although PBDEs are tightly regulated in the European Union they are less so in the United States (Siddiqi et al., 2003).

Both PCBs and PBDEs have similar structures and are known to be toxic. They diffuse out of polymer matrices and are widely dispersed in the environment including in sediments, soils, and biosolids particularly as a result of uncontrolled disposal in landfills. PCBs may be less prone to environmental degradation because carbon-chlorine bonds are stronger than carbon-bromine (Schmitt et al., 2021; Siddiqi et al., 2003). In humans, PCBs and PBDEs are measured as congeners. The half-lives of PCBs are long, ranging from 10 – 15 years whereas half-lives of PBDEs are up to 3 months depending on the congener mixture (Ritter et al., 2011; Thuresson et al., 2006).

PBDEs are measured in blood, breast milk, or fat tissue, and also have bioaccumulative properties similar to PCBs. Due to the weaker bromine-carbon versus chlorine-carbon bond, PBDEs have a shorter half-life than PCBs (Siddiqi et al., 2003).

Per- and polyfluoroalkyl substances (PFAS) describe a large class thousands of industrial chemicals that are aliphatic (straight carbon chains as opposed to aromatic carbon rings) substances (Kwiatkowski et al., 2020; OECD, 2018). Perfluoroalkyl substances are ones in which all of the hydrogen atoms attached to carbon atoms in the nonfluorinated substances from which they have been derived are replaced by fluorine atoms; polyfluoroalkyl substances are those in which at least one, but not all, C atoms have been replaced by fluorine atoms (for full explanation, see (Buck et al., 2011)). Major subclasses are perfluoroalkyl acids and perfluoroalkylether acids and their precursors, fluoropolymers and perfluoropolyethers, the most well-known of which are perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) (Kwiatkowski et al., 2020). The large number of PFAS coupled with the transformation of various precursors into the same end-products, multiple applications and lack of regulation has resulted in very little available data on historical or ongoing production volumes (Glüge et al., 2022; Ng et al., 2021).

PFAS were discovered by accident in 1938 during work on fluorocarbon refrigerants at Dupont. Recognition of their extremely low friction properties resulted in an extremely wide range of applications (EPA, 2021a). These include war heads, liquid fuel tanks and the nuclear bomb during World War II and the Apollo space program (Renfrew and Pearson, 2021). PFAS's non-stick properties also enabled multiple water-proofing, grease-proofing and stain-proofing applications in commercial and consumer goods in such carpets, glass, paper, clothing and other textiles, paper, plastic articles, cookware, food packaging, electronics, and personal

care products (Kwiatkowski et al., 2020). Perfluorinated plastics such as polytetrafluoroethylene (PTFE; also known as Teflonä in some applications) was also used in non-stick cookware and waterproof fabrics (EPA, 2021b; Forns et al., 2020). PFAS are also highly thermally stable and have been used in firefighting foams at military installations, airports and fire stations (EPA, 2021a; Renfrew and Pearson, 2021). PFAS may also form from surface fluorination of plastic products, a chemical process used to make plastic products such as packaging more resilient for containers of chemicals such as cleaners, solvents, oils, and pesticides. This can then lead to release of those PFAS chemicals into the product (Rand and Mabury, 2011).

PFAS are also chemically stable due to the strength of the carbon-fluorine bonds which do not break down, or only very slowly under natural conditions, resulting in them being described as “forever chemicals” (Kwiatkowski et al., 2020). Their widespread use, mobility and persistence in the environment has resulted in global contamination of water, air, sediment, soil, biosolids and plants and accumulation in landfill (Kurwadkar et al., 2022; Lang et al., 2017). Although PFAS have been in use for over 60 years, their impacts on environmental and human health have only begun to been recognised in the last 10 or so years (Grandjean, 2018). The half-life of PFAS in humans ranges from 4-8 years and, because of their chemical stability, they are measured as the original compound and not as a metabolite (Guo et al., 2022).

APPENDIX 2 – SEARCH STRATEGIES

Epistemonikos search (26 August 2020)

Plastics and plastic polymers	Plastic*” OR “ microplastic*” OR “polyethylene*” OR “polypropylene*” OR “polyethylene terephthalate*” OR “polystyrene*” OR “polyvinyl chloride*” OR “polycarbonate*” OR “polylactide*” OR “teflon”
Plastic-related chemicals	
Bisphenols	bisphen* OR diphen* OR BPA OR 4,4'-isopropylidenediphenol OR 2,2-Bis(4-hydroxyphenyl)propane OR Diphenylolpropane OR 4,4'-(propane-2,2-diyl)diphenol
Plasticisers	“plasticiser*" OR "plasticizer*" OR "phthalate*" OR "phthalic acid" OR "orthophthal*" OR "ortho-phthal*" OR "benzene-1,2-dicarboxy" OR "benzenedicarboxy*" OR "DEHP" OR "terephthalate*" OR "adipate*" OR "sebacate*" OR "trimellitate*" OR "tricresyl*" OR "cresyldiphenyl*" OR "cyclohexanoate*" OR "dibenzoate*" OR "Acetyl tributyl citrate"
Flame retardants & PFAS	“flame retardant*" OR "fire retardant*" OR "fire proof*" OR "fireproof*" OR "polycholorinated biphenyl*" OR "PCB" OR "PCBs" OR "polycholorinated*" OR "tetradecachloro*" OR "polybrominated biphenyl*" OR "Polybrominated Diphenyl Ether*" OR "PBDE" OR "PBDEs" OR "polybrom*" OR "decabromo*" OR "hexabromocyclododecan*" OR "HBCD" OR "tetrabromobisphenol*" OR "TBBP-A" OR "TBBPA" OR "TBBP" OR "tetrabrom*" OR "organophosphate ester*" OR "triphenyl phosphate*" OR "Triphenylphosphate" OR "triphenyl ester" OR "tricresyl*" OR "trixylyl*" OR "trixylenyl*" OR "tris(2-chloroethyl)phosphate" OR "TCEP" OR "tris(chloropropyl)phosphate" OR "TCPP" OR "tris(1,3-dichloro-2-propyl)phosphate" OR "TDCPP" OR "resorcinol bis*" OR "RDP" OR "bisphenol A diphenyl phosphate" OR "BADP" OR "melamine polyphosphate*" OR "diphenylcresylphosphate*" OR "Tetrachlorophthal*" OR "fluoropolymer*" OR "Polyfluor*" OR "Perfluor*" OR "PFOA" OR "PFOS" OR "PFAS" OR "hexafluoropropylene" OR "GENX" OR "polytetrafluoroethylene" OR "PTFE"
Endocrine disrupting chemicals	"endocrine-disrupting" OR "endocrine disrupting" OR "environmental endocrine disrupting" OR "endocrine disruptor" OR "endocrine-disruptor”
Limits	NOT surgery Systematic reviews only

PubMed search (30 September 2020)

Plastics and plastic polymers	"plastics"[mh:noexp] OR plastic*[tiab] OR "microplastics"[mh] OR microplastic*[tiab] OR "polyethylenes"[mh] OR polyethylene*[tiab] OR "polypropylenes"[mh] OR polypropylene*[tiab] OR "polystyrenes"[mh] OR polystyrene*[tiab] OR "polyvinyl chloride"[mh] OR polyvinyl chloride*[tiab] OR polycarbonate*[tiab] OR teflon[tiab] OR nylon[tiab] OR "plasticizers"[mh] OR "flame retardants"[mh] OR "endocrine disruptors"[mh] OR endocrine disrupt*[tiab]
Plastic-related chemicals	
Bisphenols	bisphen*[tiab] OR diphen*[tiab] OR BPA[tiab] OR 4,4'-isopropylidenediphenol[tiab] OR 2,2-Bis(4-hydroxyphenyl)propane[tiab] OR Diphenylolpropane[tiab] OR 4,4'-(propane-2,2-diyl)diphenol[tiab]
Plasticisers	plasticiser*[tiab] OR plasticizer*[tiab] OR phthalate*[tiab] OR phthalic acid[tiab] OR orthophthal*[tiab] OR ortho-phthal*[tiab] OR benzene-1,2-dicarboxy[tiab] OR benzenedicarboxy*[tiab] OR DEHP[tiab] OR terephthalate*[tiab] OR adipate*[tiab] OR sebacate*[tiab] OR trimellitate*[tiab] OR tricresyl*[tiab] OR cresyldiphenyl*[tiab] OR cyclohexanoate*[tiab] OR dibenzoate*[tiab] OR Acetyl tributyl citrate[tiab]
Flame retardants & PFAS	flame retardant*[tiab] OR fire retardant*[tiab] OR fireproof[tiab] OR polycholorinated biphenyl*[tiab] OR PCBs[tiab] OR polycholorinated biphenyl*[tiab] OR tetradecachloro*[tiab] OR "polybrominated biphenyl"[tiab] OR polybrominated biphenyl*[tiab] OR Polybrominated Diphenyl Ether*[tiab] OR PBDEs[tiab] OR polybrom*[tiab] OR decabromo*[tiab] OR hexabromocyclododecan*[tiab] OR "HBCD"[tiab] OR tetrabromobisphenol*[tiab] OR TBBPA[tiab] OR TBBP[tiab] OR tetrabrom*[tiab] OR organophosphate ester*[tiab] OR triphenyl phosphate*[tiab] OR Triphenylphosphate*[tiab] OR triphenyl ester*[tiab] OR "tricresyl"[tiab] OR trixylyl*[tiab] OR trixylenyl*[tiab] OR tris(2-chloroethyl)phosphate[tiab] OR TCEP[tiab] OR tris(chloropropyl)phosphate[tiab] OR TCPP[tiab] OR tris(1,3-dichloro-2-propyl)phosphate*[tiab] OR TDCPP[tiab] OR resorcinol bis*[tiab] OR RDP[tiab] OR bisphenol A diphenyl phosphate[tiab] OR BADP[tiab] OR melamine polyphosphate*[tiab] OR diphenylcresylphosphate*[tiab] OR Tetrachlorophthal*[tiab] OR fluoropolymer*[tiab] OR Polyfluor*[tiab] OR Perfluor*[tiab] OR PFOA[tiab] OR PFOS[tiab] OR PFS[tiab] OR hexafluoropropylene*[tiab] OR GENX[tiab] OR polytetrafluoroethylene*[tiab] OR PTFE[tiab]
Systematic review/ meta-analysis	AND (Systematic review [sb] OR meta-analysis)
Limits	NOT surgery

APPENDIX 3 – AMSTAR: A MEASUREMENT TOOL TO ASSESS THE METHODOLOGICAL QUALITY OF SYSTEMATIC REVIEWS

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

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2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

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3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., CENTRAL, EMBASE and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers, or experts in the particular field of study, and by reviewing the references in the studies found.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane Register/CENTRAL counts as 2 sources; a grey literature search counts as supplementary).

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4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings and trial

registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

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5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

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6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases should be reported.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Acceptable if not in table format as long as they are described as above.

---

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

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8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

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9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

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10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

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11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

Shea *et al. BMC Medical Research Methodology* 2007 **7**:10 doi:10.1186/1471-2288-7-10

APPENDIX 4 – DATASET REFERENCES

The following list of references pertains to the included systematic reviews cited in Figures 2.1 - 2.9.

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25. Li MC, Chen PC, Tsai PC, Furue M, Onozuka D, Hagihara A, Uchi H, Yoshimura T, Guo YL 2015, 'Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a meta-analysis of two highly exposed cohorts', *International Journal of Cancer,* vol. 137, no. 6, pp. 1427-32.

26. Liu P, Yang F, Wang Y, Yuan Z 2018. 'Perfluorooctanoic acid (PFOA) exposure in early life increases risk of childhood adiposity: a meta-analysis of prospective cohort studies, *International Journal of Environmental Research and Public Health,* vol. 15, no. 10, pp. 2070.

27. Luo Y, Deji Z, Huang Z 2020, 'Exposure to perfluoroalkyl substances and allergic outcomes in children: a systematic review and meta-analysis', *Environmental Research,* vol. 191, pp. 110145.

28. Negri E, Metruccio F, Guercio V, Tosti L, Benfenati E, Bonzi R, La Vecchia C, Moretto A 2017, 'Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data', *Critical Reviews in Toxicology,* vol. 47, no. 6, pp. 482-508.

29. Nelson W, Liu DY, Yang Y, Zhong ZH, Wang YX, Ding YB 2020, 'In utero exposure to persistent and nonpersistent endocrine-disrupting chemicals and anogenital distance. a systematic review of epidemiological studies', *Biology of Reproduction,* vol. 102, no. 2, pp. 276-91.

30. Nieminen P, Lehtiniemi H, Huusko A, Vähäkangas K, Rautio A 2013, 'Polychlorinated biphenyls (PCBs) in relation to secondary sex ratio--a systematic review of published studies', *Chemosphere,* vol. 91, no. 2, pp. 131-8.

31. Park SH, Lim JE, Park H, Jee SH 2016, 'Body burden of persistent organic pollutants on hypertension: a meta-analysis', *Environmental Science and Pollution Research International,* vol. 23, no. 14, pp. 14284-93.

32. Radke EG, Braun JM, Nachman RM, Cooper GS 2020, 'Phthalate exposure and neurodevelopment: a systematic review and meta-analysis of human epidemiological evidence', *Environment International,* vol. 137, pp. 105408.

33. Rancière F, Lyons JG, Loh VH, Botton J, Galloway T, Wang T, Shaw JE, Magliano DJ 2015, 'Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence', *Environmental Health,* Vol. 14, no. 46.

34. Ribeiro C, Mendes V, Peleteiro B, Delgado I, Araújo J, Aggerbeck M, Annesi-Maesano I, Sarigiannis, D, Ramos E 2019, 'Association between the exposure to phthalates and adiposity: a meta-analysis in children and adults', *Environmental Research,* vol. 179, no. Pt A, pp. 108780.

35. Ribeiro CM, Beserra BTS, Silva NG, Lima CL, Rocha PRS, Coelho MS, Neves FAR, Amato AA 2020, 'Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis', *BMJ Open,* vol. 10, pp. e033509.

36. Roy D, Morgan M, Yoo C, Deoraj A, Roy S, Yadav VK, Garoub M, Assaggaf H, Doke M 2015, 'Integrated bioinformatics, environmental epidemiologic and genomic approaches to identify environmental and molecular links between endometriosis and breast cancer', *International Journal of Molecular Sciences,* vol. 16, no. 10, pp. 25285-322.

37. Shoshtari-Yeganeh B, Zarean M, Mansourian M, Riahi R, Poursafa P, Teiri H, Rafiei N, Dehdashti B, Kelishadi R 2019, 'Systematic review and meta-analysis on the association between phthalates exposure and insulin resistance', *Environmental Science and Pollution Research International,* vol. 26, no. 10, pp. 9435-42.

38. Song Y, Chou EL, Baecker A, You NY, Song Y, Sun Q, Liu S 2016, 'Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: a systematic review and meta-analysis', *Journal of Diabetes,* vol. 8, no. 4, pp. 516-32.

39. Steenland K, Barry V, Savitz D 2018, 'Serum perfluorooctanoic acid (PFOA) and birthweight: an updated meta-analysis with bias analysis', *Epidemiology (Cambridge, Mass.),* vol. 29, no. 6, pp. 765-76.

40. Wen X, Xiong Y, Qu X, Jin L, Zhou C, Zhang M, Zhang Y 2019, 'The risk of endometriosis after exposure to endocrine-disrupting chemicals: a meta-analysis of 30 epidemiology studies. *Gynecological Endocrinology,* vol. 35, no. 8, pp. 1-6.

41. Wen Y, Liu SD, Lei X, Ling YS, Luo Y, Liu Q 2015, 'Association of PAEs with precocious puberty in children: a systematic review and meta-analysis', *International Journal of Environmental Research and Public Health,* vol. 12, no. 12, pp. 15254-68.

42. Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P, Sun Q 2013, 'Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis', *Environmental Health Perspectives,* vol. 121, no. 2, pp. 153-61.

43. Wu W, Li M, Liu A, Wu C, Li D, Deng Q, Zhang B, Du J, Gao X, Hong Y 2020, 'Bisphenol A and the risk of obesity a systematic review with meta-analysis of the epidemiological evidence', *Dose-Response*, vol. 18, no. 2, pp. 1559325820916949.

44. Wu W, Wu C, Ji C, Diao F, Peng J, Luo D, Mu X, Ruan X 2020, 'Association between phthalate exposure and asthma risk: a meta-analysis of observational studies', *International Journal of Hygiene and Environmental Health,* vol. 228, pp. 113539.

45. Zani C, Ceretti E, Covolo L, Donato F 2017, 'Do polychlorinated biphenyls cause cancer? A systematic review and meta-analysis of epidemiological studies on risk of cutaneous melanoma and non-Hodgkin lymphoma', *Chemosphere,* vol. 183, pp. 97-106.

46. Zani C, Toninelli G, Filisetti B, Donato F 2013, 'Polychlorinated biphenyls and cancer: an epidemiological assessment', *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews,* vol. 31, no. 2, pp. 99-144.

47. Zhang H, Gao F, Ben Y, Su Y 2020, 'Association between phthalate exposure and risk of spontaneous pregnancy loss: A systematic review and meta-analysis', *Environmental Pollution*, vol. 267, pp. 115446.

48. Zhang J, Huang Y, Wang X, Lin K, Wu K 2015, 'Environmental polychlorinated biphenyl exposure and breast cancer risk: a meta-analysis of observational studies', *PloS One,* vol. 10,

no. 11, pp. e0142513.

49. Zhao X, Peng S, Xiang Y, Yang Y, Li J, Shan Z, Teng W 2017, 'Correlation between prenatal exposure to polybrominated diphenyl ethers (PBDEs) and infant birth outcomes: a meta-analysis and an experimental study', *International Journal of Environmental Research and Public Health,* vol. 14, no. 3, pp. 268.

50. Zhao X, Wang H, Li J, Shan Z, Teng W, Teng X 2015, 'The correlation between polybrominated diphenyl ethers (PBDEs) and thyroid hormones in the general population: a meta-analysis', *PloS One,* vol. 10, no. 5, pp. e0126989.

51. Zhong Q, Peng M, He J, Yang W, Huang F 2020, 'Association of prenatal exposure to phenols and parabens with birth size: a systematic review and meta-analysis', *The Science of the Total Environment,* vol. 703, pp. 134720.

52. Zou H, Lin Y, Yang L, Ou C, Geng F, Wang Y, Chen W, Niu Y, Liang R, Su Q, Sun Y 2019, 'Neonatal weight and prenatal exposure to polychlorinated biphenyls: a meta-analysis', *Asian Pacific Journal of Cancer Prevention,* vol. 20, no. 11, pp. 3251-8.

APPENDIX 5 – EXCLUDED STUDIES

Table A5.1 Studies excluded after full text assessment against eligibility criteria

Citation	Reason for exclusion
AMSTER, E. 2019. Public health impact of coal-fired power plants: a critical systematic review of the epidemiological literature. *International Journal of Environmental Health Research*, 31(5), 1-23.	Not plastic associated chemicals
AZARPAZHOOH, A. & MAIN, P.A. 2008. Is there a risk of harm or toxicity in the placement of pit and fissure sealant materials? A systematic review. Journal of the Canadian Dental Association, 74(2), 179-83.	No meta-analysis
BACH, C.C., BECH, B.H., BRIX, N., NOHR, E.A., BONDE, J.P. & HENRIKSEN, T.B. 2015. Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: A systematic review. *Critical Reviews in Toxicology*, 45(1), 1-15.	No meta-analysis
BACH, C.C., VESTED, A., JØRGENSEN, K.T., BONDE, J.P., HENRIKSEN, T.B. & TOFT, G. 2016. Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review. *Critical Reviews in Toxicology*, 46(9), 1-21.	No meta-analysis
BALLESTEROS, V., COSTA, O., IÑIGUEZ, C., FLETCHER, T., BALLESTER, F. & LOPEZ-ESPINOSA, M.J. 2017. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. *Environment International*, 99, 15-28.	No meta-analysis
BARROS, N., TULVE, N.S., HEGGEM, D.T. & BAILEY, K. 2018. Review of built and natural environment stressors impacting American-Indian/Alaska-Native children. *Reviews on Environmental Health*, 33(4), 349-81.	No meta-analysis
BÉRANGER, R., LE CORNET, C., SCHÜZ, J. & FERVERS, B. 2013. Occupational and environmental exposures associated with testicular germ cell tumours: Systematic review of prenatal and life-long exposures. PloS One, 8(10), e77130.	No meta-analysis
BONDE, J.P., FLACHS, E.M., RIMBORG, S., GLAZER, C.H., GIWERCMAN, A., RAMLAU-HANSEN, C.H., HOUGAARD, K.S., HØYER, B.B., HÆRVIG, K.K., PETERSEN, S.B., RYLANDER, L., SPECHT, I.O., TOFT, G. & BRÄUNER, E.V. 2016. The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis. *Human Reproduction Update*, 23(1), 104-125.	EDCs with pesticides
BORRELLI, I. 2007. [Endocrine disruptors: literature review on toxicology and application field in occupational medicine]. *Giornale Italiano di Medicina del Lavoro ed Ergonomia*, 29(3 Suppl), 526-8	Italian
BOWMAN, J.D. & CHOUDHURY, M. 2016. Phthalates in neonatal health: friend or foe? *Journal of Developmental Origins of Health and Disease*, 7(6), 652-64.	No meta-analysis
CAPOROSSI, L. & PAPALEO, B. 2015. Exposure to bisphenol a and gender differences: from rodents to humans evidences and hypothesis about the health effects. *Journal of Xenobiotics*, 5(1), 5264.	No meta-analysis
CARRÉ, J., GATIMEL, N., MOREAU, J., PARINAUD, J. & LÉANDRI, R. 2017. Does air pollution play a role in infertility?: A systematic review. *Environmental Health*, 16(1), 82.	No meta-analysis

CESARIO, S.K. & HUGHES, L.A. 2007. Precocious puberty: A comprehensive review of literature. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, 36(3), 263-74.	No meta-analysis
CHEN ZEE, E., CORNET, P., LAZIMI, G., RONDET, C., LOCHARD, M., MAGNIER, A.M. & IBANEZ, G. 2013. Impact of endocrine disrupting chemicals on birth outcomes. *Gynécologie, Obstétrique & Fertilité*, 41(10), 601-10.	French
COCUZZA, M. & ESTEVES, S.C. 2014. Shedding light on the controversy surrounding the temporal decline in human sperm counts: a systematic review. *TheScientificWorldJournal*, 2014, 365691.	No meta-analysis
DAI, Y., HUO, X., CHENG, Z., FAAS, M.M. & XU, X. 2020. Early-life exposure to widespread environmental toxicants and maternal-fetal health risk: A focus on metabolomic biomarkers. *The Science of the Total Environment*, 739, 139626	No meta-analysis
DE COCK, M., MAAS, Y G. & VAN DE BOR, M. 2012. Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? *Review. Acta Paediatrica*, 101(8), 811-8.	No meta-analysis
DE COCK, M. & VAN DE BOR, M. 2014. Obesogenic effects of endocrine disruptors, what do we know from animal and human studies? *Environment International*, 70, 15-24.	No meta-analysis
DZIEWIRSKA, E., HANKE, W. & JUREWICZ, J. 2018. Environmental non-persistent endocrine-disrupting chemicals exposure and reproductive hormones levels in adult men. *International Journal of Occupational Medicine and Environmental Health*, 31(5), 551-73.	No meta-analysis
EJAREDAR, M., LEE, Y., ROBERTS, D.J., SAUVE, R. & DEWEY, D. 2017. Bisphenol A exposure and children's behavior: A systematic review. *Journal of Exposure Science & Environmental Epidemiology*, 27**,** 175-183.	No meta-analysis
EJAREDAR, M., NYANZA, E.C., TEN EYCKE, K. & DEWEY, D. 2015. Phthalate exposure and childrens neurodevelopment: A systematic review. *Environmental Research*, 142, 51-60.	No meta-analysis
FERNÁNDEZ, M.F., OLMOS, B. & OLEA, N. 2007. [Exposure to endocrine disruptors and male urogenital tract malformations [cryptorchidism and hypospadias]]. *Gaceta Sanitaria*, 21(6), 500-14.	Spanish
GASCON, M., MORALES, E., SUNYER, J. & VRIJHEID, M. 2013. Effects of persistent organic pollutants on the developing respiratory and immune systems: a systematic review. *Environment International*, 52, 51-65.	No meta-analysis
GÓMEZ-MERCADO, C.A., MEJÍA-SANDOVAL, G., SEGURA-CARDONA, Á.M., ARANGO-ÁLZATE, C.M., HERNÁNDEZ-GONZÁLEZ, S.I., PATIÑO-GARCÍA, D.F. & BARRAZA-VILLARREAL, A. 2018. Pregnant women's exposure to bisphenol A (BPA) and its relation to their children's obesity: A systematic Review. *Revista Facultad Nacional de Salud Pública,* 36, 66-74.	No meta-analysis
GOODMAN, M., LAKIND, J.S. & MATTISON, D.R. 2014. Do phthalates act as obesogens in humans? A systematic review of the epidemiological literature. *Critical Reviews in Toxicology*, 44(2), 151-75.	No meta-analysis

GUTIÉRREZ-TORRES, D.S., BARRAZA-VILLARREAL, A., HERNANDEZ-CADENA, L., ESCAMILLA-NUÑEZ, C. & ROMIEU, I. 2018. Prenatal exposure to endocrine disruptors and cardiometabolic risk in preschoolers: A systematic review based on cohort studies. *Annals of Global Health*, 84(2), 239-49.	No meta-analysis
HAREL, Z., HAREL, S., SHAH, P.S., WALD, R., PERL, J. & BELL, C.M. 2013. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: A systematic review. *The American Journal of Medicine*, 126(3), 264.e9-264.e24	No meta-analysis
HIPWELL, A.E., KAHN, L.G., FACTOR-LITVAK, P., PORUCZNIK, C.A., SIEGEL, E.L., FICHOROVA, R.N., HAMMAN, R.F., KLEIN-FEDYSHIN, M., HARLEY, K.G. & PROGRAM COLLABORATORS FOR ENVIRONMENTAL INFLUENCES ON CHILD HEALTH, O. 2019. Exposure to non-persistent chemicals in consumer products and fecundability: A systematic review. *Human Reproduction Update*, 25(1), 51-71.	No meta-analysis
HØYER, B.B., LENTERS, V., GIWERCMAN, A., JÖNSSON, B.A.G., TOFT, G., HOUGAARD, K.S., BONDE, J.P.E. & SPECHT, I.O. 2018. Impact of Di-2-ethylhexyl phthalate metabolites on male reproductive function: a systematic review of human evidence. *Current Environmental Health Reports*, 5(1), 20-33.	No meta-analysis
JAACKS, L.M. & STAIMEZ, L.R. 2015. Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: A systematic review. *Environment International*, 76*,* 57-70.	No meta-analysis
JEDDI, M.Z., JANANI, L., MEMARI, A.H., AKHONDZADEH, S. & YUNESIAN, M. 2016. The role of phthalate esters in autism development: A systematic review. *Environmental Research*, 151, 493-504.	No meta-analysis
KALKBRENNER, A.E., SCHMIDT, R.J. & PENLESKY, A.C. 2014. Environmental chemical exposures and autism spectrum disorders: A review of the epidemiological evidence. *Current Problems in Pediatric and Adolescent Health Care*, 44(10), 277-318.	No meta-analysis
KALLIORA, C., MAMOULAKIS, C., VASILOPOULOS, E., STAMATIADES, G.A., KALAFATI, L., BAROUNI, R., KARAKOUSI, T., ABDOLLAHI, M. & TSATSAKIS, A. 2018. Association of pesticide exposure with human congenital abnormalities. *Toxicology and Applied Pharmacology*, 346, 58-75.	No meta-analysis
KAY, V.R., BLOOM, M.S. & FOSTER, W. G. 2014. Reproductive and developmental effects of phthalate diesters in males. *Critical Reviews in Toxicology*, 44(6), 1-32.	No meta-analysis
KAY, V.R., CHAMBERS, C. & FOSTER, W.G. 2013. Reproductive and developmental effects of phthalate diesters in females. *Critical Reviews in Toxicology*, 43(3), 200-19.	No meta-analysis
KERN, J.K., GEIER, D.A., HOMME, K.G., KING, P.G., BJØRKLUND, G., CHIRUMBOLO, S. & GEIER, M.R. 2017. Developmental neurotoxicants and the vulnerable male brain: a systematic review of suspected neurotoxicants that disproportionally affect males. *Acta Neurobiologiae Experimentalis*, 77(4), 269-96.	No meta-analysis
KILCOYNE, K.R. & MITCHELL, R.T. 2019. Effect of environmental and pharmaceutical exposures on fetal testis development and function: a systematic review of human experimental data. Human Reproduction Update, 25(4), 397-421.	No meta-analysis

KIM, Y.R., PACELLA, R.E., HARDEN, F.A., WHITE, N. & TOMS, L.L. 2019. A systematic review: Impact of endocrine disrupting chemicals exposure on fecundity as measured by time to pregnancy. *Environmental Research*, 171, 119-33.	No meta-analysis
KRAMER, S., HIKEL, S.M., ADAMS, K., HINDS, D. & MOON, K. 2012. Current status of the epidemiologic evidence linking polychlorinated biphenyls and non-hodgkin lymphoma, and the role of immune dysregulation. *Environmental Health Perspectives*, 120(8), 1067-75.	No meta-analysis
KUO, C.C., MOON, K., THAYER, K.A. & NAVAS-ACIEN, A. 2013. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. *Current Diabetes Reports,* 13(6), 831-49.	No meta-analysis
JAAKKOLA, J.J.K., KNIGHT, T.L., 2008. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environmental Health Perspectives,* 116(7), 845-53.	Indirect measure of exposure
LAKIND, J.S., GOODMAN, M. & MATTISON, D.R. 2014. Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: A systematic review of epidemiologic research. *Critical Reviews in Toxicology*, 44(2), 121-50.	No meta-analysis
LAM, J., KOUSTAS, E., SUTTON, P., JOHNSON, P.I., ATCHLEY, D.S., SEN, S., ROBINSON, K.A., AXELRAD, D.A. & WOODRUFF, T.J. 2014. The navigation guide—evidence-based medicine meets environmental health: Integration of animal and human evidence for PFOA effects on fetal growth. *Environmental Health Perspectives*, 122(10), 1040-51.	No meta-analysis
LINDBOHM, M. L. 1993. Effects of styrene on the reproductive health of women: A review. IARC Scientific Publications, 127, 163-9.	No meta-analysis
MALLOZZI, M., LEONE, C., MANURITA, F., BELLATI, F. & CASERTA, D. 2017. Endocrine disrupting chemicals and endometrial cancer: An overview of recent laboratory evidence and epidemiological studies. International Journal of Environmental Research and Public Health, 14(3), 334.	No meta-analysis
MARÍ-BAUSET, S., DONAT-VARGAS, C., LLÓPIS-GONZÁLEZ, A., MARÍ-SANCHIS, A., PERAITA-COSTA, I., LLOPIS-MORALES, J. & MORALES-SUÁREZ-VARELA, M. 2018. Endocrine disruptors and autism spectrum disorder in pregnancy: A review and evaluation of the quality of the epidemiological evidence. Children (Basel, Switzerland), 5(12), 157.	No meta-analysis
MÍNGUEZ-ALARCÓN, L., HAUSER, R. & GASKINS, A.J. 2016. Effects of bisphenol A on male and couple reproductive health: a review. *Fertility and Sterility*, 106(4), 864-70.	No meta-analysis
NEGRI, E., BOSETTI, C., FATTORE, E. & LA VECCHIA, C. 2003. Environmental exposure to polychlorinated biphenyls (PCBs) and breast cancer: A systematic review of the epidemiological evidence*. European Journal of Cancer Prevention*, 12(6), 509-16.	No meta-analysis
NORTH, M.L., TAKARO, T.K., DIAMOND, M.L. & ELLIS, A.K. 2014. Effects of phthalates on the development and expression of allergic disease and asthma. Annals of Allergy, Asthma & Immunology, 112(6), 496-502.	No meta-analysis

OPPENEER, S.J. & ROBIEN, K. 2015. Bisphenol A exposure and associations with obesity among adults: A critical review. Public Health Nutrition, 18(10), 1-17.	No meta-analysis
OVERGAARD, L.E., BONEFELD, C.M., FREDERIKSEN, H., MAIN, K.M. & THYSSEN, J.P. 2016. The association between phthalate exposure and atopic dermatitis with a discussion of phthalate induced secretion of interleukin-1β and thymic stromal lymphopoietin. *Expert Review of Clinical Immunology*, 12(6), 609-16.	No meta-analysis
PEINADO, F.M., ARTACHO-CORDÓN, F., BARRIOS-RODRÍGUEZ, R. & ARREBOLA, J.P. 2020. Influence of polychlorinated biphenyls and organochlorine pesticides on the inflammatory milieu. A systematic review of in vitro, in vivo and epidemiological studies. *Environmental Research*, 186, 109561.	No meta-analysis
PERETZ, J., VROOMAN, L., RICKE, W.A., HUNT, P.A., EHRLICH, S., HAUSER, R., PADMANABHAN, V., TAYLOR, H.S., SWAN, S.H., VANDEVOORT, C.A. & FLAWS, J.A. 2014. Bisphenol a and reproductive health: update of experimental and human evidence, 2007-2013. *Environmental Health Perspectives*, 122(8), 775-86.	No meta-analysis
PERGIALIOTIS, V., KOTROGIANNI, P., CHRISTOPOULOS-TIMOGIANNAKIS, E., KOUTAKI, D., DASKALAKIS, G. & PAPANTONIOU, N. 2018. Bisphenol A and adverse pregnancy outcomes: a systematic review of the literature. *The Journal of Maternal-Fetal & Neonatal Medicine*, 31(24), 1-15.	No meta-analysis
PETERSEN, K.U., LARSEN, J.R., DEEN, L., FLACHS, E.M., HÆRVIG, K.K., HULL, S.D., BONDE, J. P.E. & TØTTENBORG, S.S. 2020. Per- and polyfluoroalkyl substances and male reproductive health: a systematic review of the epidemiological evidence. *Journal of Toxicology and Environmental Health. Part B, Critical reviews*, 23(6), 276-91.	No meta-analysis
POLAŃSKA, K., JUREWICZ, J. & HANKE, W. 2013. Review of current evidence on the impact of pesticides, polychlorinated biphenyls and selected metals on attention deficit / hyperactivity disorder in children. *International Journal of Occupational Medicine and Environmental Health*, 26(1), 16-38.	No meta-analysis
RADKE, E.G., BRAUN, J.M., MEEKER, J.D. & COOPER, G.S. 2018. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. *Environment International*, 121(Pt 1), 764-93.	No meta-analysis
RADKE, E.G., GALIZIA, A., THAYER, K.A. & COOPER, G.S. 2019. Phthalate exposure and metabolic effects: a systematic review of the human epidemiological evidence. Environment international, 132**,** 104768.	No meta-analysis
RADKE, E.G., GLENN, B.S., BRAUN, J.M. & COOPER, G.S. 2019. Phthalate exposure and female reproductive and developmental outcomes: A systematic review of the human epidemiological evidence. *Environment International*, 130, 104580.	No meta-analysis
RANJIT, N., SIEFERT, K. & PADMANABHAN, V. 2010. Bisphenol-A and disparities in birth outcomes: a review and directions for future research. *Journal of Perinatology*, 30(1), 2-9.	No meta-analysis
RAPPAZZO, K.M., COFFMAN, E. & HINES, E.P. 2017. Exposure to perfluorinated alkyl substances and health outcomes in children: A systematic review of the epidemiologic literature. *International Journal of Environmental Research and Public Health*, 14(7), 691.	No meta-analysis

RIVOLLIER, F., KREBS, M.O. & KEBIR, O. 2019. Perinatal exposure to environmental endocrine disruptors in the emergence of neurodevelopmental psychiatric diseases: A systematic review. *International Journal of Environmental Research and Public Health*, 16(8), 1318.	No meta-analysis
ROCHESTER, J.R., BOLDEN, A.L. & KWIATKOWSKI, C.F. 2018. Prenatal exposure to bisphenol A and hyperactivity in children: A systematic review and meta-analysis. *Environment International*, 114, 343-56.	No meta-analysis
ROSSIGNOL, D. A., GENUIS, S. J. & FRYE, R. E. 2014. Environmental toxicants and autism spectrum disorders: a systematic review. Translational psychiatry, 4**,** e360.	No meta-analysis
ROTH, N. & WILKS, M.F. 2014. Neurodevelopmental and neurobehavioural effects of polybrominated and perfluorinated chemicals: A systematic review of the epidemiological literature using a quality assessment scheme. *Toxicology Letters*, 230(2), 271-81.	No meta-analysis
RUIZ-HERNANDEZ, A., KUO, C.C., RENTERO-GARRIDO, P., TANG, W.Y., REDON, J., ORDOVAS, J.M., NAVAS-ACIEN, A. & TELLEZ-PLAZA, M. 2015. Environmental chemicals and DNA methylation in adults: A systematic review of the epidemiologic evidence. *Clinical Epigenetics,* 7(1), 55.	No meta-analysis
SAIKAT, S., KREIS, I., DAVIES, B., BRIDGMAN, S. & KAMANYIRE, R. 2013. The impact of PFOS on health in the general population: a review. *Environmental Science Processes & Impacts*, 15(2), 329-35.	No meta-analysis
SALAY, E. & GARABRANT, D. 2009. Polychlorinated biphenyls and thyroid hormones in adults: a systematic review appraisal of epidemiological studies. *Chemosphere*, 74(11), 1413-9.	No meta-analysis
SHARP, D. 2009. Environmental toxins, a potential risk factor for diabetes among Canadian Aboriginals. *International journal of circumpolar health*, 68(4), 316-26.	Not plastics
SOAVE, I., OCCHIALI, T., ASSORGI, C., MARCI, R. & CASERTA, D. 2020. Environmental toxin exposure in polycystic ovary syndrome women and possible ovarian neoplastic repercussion. *Current Medical Research & Opinion*, 36(4), 693-703.	No meta-analysis
SOAVE, I., OCCHIALI, T., ASSORGI, C., MARCI, R. & CASERTA, D. 2020. Environmental toxins exposure in PCOS women and possible ovarian neoplastic repercussion. *Current Medical Research and Opinion*, 36(4), 693-703.	No meta-analysis
SOWLAT, M.H., LOTFI, S., YUNESIAN, M., AHMADKHANIHA, R. & RASTKARI, N. 2016. The association between bisphenol A exposure and type-2 diabetes: A world systematic review. *Environmental Science and Pollution Research International*, 23(21), 21125-40.	No meta-analysis
STANIFER, J.W., STAPLETON, H.M., SOUMA, T., WITTMER, A., ZHAO, X. & BOULWARE, L.E. 2018. Perfluorinated chemicals as emerging environmental threats to kidney health: A scoping review. Clinical Journal of the American Society of Nephrology, 13, 1479-92.	No meta-analysis
STRAKOVSKY, R.S. & SCHANTZ, S.L. 2018. Impacts of bisphenol A (BPA) and phthalate exposures on epigenetic outcomes in the human placenta. *Environmental Epigenetics*, 4(3), dvy022.	No meta-analysis

SUGENG, E. J., DE COCK, M., SCHOONMADE, L.J. & VAN DE BOR, M. 2017. Toddler exposure to flame retardant chemicals: Magnitude, health concern and potential risk- or protective factors of exposure: Observational studies summarized in a systematic review. *Chemosphere*, 184, 820-31.	No meta-analysis
SUN, D., WANG, Q., CHEN, H., XU, F., ZHANG, Y., ZHANG, T., LIU, H. & YE, L. 2017. Changes of serum thyroid hormone levels in DEHP exposure population: A meta-analysis. *Journal of Jilin University Medicine Edition*, 43, 66-72.	Chinese
SWEENEY, M.R., O'LEARY, K.G., JENEY, Z., BRAUNLIN, M.C. & GIBB, H.J. 2019. Systematic review and quality ranking of studies of two phthalate metabolites and anogenital distance, bone health, inflammation, and oxidative stress. *Critical Reviews in Toxicology*, 49(4), 281-201.	No meta-analysis
TERRELL, M.L., HARTNETT, K.P. & MARCUS, M. 2011. Can environmental or occupational hazards alter the sex ratio at birth? A systematic review. *Emerging Health Threats Journal*, 4, 7109.	No meta-analysis
TOMZA-MARCINIAK, A., STEPKOWSKA, P., KUBA, J. & PILARCZYK, B. 2018. Effect of bisphenol A on reproductive processes: A review of in vitro, in vivo and epidemiological studies. *Journal of Applied Toxicology*, 38(1), 51-80.	No meta-analysis
TSAI, M.S., CHEN, M.H., LIN, C.C., NG, S., HSIEH, C.J., LIU, C.Y., HSIEH, W.S. & CHEN, P.C. 2017. Children's environmental health based on birth cohort studies of Asia. *The Science of the Total Environment,* 609, 396-409.	No meta-analysis
VABRE, P., GATIMEL, N., MOREAU, J., GAYRARD, V., PICARD-HAGEN, N., PARINAUD, J. & LEANDRI, R.D. 2017. Environmental pollutants, a possible etiology for premature ovarian insufficiency: a narrative review of animal and human data. *Environmental Health*, 16(1), 37.	No meta-analysis
VAN CAUWENBERGH, O., DI SERAFINO, A., TYTGAT, J. & SOUBRY, A. 2020. Transgenerational epigenetic effects from male exposure to endocrine-disrupting compounds: A systematic review on research in mammals. *Clinical Epigenetics*, 12(1), 65.	No meta-analysis
VERNER, M.A., LOCCISANO, A.E., MORKEN, N.H., YOON, M., WU, H., MCDOUGALL, R., MAISONET, M., MARCUS, M., KISHI, R., MIYASHITA, C., CHEN, M.H., HSIEH, W.S., ANDERSEN, M.E., CLEWELL, H.J. & LONGNECKER, M.P. 2015. Associations of perfluoroalkyl substances (PFAS) with lower birth weight: An evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK). *Environmental Health Perspectives*, 123(12), 1317-24.	Simulated population
XIE, M.Y., NI, H., ZHAO, D.S., WEN, L.Y., LI, K.S., YANG, H.H., WANG, S.S., ZHANG, H. & SU, H. 2016. Exposure to bisphenol A and the development of asthma: A systematic review of cohort studies. *Reproductive Toxicology (Elmsford, N.Y.)*, 65, 224-9.	No meta-analysis
XU, J., CHEN, H., XU, F., WANG, Q., ZHANG, Y., LIU, H., ZHANG, T. & YE, L. 2017. Association between phthalate ester exposure and population obesity: A Meta-analysis. *Journal of Jilin University Medicine Edition*, 43, 306-310	Chinese
YAGHJYAN, L., GHITA, G.L., DUMONT-DRISCOLL, M., YOST, R.A. & CHANG, S.H. 2016. Maternal exposure to di-2-ethylhexylphthalate and adverse delivery outcomes: a systematic review. *Reproductive Toxicology (Elmsford, N.Y.),* 65, 76-86.	No meta-analysis

YANG, L., SHANG, L., WANG, S., YANG, W., HUANG, L., QI, C., GURCAN, A., YANG, Z. & CHUNG, M.C. 2020. The association between prenatal exposure to polycyclic aromatic hydrocarbons and birth weight: A meta-analysis. PloS One, 15(8), e0236708.	Not plastics
ZAMKOWSKA, D., KARWACKA, A., JUREWICZ, J. & RADWAN, M. 2018. Environmental exposure to non-persistent endocrine disrupting chemicals and semen quality: An overview of the current epidemiological evidence. *International Journal of Occupational Medicine and Environmental Health,* 31(4), 377-414.	No meta-analysis
ZAREAN, M., KEIKHA, M., POURSAFA, P., KHALIGHINEJAD, P., AMIN, M. & KELISHADI, R. 2016. A systematic review on the adverse health effects of di-2-ethylhexyl phthalate. *Environmental Science and Pollution Research International*, 23(24), 24642-93.	No meta-analysis
ZAREAN, M., POURSAFA, P., AMIN, M. M. & KELISHADI, R. 2018. Association of Endocrine Disrupting Chemicals, Bisphenol A and Phthalates, with Childhood Obesity: A Systematic Review. Journal of Pediatrics Review, 6**,** 1-16.	No meta-analysis
ZEINOMAR, N., OSKAR, S., KEHM, R.D., SAHEBZEDA, S. & TERRY, M.B. 2020. Environmental exposures and breast cancer risk in the context of underlying susceptibility: A systematic review of the epidemiological literature. *Environmental Research*, 187, 109346.	No meta-analysis
ZHANG, Q., CHEN, X.Z., HUANG, X., WANG, M. & WU, J. 2019. The association between prenatal exposure to phthalates and cognition and neurobehavior of children-evidence from birth cohorts. *Neurotoxicology*, 73, 199-212.	No meta-analysis
ZHENG, L.Y., SANDERS, A.P., SALAND, J.M., WRIGHT, R.O. & ARORA, M. 2017. Environmental exposures and pediatric kidney function and disease: A systematic review. *Environmental Research*, 158, 625-48.	No meta-analysis
ZUCCARELLO, P., CONTI, G.O., CAVALLARO, F., COPAT, C., CRISTALDI, A., FIORE, M. & FERRANTE, M. 2018. Implication of dietary phthalates in breast cancer. A systematic review. *Food and Chemical Toxicology*, 118, 667-74.	No meta-analysis

Table A5.2 Studies excluded due to invalid data identified during appraisal and extraction stages

Citation	**Reason for exclusion**
BOFFETTA, P., CATALANI, S., TOMASI, C., PIRA, E. & APOSTOLI, P. 2018. Occupational exposure to polychlorinated biphenyls and risk of cutaneous melanoma: A meta-analysis. *European Journal of Cancer Prevention*, 27(1), 62-9.	Multiple use of the same data in the analyses
BLIATKA, D., NIGDELIS, M.P., CHATZIMELETIOU, K., MASTORAKOS, G., LYMPERI, S. & GOULIS, D G. 2020. The effects of postnatal exposure of endocrine disruptors on testicular function: a systematic review and a meta-analysis. *Hormones (Athens, Greece),* 19(2), 157-69.	Multiple use of the same data in the analyses
FREEMAN, M.D. & KOHLES, S.S. 2012. Plasma levels of polychlorinated biphenyls, non-Hodgkin lymphoma, and causation. *Journal of Environmental and Public Health,* 2012, 258981.	Multiple use of the same data in the analyses

FU, Z., ZHAO, F., CHEN, K., XU, J., LI, P., XIA, D. & WU, Y. 2017. Association between urinary phthalate metabolites and risk of breast cancer and uterine leiomyoma. *Reproductive Toxicology.* 74, 132-42.	Multiple use of the same data in the analyses
LIM, J. E., PARK, S. H., JEE, S. H. & PARK, H. 2015. Body concentrations of persistent organic pollutants and prostate cancer: a meta-analysis. *Environmental Science and Pollution Research International,* 22(15), 11275-84.	Multiple use of the same data in the analyses
NILSEN, F.M. & TULVE, N.S. 2020. A systematic review and meta-analysis examining the interrelationships between chemical and non-chemical stressors and inherent characteristics in children with ADHD. *Environmental research,* 180, 108884.	Multiple use of the same data in the analyses
TANG, M., CHEN, K., YANG, F. & LIU, W. 2014. Exposure to organochlorine pollutants and type 2 diabetes: a systematic review and meta-analysis. *PloS One,* 9(10), e85556.	Multiple use of the same data in the analyses
WANG, C., YANG, L., WANG, S., ZHANG, Z., YU, Y., WANG, M., CROMIE, M., GAO, W. & WANG, S. L. 2016. The classic EDCs, phthalate esters and organochlorines, in relation to abnormal sperm quality: a systematic review with meta-analysis. *Scientific reports,* 6**,** 19982.	Multiple use of the same data in the analyses
ZAREAN, M., KEIKHA, M., FEIZI, A., KAZEMITABAEE, M. & KELISHADI, R. 2019. The role of exposure to phthalates in variations of anogenital distance: A systematic review and meta-analysis. *Environmental Pollution (Barking, Essex: 1987)*, 247, 172-9.	Multiple use of the same data in the analyses (both exposure and outcomes)
ZHOU, Z., LEI, Y., WEI, W., ZHAO, Y., JIANG, Y., WANG, N., LI, X. & CHEN, X. 2019. Association between prenatal exposure to bisphenol a and birth outcomes: A systematic review with meta-analysis. *Medicine,* 98(44), e17672.	Multiple use of the same data in the analyses

APPENDIX 6 – TABLE OF CHARACTERISTICS OF INCLUDED REVIEWS AND POOLED ANALYSES ON BISPHENOL A (BPA)

Table 6.1: Characteristics of included reviews and pooled analyses on bisphenol A (BPA)

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Bigambo 2020 - Association between phenols exposure and earlier puberty in children: A systematic review and meta-analysis - No COIs declared							
Last search Feb-20 **Study types** Cohort (n=4); Case control (n=3); Cross sectional (n=2) **Included studies in the review =** 9 **Included studies in the meta-analysis =** 9	Newcastle-Ottawa Scale (Supornsilchai et al., 2016) was used to assess the quality of the included cohort and case-control studies, and the adapted Newcastle-Ottawa cohort Scale form was used to assess the cross-sectional studies (Herzog et al., 2013): low quality with score 0–3, moderate quality with score 4–6, and high quality with score 7–9. Two studies moderate quality with a moderate risk of bias (cross sectional) and seven of high quality with low risk of bias.	Girls N = 4,737	**Type** Bisphenol A (BPA) **Route** Unspecified **Measure** Urine **Exposure time** Unspecified	risk of earlier puberty (precocious puberty, earlier puberty, idiopathic central precocious puberty, premature thelarche, earlier menarche, and earlier pubarche) odds ratio (OR) and Hazard ratio (HR) combined in meta-analysis to overall effect size (ES) - dichotomous variables	No association between BPA and risk of earlier puberty in girls (ES=1.09, 95%CI: 0.88, 1.35; 8 studies, 3498 participants)	No subgroup analysis conducted. Sensitivity analyses performed for each individual study.	5
Dunder 2019 - Urinary bisphenol A and serum lipids: a meta-analysis of six NHAMES examination cycles (2003-2014)- No COIs declared							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search 2003-2014 **Study types** Continuous cross-sectional surveillance data **Included studies in the review =** NA **Included studies in the meta-analysis =** NA	no studies to appraise	Children (≤ 17 years; n=4604); Adults (≥ 18 years; n=10989) N = 15,593	**Type** BPA **Route** NR **Measure** Urinary (mmol/L) **Exposure time** NR	Concentration BPA in low-density lipoprotein cholesterol (LDL-C) Beta coefficient and 95%CI	No association found between urinary BPA levels and LDL-C (b=-0.02, 95%CI: -0.05,0.01)	**Children - standard adjusted model**: No association found between urinary BPA levels and LDL-C (b=-0.005, 95%CI: -0.05,0.05) **Children - fully adjusted model**: No association found between urinary BPA levels and LDL-C (b=0.003, 95%CI: -0.05,0.05) No association between urinary BPA levels and LDL-C in boys (β −0.03, 95%CI: −0.09 to 0.04) and girls (β 0.04, 95%CI: −0.04 to 0.11) (participants unspecified).	4
				Beta coefficient and 95%CI		**Adults - standard adjusted model**: No association found between urinary BPA levels and LDL-C (b=--0.02, 95%CI: -0.05,0.01; p=0.22 (); **Adults - fully adjusted model**: No association found between urinary BPA levels and LDL-C (b=--0.02, 95%CI: -0.05,0.01) No association between urinary BPA levels and LDL-C in males (β −0.02, 95%CI: −0.07 to 0.02; 6 studies, participants unspecified) and in females (β −0.01, 95%CI: −0.05 to 0.03; 6 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Concentration BPA in high-density lipoprotein cholesterol (HDL-C) Beta coefficient and 95%CI	No association found between urinary BPA levels and HDL-C (b=-0.01, 95%CI: -0.02,0.00)	**Children - standard adjusted model**: No association found between urinary BPA levels and HDL-C (b=--0.01, 95%CI: -0.02,0.002); **Children - fully adjusted model**: No association found between urinary BPA levels and HDL-C (b=--0.01, 95%CI: -0.02,0.002) No association between urinary BPA levels and HDL-C in boys (β -0.01, 95%CI: −0.03 to 0.003; 6 studies, participants unspecified) and girls (β -0.01, 95%CI: −0.03 to 0.007; 6 studies, participants unspecified)	
				Beta coefficient and 95%CI		**Adults - standard adjusted model**: No association found between urinary BPA levels and HDL-C (b=-0.012, 95%CI: -0.02,0.001); **Adults - fully adjusted model**: No association found between urinary BPA levels and HDL-C (b=-0.006, 95%CI: -0.01,0.003 No association between urinary BPA levels and HDL-C in males (β -0.008, 95%CI: −0.02 to 0.004; 6 studies, participants unspecified) and in females (β -0.01, 95%CI: −0.03 to 0.0002; 6 studies, participants unspecified)	
				Concentration in total cholesterol (TC) Beta coefficient and 95%CI	No association found between urinary BPA levels and TC (b=-0.02, 95%CI: -0.04,0.00)	**Children - standard adjusted model**: No association found between urinary BPA levels and TC (b= 0.008, 95%CI: -0.03,0.05); **Children - fully adjusted model.** No association found between urinary BPA levels and TC (b= 0.01, 95%CI: -0.03,0.05) No association between urinary BPA	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						levels and TC in boys (β 0.02, 95%CI: −0.04 to 0.07; 6 studies, participants unspecified) and girls (β -0.02, 95%CI: −0.08 to 0.04; 6 studies, participants unspecified)	
				Beta coefficient and 95%CI		**Adults - standard adjusted model**: No association found between urinary BPA levels and TC (b=--0.02, 95%CI: -0.04,0.004); **Adults - fully adjusted model**: No association found between urinary BPA levels and TC (b=--0.02, 95%CI: -0.01,0.003) No association between urinary BPA levels and TC in males (β -0.02, 95%CI: −0.05 to 0.01; 6 studies, participants unspecified) and females (β -0.02, 95%CI: −0.05 to 0.02; 6 studies, participants unspecified)	
				Concentration in triglycerides (TG) Beta coefficient and 95%CI	No association found between urinary BPA levels and TG (b=--0.01, 95%CI: -0.03,0.01)	**Children - standard adjusted model**: No association found between urinary BPA levels and TG (b= 0.01, 95%CI: -0.02,0.05); **Children - fully adjusted model**: No association found between urinary BPA levels and TG (b= 0.01, 95%CI: -0.02,0.05) No association between urinary BPA levels and TG in boys (β 0.04, 95%CI −0.003 to 0.09; 6 studies, participants unspecified) and girls (β -0.02, 95%CI −0.07 to 0.03; 6 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Beta coefficient and 95%CI		**Adults - standard adjusted model**: No association found between urinary BPA levels and TG (b=-0.02, 95%CI: -0.04,0.004); **Adults - fully adjusted model**: No association found between urinary BPA levels and TG (b=-0.021, 95%CI: -0.01,0.003) No association between urinary BPA levels and TG in males (β -0.01, 95%CI −0.04 to 0.02; 6 studies, participants) and females (β -0.01, 95%CI −0.04 to 0.01; 6 studies, participants unspecified)	
				Concentration in apolipoprotein B (ApoB) Beta coefficient and 95%CI	No association found between urinary BPA levels and ApoB (b=--0.89, 95%CI: -1.843,0.06)	**Children - standard adjusted model**: No association found between urinary BPA levels and ApoB (b=--0.48, 95%CI: -2.1,1.2); **Children - fully adjusted model**: No association found between urinary BPA levels and ApoB (b=-0.54, 95%CI: -2.3,1.2) No association between urinary BPA levels and ApoB in boys (β -0.72, 95%CI: −2.8 to 1.4; 6 studies, participants unspecified) and girls (β -0.18, 95%CI: −2.9 to 2.6; 6 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Beta coefficient and 95%CI		**Adults - standard adjusted model**: No association found between urinary BPA levels and ApoB (b=-0.89, 95%CI: -1.8,0.06); **Adults - fully adjusted model**: No association found between urinary BPA levels and ApoB (b=-0.91, 95%CI: -1.82,-0.02) No association between urinary BPA levels and ApoB in males (β -0.66, 95%CI: −1.9 to 0.6; 6 studies, participants unspecified) and females (β -0.98, 95%CI: −2.3 to 0.4; 6 studies, participants unspecified)	
Fu 2020 - The association between environmental endocrine disruptors and cardiovascular disease: A systematic review and meta-analysis - No COIs reported							
Last search Jan-19 **Study types** Cross sectional (n=17) Retrospective cohort (n=7) Prospective cohort (n=4) Case control (n=1) **Included studies in the review =** 29 **Included studies in the meta-analysis =** 10	Newcastle-Ottawa Scale. The authors only provide the final score per study with the following statement "The literatures were considered as high quality, medium quality, and low quality with the corresponding scores of ≥7, 5–7, and<5."	Anybody in whom EED (environmental endocrine disruptor) exposure was pre-determined. No age limitations. N = 41854	**Type** Bisphenol A (BPA) **Route** Unspecified **Measure** Unspecified **Exposure time** Unspecified	Incidence of cardiovascular disease (CVD) OR and 95%CI no logistic regression	Positive association between exposure to BPA and incidence of CVD (OR=1.19, 95%CI:1.03, 1.37; 10 studies, 23953 participants).	No subgroup analysis conducted	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Hu 2018a-The association between prenatal bisphenol A exposure and birth weight: a meta-analysis- No COI declared							
Last search Aug-17 **Study types** Case control (n=2) and cohort (n=12) **Included studies in the review =** 14 **Included studies in the meta-analysis =** 8	Office of Health Assessment (OHAT) critical appraisal tool. In summary, there were 2 (25%) studies scored as high quality, 6 (75%) studies scored as medium quality.	Pregnant women and their infants. N = 6,208	**Type** Bisphenol A (BPA) **Route** in utero/ maternal exposure **Measure** ng/ml or µg/g Maternal urine sample/ maternal blood sample/ amniotic fluid **Exposure time** NR	Birth Weight Beta coefficient and 95% Cis	No association between prenatal BPA exposure and birth weight in infants (ES=4.42g, 95%CI: -8.83, 17.67; 8 studies, 2876 participants).	No association between prenatal BPA exposure measured during the first trimester and birth weight in infants (ES=44.41g, 95%CI: -113.45, 202.67; 2 studies, 395 participants). No association between prenatal BPA exposure measured during the second trimester and birth weight in infants (ES=37.89g, 95%CI: -209.68, 285.46; 2 studies, 292 participants). No association between prenatal BPA exposure measured during the third trimester and birth weight in infants (ES= -34.38g, 95%CI: -16.69, 85.49; 3 studies, 1512 participants). No association between prenatal BPA exposure and birth weight in adjusted confounders group (ES 4.42g, 95% CI: −8.83 to 17.67; 8 studies, 2,876 participants) and unadjusted for confounders in infants (b=31.42g, 95%CI: -19.14, 81.98; 3 studies, 1543).	8
Hu 2018b - The association between the environmental endocrine disruptor bisphenol A and polycystic ovary syndrome: a systematic review and meta-analysis - No COI declared							
Last search Aug-17 **Study types** Case control (n=9) **Included studies in the review =** 9	Newcastle-Ottawa quality assessment scale (NOS) - studies medium to high	Women (PCOS) age and BMI matched controls N = 933	**Type** BPA **Route** NR **Measure**	Polycystic ovary syndrome (PCOS) SMD and 95%CI	Women with PCOS in women were found to have significantly higher BPA levels than women without PCOS (SMD 2.437; 95%CI: 1.265, 3.609, 11 studies, 933 participants)	Serum samples SMD 2.515, 95%CI: 1.241 to 3.789; 10 studies, participants unspecified Asian SMD 3.209, 95%CI: 1.276 to 5.142; 6 studies, participants unspecified Caucasian SMD 1.511, 95%CI: -0.165 to 3.187; 4 studies, participants unspecified	9

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the meta-analysis = 8 (2 studies with subsets)			serum (n=8); follicular fluid (n=1) - ng/ml **Exposure time** NR			>19 years SMD 2.311, 95%CI: 1.009 to 3.612; 9 studies, participants unspecified	
						Exposure to BPA was positively associated with high BMI (serum samples) (SMD=0.512, 95%CI: 0.180, 0.843; 8 studies, 760 participants)	
						BMI >25 SMD 1.560, 95%CI: -0.433 to 3.553; 4 studies, participants unspecified BMI <25 SMD 2.793, 95%CI: 1.027 to 4.559; 5 studies, participants unspecified	
						Sample >50 SMD 4.730, 95%CI: 4.267 to 5.193; 3 studies, participants unspecified Sample <50 SMD 1.389, 95%CI: 0.685 to 2.093; 7 studies, participants unspecified	
						ELISA (the enzyme-linked immunosorbent assay) method SMD 1.957, 95%CI: 0.716 to 3.198; 8 studies, participants unspecified HPLC (high-performance liquid chromatography) method SMD 4.642, 95%CI: 3.900 to 5.383; 2 studies, participants unspecified	
						HOMA- IR >2.5 SMD 1.726, 95%CI: -0.690 to 4.143; 3 studies, participants unspecified	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						HOMA-IR levels unknown SMD 3.209, 95%CI: 1.276 to 5.142; 6 studies, participants unspecified LH/FSH <1.5 SMD 0.726, 95%CI: 0.411 to 1.040; 2 studies, participants unspecified LH/FSH levels unknown SMD 2.694, 95%CI: 1.062 to 4.326; 7 studies, participants unspecified	
						HOMA- IR >2.5 SMD 1.726, 95%CI: -0.690 to 4.143; 3 studies, participants unspecified HOMA-IR levels unknown SMD 3.209, 95%CI: 1.276 to 5.142; 6 studies, participants unspecified LH/FSH <1.5 SMD 0.726, 95%CI: 0.411 to 1.040; 2 studies, participants unspecified LH/FSH levels unknown SMD 2.694, 95%CI: 1.062 to 4.326; 7 studies, participants unspecified	
Hwang 2018 - Bisphenol A exposure and type 2 diabetesmellitus risk: a meta-analysis: No COI declared							
Last search Dec-18 **Study types** Cross sectional (n=12); Case control (n=3);	Downs and Black score. The average quality score was 16 with scores ranging from 13 to 18	NR N = 41320	**Type** Bisphenol A (BPA) **Route** NR **Measure**	Risk of T2D OR and 95%CI	BPA exposure was positively associated with T2D risk in humans (OR [fixed-effects model] 1.28; 95% CI: 1.14-1.44, I2=89.2%, p=0.000; 16 studies).	Urine samples OR 1.01, 95%CI: 1.00 to 1.02; 14 studies, 38,298 participants Serum samples OR 1.59, 95%CI: 1.06 to 2.38; 2 studies, 3,022 participants	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Observational (n=1) **Included studies in the review =** 16 **Included studies in the meta-analysis =** 16			Urinary and serum BPA levels (ng/mL) **Exposure time** NR		Sensitivity analysis (after exclusion of serum BPA levels and high heterogeneity) Random effects OR 1.20, 95% CI: 1.09 to 1.31; 14 studies; 38,059 participants		
Kim 2019a - The association between Bisphenol A exposure and obesity in children - A systematic review with meta-analysis - No COI declared							
Last search Oct-17 **Study types** Cross sectional (n=8); Case control (n=2); Observational (n=3) **Included studies in the review =** 13 **Included studies in the meta-analysis =** 13	Newcastle-Ottawa quality assessment scale (NOS) - score of 9 (n=7); score of 8 (n=2); score of 7 (n=3); score of 6 (n=1)	Age: 14 months to 19 years N = 11,303	**Type** BPA **Route** postnatal **Measure** Urinary - µg/L **Exposure time** NR	Obesity OR and 95%CI (Unspecified how measured in primary studies)	Exposure to BPA was associated with an increased odd of obesity (BMI) when compared to low exposure (reference group) (1.57; 95%CI 1.10,2.23; 7 studies, 9,602 participants)	Relatively high exposed group OR 1.58, 95%CI: 1.077 to 2.315; 6 studies; 9,522 participants	6
				Obesity SMD and 95%CI	No association found between urinary BPA levels and being obese compared to normal weight (SMD=0.166, 95%CI: -0.121,0.453; 8 studies, 2,092 participants)	Obese vs normal weight children (excluding pilot studies) SMD 0.044, 95%CI: -0.088 to 0.176; 6 studies, 1,962 participants	
Nelson 2020 - In utero exposure to persistent and nonpersistent endocrine-disrupting chemicals and anogenital distance. A systematic review of epidemiological studies† - No COI declared.							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Sep-19 **Study types** prospective cohort (n=13), cross sectional (n=2), retrospective (n=1) **Included studies in the review =** 16 **Included studies in the meta-analysis =** 3	Newcastle-Ottawa Scale (NOS) with 15 items; good-quality studies (13–15 points); fair quality (10-12 points) and poor quality (less than 9). Eleven articles of good quality, three of fair quality and two poor quality.	Pregnant women and children (newborn up to 12 months) N = NR	**Type** BPA **Route** maternal (prenatal) **Measure** Urinary BPA (µg/L) in first trimester; median concentration range 0.82-0.99µg/L in two studies and 1.26 µg/g Cr (adjusted for creatinine) in one study **Exposure time** NR	anogenital distance (AGD) specifically AGDAC (ano genital distance anal-clitoral distance) and AGDAF (ano genital distance anal-fourchette distance) in female children at birth beta coefficients standardised to a percent change per log10 change; standardisation done by dividing each reported beta coefficient by the mean value of the AGD	Significant summary estimate for the change in AGDAC (b=−1.374, 95% CI: −2.475 to −0.274; P = 0.014) per log10 increase in maternal urinary BPA concentrations (3 studies, 1760 participants)	No subgroup analysis conducted	7
					Nonsignificant estimate for the change in AGDAF (b=−1.069, 95% CI: −3.648 to −1.511; p = 0.417) per log10 increase in maternal urinary BPA concentrations (3 studies, 1760 participants)	No subgroup analysis conducted	
Ranciere 2015 - Bisphenol A and the risk of cardiometabolic disorders: a systematic review with metaanalysis of the epidemiological evidence- No DOI declared							
Last search Aug-14 **Study types**	A scoring system based on the established OHAT guidelines [31] adapted to reflect the characteristics of the included	Adults or children (however, only diabetes in adults, in an attempt to limit the analysis to type 2).	**Type** Bisphenol A **Route** Non-specific	Diabetes OR with 95% CI	Exposure to BPA was +ve associated with prevalent diabetes in the general population 1.47 (95%CI: 1.21,1.80,3 studies, 9291 participants; lowest to highest quartile)	1.33 (95%CI: 1.10,1.61,3 studies, 9291 participants; lowest to second quartile) and 1.18 (95%CI: 0.97,1.44,3 studies, 9291 participants; lowest to third quartile)	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Cross sectional (n=28) and Prospective Longitudinal (n=5) (pooled together) **Included studies in the review =** 33 **Included studies in the meta-analysis =** 12	studies: longitudinal design (2 points), population-based study (1 point), outcome assessment including measurements (1 point), collection of at least 2 urine samples per participant (1 point), control for urine dilution (1 point), adjustment for dietary intake (1 point), and adjustment for socioeconomic variables (1 point). Studies were then classified as 'low quality' (total score between 0 and 2), 'medium quality' (total score between 3 and 5), or 'high quality' (total score between 6 and 8). Studies ranged from low, medium to high.	Pregnant women were excluded. N = 69,486	**Measure** Urinary BPA and amniotic fluid (µg/L). Compared with extreme categories of urinary BPA levels (the highest vs. the lowest). Highest levels found a mean (SE) of 5.0 (0.3) ng/mL in boys and 4.6 (0.3) ng/mL in girls. Lowest: a median (interquartile range, IQR) of 0.60 (0.20–1.37) ng/mL. **Exposure time** non-specific	Prediabetes OR with 95% CI	No pooled estimates provided	No subgroup analysis	
				Hyperglycaemia NR	No pooled estimates provided	NR	
				Overweight OR with 95% CI	No association between BPA and prevalent overweight in children and adults 1.21 95% CI:0.98,1.50, 7 studies, no participant data recorded)	No association between BPA and prevalent overweight in children 1.24 (95% CI:.88, 1.75,5 studies, no participant data reported). Exposure to BPA was +ve associated with prevalent overweight in adults 1.25 (95% CI:0.98,1.5,2 studies, no participant data reported)	
				Obesity OR with 95% CI	Exposure to BPA was +ve associated with prevalent obesity in children and adults 1.67 (95% CI:1.41,1.98, 3 studies, no participant data reported)	Exposure to BPA was +ve associated with prevalent obesity in children 2.05(95% CI:.1.38,3.04, 1 study, no participant data reported). Exposure to BPA was +ve associated with prevalent obesity in adults 1.60 (95% CI:1.32, 1.93, 2 studies, no participant data reported)	
				Elevated Waist Circumference OR with 95% CI	Exposure to BPA was +ve associated with prevalent waist circumference in children and adults 1.48(95% CI:1.25,1.76, 4 studies, no participant data reported)	No association between BPA and prevalent elevated waist circumference in children 1.4 (95% CI:0.91,2.15, 1 study, no participant data reported). Exposure to BPA was +ve associated with prevalent waist circumference	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
	No discussion on the implications of quality on findings.					in adults 1.52 (1.21,1.90, 3 studies, no participant data reported).	
				Cardiovascular disease NR	No pooled estimates provided	NR	
				Hypertension OR with 95% CI	Exposure to BPA was +ve associated with hypertension in adults 1.41(95% CI:1.12,1.79, 2 studies, 4488 participants)	No subgroup analysis	
Riberio 2020 - Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis - No COIs declared							
Last search Jun-18 **Study types** Cross sectional **Included studies in the review =** 9	Newcastle-Ottawa Scale. Quality assessment using the Newcastle-Ottawa Scale indicated that 65% of cross-sectional studies and all prospective studies (note-	Adults and children from the general population, from 6-74 years N = 23,214	**Type** BPA **Route** Unspecified **Measure**	Prevalent Elevated Waist Circumference (Methods of categorisation unspecified) OR and 95%CI no logistic regression	Positive association between BPA exposure and prevalence of an elevated waist circumference (OR=1.49, 95%CI: 1.29, 1.72; 6 studies; 10005 participants)	When grouped based on age, there was no association between BPA exposure and prevalence of an elevated waist circumference in children (OR=1.62, 95%CI: 0.97, 2.72; 3 studies; 3836 participants). There was an association between BPA exposure and an elevated waist circumference in adults (OR=1.25, 95%CI: 1.27, 1.78; 2 studies, 6137 participants).	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the meta-analysis = 6	these were not included in the MA) had a low or medium risk of bias.		Urinary [BPA] (units not specified) **Exposure time** Unspecified	Prevalent Overweight (as classified by BMI) OR and 95%CI no logistic regression	Positive association between BPA exposure and prevalence of being overweight (OR=1.32, 95%CI: 1.01, 1.72; 5 studies, 11339 participants)	When grouped based on age, there was no association between BPA exposure and prevalence of being overweight in children (OR=1.67, 95%CI: 0.82, 3.38; 3 studies; 5202 participants). There was an association between BPA exposure and prevalence of being overweight in adults (OR=1.25, 95%CI: 1.01, 1.56; 2 studies, 6137 participants).	
				Prevalent Obese (as classified by BMI) OR and 95%CI no logistic regression	Positive association between BPA exposure and prevalence of obesity (OR=1.57, 95%CI: 1.35, 1.83; 5 studies, 12749 participants)	When grouped based on age, there were still positive association between BPA exposure for both children (OR=2.05, 95%CI 1.38, 3.04; 1 study, 3370 participants) and adults (OR=1.50, 95%CI: 1.35, 1.83; 4 studies, 9379 participants)	
Song 2016- Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. No COI declared.							
Last search Mar-14 **Study types** cross sectional (n=41), cohort (n=8) **Included studies in the review =** 49	Unspecified	Unspecified N = 28,641	**Type** BPA **Route** Unspecified **Measure** Urinary (ng/mL) **Exposure time** Unspecified	Type 2 diabetes Risk ratio and Cis; Highest versus Lowest exposure categories (cut-offs NR)	There was a positive association between BPA exposure and type 2 diabetes (RR= 1.45, 95%CI: 1.13, 1.97; 4 studies, 10541 participants). Dose-response MA from highest (>1.43 to >4.20 ng/mL) versus lowest (<0.47 to <1.36 ng/mL) exposure ranges and reported a dose-response RR of 1.09 per 1ng/mL increase (95%CI 1.03 to 1.15).	No subgroup analysis conducted	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the meta-analysis = BPA (4)				Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) Weighted mean difference and 95%Cis	Higher HOMA-IR was associated with higher BPA concentrations (WMD=0.80, 95%CI: 0.36-1.25; 4 studies, 6,520 participants).	No subgroup analysis conducted	
				Fasting glucose Weighted mean difference and 95%Cis	No association between BPA and fasting glucose (MD 0.97mg/dL, 95%CI: -0.19, 2.14; 4 studies, 9,854 participants)	No subgroup analysis conducted	
				Fasting insulin Weighted mean difference and 95%Cis	No association between BPA and fasting insulin (MD 0.15, 95%CI; -0.12 - 0.41; 4 studies, 9,854 participants)		
Wen 2019 - The risk of endometriosis after exposure to endocrine-disrupting chemicals: a meta-analysis of 30 epidemiology studies - No COIs declared							
Last search Jan-18 **Study types** Case control (n=21) Cohort (n=8) Cross sectional (n=1) **Included studies in the review =** 30	A modification of the Newcastle-Ottawa Scale (NOS) was used to assess quality of case-control studies and cohort studies for three aspects: the selection of study groups, comparability of groups and ascertainment of either the exposure or outcome of interest. Cross-	Only participant details provided was if the study sample was sourced from the general population or from a hospitalised population. N = 7,127	**Type** BPA **Route** Unspecified **Measure** Concentration in urine (µg/L), serum (µg/g) or fat (ng/g fat) (combined for meta-analysis) **Exposure time**	Prevalence Endometriosis OR and 95%CI no logistic regression	There was no association between BPA exposure and odds of endometriosis (OR=1.4, 95%CI 0.94, 2.08; 4 studies, 1130 participants)	Significant associations were found in the following subgroups: Population sample OR 1.61, 95%CI: 1.03 to 2.52; 2 studies, participants unspecified Case-control studies OR 1.72, 95%CI: 1.40 to 2.12; 2 studies, participants unspecified No associations were found in: Hospital sample OR 1.29, 95%CI: 0.72 to 2.31; 2 studies, participants unspecified Caucasians	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the meta-analysis = 4	sectional study was assessed by using Agency for Healthcare Research and Quality (AHRQ) with 11-item checklist. Quality was assessed by two independent authors. Quality assessment was depicted in Supplemental Table S3, the quality of all included studies was acceptable with score range 5–8.		Unspecified			OR 1.23, 95%CI 0.82 to 1.84; 3 studies, participants unspecified Cohort studies OR 1.19, 95%CI 0.70 to 2.04; 2 studies, participants unspecified	
Wu 2020a- Bisphenol A and the Risk of Obesity a Systematic Review with Meta-Analysis of the Epidemiological Evidence; No COI declared							
Last search 01-Jan-20 **Study types** Cross sectional (n=6) Survey (n=3) Cohort (n=1)	Newcastle-Ottawa Scale (0-9) Quality score of all 10 publications ranged from 6 to 8, with a median score of 7.	Children, adults and elderly (range, 6-79 years) N = 27,993	**Type** Bisphenol A (BPA) **Route** NR	Obesity obesity risk reported using odds ratios (ORs), hazard ratios (HRs), or relative risk ratios (RRs) with the corresponding 95% confidence interval for the highest level versus lowest level of BPA exposure	Overall values for obesity not extracted due to duplicate counting of data		5

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the review = 10 **Included studies in the meta-analysis =** 10			**Measure** Urinary BPA (ng/mL or µg/L) **Exposure time** NR	Abdominal obesity	Exposure to BPA was associated with an increase in odds in developing abdominal obesity across all populations (OR:1.43, 95% CI: 1.27-1.62, I2=0%, P= 0.651, 7 studies, 21,629 participants)	A dose-response analysis revealed that 1-ng/mL increase in BPA increased the risk of abdominal obesity by 12% (OR: 1.12, 95% CI: 1.09-1.14, p-value for a linear trend test <.001). No evidence of non-linear association was found between BPA and abdominal obesity risk.	
				Generalised obesity	Exposure to BPA was associated with an increase in odds in developing generalised obesity across all populations (OR: 1.83, 95% CI: 1.58-2.12, I2=16.7%, P= 0.299. 8 studies, 25,779 participants)	A dose-response analysis analysis revealed that a 1-ng/mL increase in BPA corresponded to a 16% increase in the risk of generalised obesity (OR: 1.16, 95%CI: 1.14-1.19, P-value for a linear trend test <.001). Evidence of non-linear association was found between BPA and generalised obesity risk (P=024).	
				Generalised overweight	Exposure to BPA was associated with an increase in odds in developing a generalised overweight condition across all populations (OR: 1.24, 95% CI: 1.02-1.51, I2=31.7%, P=0.198, 6 studies, 18,404 participants)	A dose-response analysis analysis revealed that a 1-ng/mL increase in BPA increased the risk of generalised overweight by 5.8% (OR: 1.058, 95% CI: 1.034-1.084, P-value for linear trend test <.001). No evidence of non-linear association was found between BPA and of generalised overweight risk.	
Zhong 2020- Association of prenatal exposure to phenols and parabens with birth size: A systematic review and meta-analysis. No COI declared.							
Last search Jul-19	No critical appraisal	Pregnant women and their infants N = 11,497	**Type** Bisphenol A (BPA)	Birth weight Beta Coefficient and 95% CI	No association between prenatal BPA exposure and neonatal birthweight in infants (b= -0.049g, 95%CI: -0.199, 0.101; 9	Heterogeneity was likely attributed to the studies conducted in the USA (p-value for heterogeneity = 0.141; I^2 = 49.0%), and in which urine was collected in the third trimester of	5

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Study types case control (n=1), cohort (n=20) **Included studies in the review =** 21 **Included studies in the meta-analysis =** 9			**Route** Maternal (prenatal) **Measure** Maternal urine (units NR) **Exposure time** Prenatal		studies, 4636 participants)	pregnancy (p-value for heterogeneity = 0.051; I2 = 54.6%)	
				Birth length Beta Coefficient and 95% CI	No association between prenatal BPA exposure and neonatal birth length in infants (b= 0.058cm, 95%CI: -0.072, 0.188; 9 studies, 4636 participants)		
				Head circumference Beta Coefficient and 95% CI	No association between prenatal BPA exposure and neonatal birth length in infants (b=-0.004cm, 95%CI: -0.119, 0.111; 9 studies, 4636 participants)		
				Gestational age Beta Coefficient and 95% CI	No association between prenatal BPA exposure and gestational age (b=-0.032 weeks, 95%CI: -0.163, 0.10; 9 studies, 4636 participants)		

APPENDIX 7 – TABLE OF CHARACTERISTICS OF INCLUDED REVIEWS AND POOLED ANALYSES ON PHTHALATES

Table 7.1: Characteristics of included reviews and pooled analyses on phthalates)

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Cai 2019- Association between Phthalate Metabolites and Risk of Endometriosis: A Meta-Analysis- No COIs declared							
Last Search Mar-19 **Study types** study total n=8 cross sectional n= 1 case control n= 5 cohort n= 7 **Included studies in the review =** 8 **Included studies in the meta-analysis =** 8	Newcastle-Ottawa Scale (NOS) was used the authors make no claims on how this could impact on interpretation of assessment. All studies scored between 6-7 (scores could range from 0-9)	Women aged between 18-54; n = 2 studies did not state their age range. Cases n = 620; control n = 1922; total = 2542	**Type** mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) **Route** Unspecified **Measure** Urine: Unspecified on measurement **Exposure time** non-specific	Endometriosis OR and (95% CI)	Exposure to MEHHP was significantly associated with the risk of endometriosis in women (OR = 1.246, 95% CI = 1.003–1.549, p=0.111)	Exposure to MEHHP was +ve associated with risk of endometriosis in Asia (OR = 1.786, 95% CI = 1.005–3.172, 3 studies, no participant data noted), but not USA (OR = 1.170, 95% CI = 0.949–1.442, 4 studies, no participant data noted). No association between MEHHP by study population: laparoscopic/laparotomy population (OR=1.337, 95% CI= 0.875, 2.043, 4 studies, no participant data noted); general population (OR= 1.327, 95% CI 0.831, 2.117, 3 studies, no participant data noted) No association between MEHHP and by study design: case control (OR=1.508, 95% CI= 0.949, 2.397, 4 studies, no participant data noted); cohort (OR=1.472, 95% CI:0.753, 2.879, 2 studies, no participant data noted); cross sectional (OR=1.070, 95% CI 0.880, 1.210, 1 study, no participant data noted). A potential statistical association between MEHHP exposure and endometriosis. The exposure of MEHHP might be a potential risk for women with endometriosis in Asia. However, positive associations between the other four Phthalate acid esters	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						(PAEs) and endometriosis were not found.	
			Type mono(2-ethylhexyl) phthalate (MEHP) **Route** Unspecified **Measure** Urine; Plasma **Exposure time** non-specific	Endometriosis OR and (95% CI)	No association between MEHP and endometriosis risk in women (OR=1.089, 95% CI=.858,1.383, 7 studies, no participant data).	MEHP was +ve associated with endometriosis risk in Asia (OR = 1.020, 95% CI = 1.003–1.038, 3 studies, no participant data noted), not USA (OR= 0.982, 95% CI= 0.530, 1.819, 4 studies, no participant data noted). No association by study population laparoscopic/laparotomy population (OR= 1.067, CI= 0.954, 1.194, 4 studies, no participant data noted) general population (OR= 0.884; 95% CI= 0.304, 2.569, 3 studies, no participant data noted) No association by study design: case control (OR=1.025, 95% CI 0.836, 1.258, 4 studies, no participant data noted); cohort (OR=1.596; 95% CI=0.770, 3.306, 4studies, no participant data noted); cross sectional OR=1.070 (95% CI=0.880, 1.210, 1 study, no participant data noted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type monoethyl phthalate (MEP) **Route** Unspecified **Measure** Urine: Unspecified on measurement **Exposure time** non-specific	Endometriosis OR and (95% CI)	No association with MEP with endometriosis in women (OR=1.073;95% CI 0.899, 1.282, 6 studies, no participant data noted)	MEP was not associated with geographic location; Asia (OR=1.179; 95% CI= 0.471, 2.951, 2 studies, no participant data noted); USA (OR=1.057; 95% CI= 0.879, 1.271, 4 studies, no participant data noted). No association by study design: case control (OR 1.493; 95% CI= 0.802, 2.778, 3 studies, no participant data noted); Cohort (OR=1.015; 95%CI= 0.834, 1.236, 2 studies, no participant data noted); Cross sectional (OR=1.120; 95% CI:0.580, 2.170,1 study, no participant data noted). No association by population: Laparoscoping/Laparotomy (OR=1.016; 95% CI=0.778, 1.448, 3 studies, no participant data noted); General population (OR=1.264; 95%CI= 0.838, 1.907, 3studies, no participant data noted).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-benzyl phthalate (MBzP) **Route** Unspecified **Measure** Urine: Unspecified on measurement **Exposure time** non-specific	Endometriosis OR and (95% CI)	MBzP was not associated with endometriosis (7 studies) (OR=0.976;95% CI 0.810, 1.176)	MBzP was not associated with geographic location; Asia (OR=1.038; 95% CI= 0.711, 1.516, 3 studies, no participant data noted); USA (OR=1.067; 95% CI= 0.769, 1.483, 4 studies, no participant data noted). Nor by study design: case control (OR 1.116; 95% CI= 0.790, 1.577, 4 studies, no participant data noted); Cohort (OR=1.018; 95%CI= 0.605, 1.715, 2 studies, no participant data noted); Cross sectional (OR= 1.160; 95% CI:0.580, 2.330, 1 study, no participant data noted). Nor by population: Laparoscoping/Laparotomy(OR=0.896; 95% CI=0.727, 1.103, 4 studies, no participant data noted); General population (OR=1.378; 95%CI= 0.908, 2.091, 3 studies, no participant data noted).	

			Type mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) **Route** Unspecified **Measure** Urine: Unspecified on measurement **Exposure time** non-specific	Endometriosis OR and (95% CI)	MEOHP was not associated with endometriosis (6 studies) (OR=1.282;95% CI 0.874, 1.881)	MEOHP was not associated with geographic location; Asia (OR=1.643; 95% CI= 0.620, 4.356, 3 studies, no participant data noted); USA (OR= 1.195; 95% CI= 0.754, 1.896, 4 studies, no participant data noted). Nor by study design: case control (OR 1.419; 95% CI= 0.811, 2.484, 3 studies, no participant data noted); Cohort (OR= 1.489; 95%CI= 0.693, 3.198, 2 studies, no participant data noted); Cross sectional (OR= 0.620; 95% CI:0.270, 1.440, 1 study, no participant data noted). Nor by population: Laparoscoping/Laparotomy (OR= 1.241; 95% CI=0.782, 1.970, 3 studies, no participant data noted); General population (OR=1.252; 95%CI= 0.574, 2.731, 3 studies, no participant data noted).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Cai 2015 - Human urinary/seminal phthalates or their metabolite levels and semen quality: A meta-analysis- No COIs declared							
Last search Oct-14 **Study types** mostly cross sectional. Did not identify other study types. **Included studies in the review** 20 studies met the inclusion criteria; 14 were further included in the meta-analysis. Total n of 20 studies = 4945 **Included studies in the meta-analysis =** 14	Used Elwood (1998) Critical Appraisal of Epidemiological Studies and Clinical Trials. Studies with a score no lower than–2 were excluded (three studies were removed) in the qualitative and quantitative analysis of the associations between phthalates or their metabolite levels in humans and semen quality	Most (no N identified) studies measuring urinary phthalate metabolites used subfertile males who were part of infertility workups. n= 3 studies were in healthy men of reproductive age from the general population Most (no N identified) studies measuring seminal phthalates chose men from the general population as their subjects. (no N identified) male subjects of reproductive age (i.e.,20–50 years), n=2 studies males of younger age, i.e., 18–22 years total participants in 20 studies = 4945	**Type** MnBP **Route** Environmental **Measure** Urinary phthalates or metabolite levels; Seminal phthalates levels; Serum phythalates levels **Exposure time** non-specific	Sperm Concentration OR and (95% CI); Beta coefficient (95% CI) NB: Risk (OR) indicative of semen quality were compared to a reference value in men at or above a sperm concentration of ≥ 20×10^6 *m*L, motility of ≥ 50% motile, and morphology of ≥ 4% normal morphology.	Exposure to MnBP levels of 7.4-25.3 µg/L was +ve associated with reduced sperm concentrations in males of reproductive age 2.6 (95% OR: 1.32, 5.15, 3 Studies, no participant data). Exposure to MnPB levels of 26.0-14459.0µg/L was +ve associated with reduced sperm concentration in males of reproductive age 2.39 (95% OR:1.26, 4.53, 5 studies, no participant data). No associations between MnBP and sperm concentrations using beta coefficients in males of reproductive age (b=0.04, 95%OR: -0.45,0.54, 3 studies, no participant data)	No subgroup analysis Meta-analysis strengthens the evidence that specific phthalates or their metabolite levels may affect semen quality. However, the meta-analysis based on a total of 14 studies demonstrated that specific phthalate exposures do associate with the incidence of decreased human semen quality. It was also noted that there were many cases where no associations between semen quality and various of the LMW phthalates were found. Longitudinal research is needed could help to confirm these tentative findings and assess whether we are seeing causal relationships between these compounds and semen quality of associations based on other lifestyle factors.	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm motility OR and (95% CI)	No association between MnPB levels of 7.4-25.3µg/L and low sperm motility in males of reproductive age 1.16 (95% OR:0.58, 2.34, 3 studies, no participant data). No association between MnPB levels of 26.0-14459.0µg/L and low sperm motility 1.35 in males of reproductive age (95% OR: 0.86, 2.11, 5 studies, no participant data).	No subgroup analysis	
				Sperm Morphology OR and (95% CI)	No association between MnPB levels of 7.4-25.3µg/L and low sperm morphology in males of reproductive age 1.00 (95% OR:0.59, 1.71, 2 studies, no participant data). No association between MnPB levels of 26.0-14459.0µg/L and low sperm morphology in males of reproductive age 1.43 (95% OR: 0.83, 2.47, 4 studies, no participant data).	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Semen volume OR and (95% CI)	No association between MnPB levels of 26.0-14459.0µg/L and sperm volume in males of reproductive age OR: 0.80 (95% 0.26, 2.40, 2 studies, no participant data)	No subgroup analysis	
				Sperm motion parameters: Straight-Line velocity (VSL) Beta coefficients and 95% Confidence intervals	No association between MnBP levels of 10.3–24.6 µg/L and Straight-line velocity (VSL) in men of reproductive age (b= -1.48 95%CI: -3.87, 0.92,3 studies, no participant data noted)) Exposure to MnBP levels 24.6–14,459.0 was associated with Straight-line velocity (VSL) in men of reproductive age (b= -2.51, 95%CI: -4.44, -0.59, 3 studies, no participant data noted)	No subgroup analysis	
				Sperm motion parameters: Curvilinear velocity (VCL) Beta coefficients and 95% Confidence intervals	No association between MnBP levels of 10.3–24.6 µg/L and Curvilinear velocity (VCL) in men of reproductive age (b= -2.60 95%CI: -5.40, 0.19, 3 studies, no participant data noted) Exposure to MnBP levels 24.6–14,459.0 was	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					associated with Curvilinear velocity (VCL) in men of reproductive age (b= -3.81 95%CI: -6.74, -0.87, 3 studies, no participant data noted)		
				Sperm motion parameters: Linearity (LIN) Beta coefficients and 95% Confidence intervals	No association between MnBP levels of 10.3–24.6 µg/L and Linearity (LIN) in men of reproductive age (b= -0.14 95%CI: -2.64, 2.36, 3 studies, no participant data noted) No association between MnBP levels of 24.6–14,459.0 and Linearity (LIN) in men of reproductive age (b= -0.70 95%CI: -2.46, 1.07, 3 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Comet extent Beta coefficients and 95% Confidence intervals	No association between MnBP (IQR 20.75 UG/l) and Comet extent in men of reproductive age (b= -0.30 95% CI: -0.79, 0.19, 2 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Percent DNA in tails Beta coefficients and 95% Confidence intervals	No association between MnBP (IQR 20.75 UG/l) and Percent DNA in tailin men of reproductive age (b=0.64 95% CI: -0.94,	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					2.23, 2 studies, no participant data noted)		
				comet assay parameters: Tail distributed moment Beta coefficients and 95% Confidence intervals	No association between MnBP (IQR 20.75 UG/l) and Tail distributed momentin men of reproductive age (b=-0.122 95% CI: -0.32, 0.08, 2 studies, no participant data noted)	No subgroup analysis	
			Type MBzP	Sperm Concentration OR and (95% CI)	No association between MBzP levels of 0-14.0µg/L and low sperm concentration in males of reproductive age1.24 (95% CI: 0.67, 2.29, 6 studies, no participant data) Exposure to MBzP levels of 14-540.2 µg/L was +ve associated with reduced sperm concentration 2.23 (95% OR: 1.16, 4.30, 3 studies, no participant data)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm motility OR and (95% CI)	No association between MBzP levels of 0-14.0µg/L and low sperm motility in males of reproductive age 1.24 (95% CI: 0.78, 1.84, 6 studies or participant data provided). No association between MBzP levels of 14-540.2 µg/L and low sperm motility in males of reproductive age1.47 (95% OR: 0.91, 2.36, 3 studies, no participant data)	No subgroup analysis	
				Sperm Morphology OR and (95% CI)	No association between MBzP levels of 0-14.0µg/L and low sperm morphology in males of reproductive age0.70 (95% CI: 0.38–1.28, 6 studies or participant data recorded). No association between MBzP levels of 14-540.2 µg/L and low sperm morphology in males of reproductive age 1027 (95% OR: 0.77, 2.08, 3 studies, no participant data)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm motion parameters: Straight-Line velocity (VSL) Beta coefficients and 95% Confidence intervals	No association between MBzP levels of 4.2–64.2 and Straight-line velocity (VSL) in men of reproductive age (b=-0.42 95%CI: -1.39, 0.55, 3 studies, no participant data noted) No association between MBzP levels of 64.2–540.2 and Straight-line velocity (VSL) in men of reproductive age (b=-1.93 95%CI: -3.98, 0.12, 3 studies, no participant data noted)	No subgroup analysis	
				Sperm motion parameters: Curvilinear velocity (VCL) Beta coefficients and 95% Confidence intervals	No association between MBzP levels of 4.2–64.2 and Curvilinear velocity (VCL) in men of reproductive age (b= -0.44 95%CI: -1.94, 1.07, 3 studies, no participant data noted) No association between MBzP levels of 64.2–540.2 and Curvilinear velocity (VCL) in men of reproductive age (b=-1.70 95%CI: -5.21, 1.82, 3 studies, no participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm motion parameters: Linearity (LIN) Beta coefficients and 95% Confidence intervals	No association between MBzP levels of 4.2–64.2 and Linearity (LIN) in men of reproductive age (b=-0.22 95%CI: -0.81, 0.38, 3 studies, no participant data noted) No association between MBzP levels of 64.2–540.2 and Linearity (LIN) in men of reproductive age (b=-1.05 95%CI: -2.51, 0.40, 3 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Comet extent Beta coefficients and 95% Confidence intervals	Exposure to MBzP (IQR 11.35UG/l) was associated with Comet extent in men of reproductive age (b=3.57 95% CI:0.89, 6.25, 2 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Percent DNA in tails Beta coefficients and 95% Confidence intervals	No association between MBzP (IQR 11.35UG/l) and Percent DNA in tailin men of reproductive age (b=0.05 95% CI: -0.38, 0.48, 2 studies, no participant data noted)	No subgroup analysis	
				comet assay parameters: Tail distributed moment Beta coefficients and 95% Confidence intervals	Exposure to MBzP (IQR 11.35UG/l) was associated with Tail distributed momentin men of reproductive age (b=1.72 95% CI:0.33,	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					3.12, 2 studies, no participant data noted)		
			Type MMP	Sperm Concentration OR and (95% CI)	No association between MMP levels of 1.5-9.0µg/L and reduced sperm concentration in males of reproductive age 0.89 (95% CI: 0.48–1.67, 6 studies or participant data noted) No association between MMP levels of 9.0-745.0µg/L and low sperm concentration in males of reproductive age 0.96 (95% CI: 0.28–3.29, 6 studies or participant data noted)	No subgroup analysis	
				Sperm motility OR and (95% CI)	No association between MMP levels of 1.5-9.0µg/L and low sperm Motility in males of reproductive age1.13 (95% CI: 0.53–2.39, 6 studies or participant data noted) No association between MMP levels of 9.0-745.0µg/L and low sperm Motilityin males of reproductive age 0.71 (95% CI: 0.39–1.32, 6 studies or participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm Morphology OR and (95% CI)	No association between MMP levels of 1.5-9.0µg/L and low sperm Morphology in males of reproductive age 0.78 (95% CI: 0.43–1.40, 6 studies or participant data noted) No association between MMP levels of 9.0-745.0µg/L and low sperm Morphology in males of reproductive age 0.84 (95% CI: 0.44–1.60, 6 studies or participant data noted)	No subgroup analysis	
				Sperm motion parameters: Straight-Line velocity (VSL) Beta coefficients and 95% Confidence intervals	No association between MMP levels of 1.5–8.3 and Straight-line velocity (VSL) in men of reproductive age (b=-0.14 95%CI: -1.76, 1.49, 3 studies, no participant data noted) No association between MMP levels of 8.3–278.1 and Straight-line velocity (VSL) in men of reproductive age (b=0.79 95%CI: -1.29, 2.88, 3 studies, no participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm motion parameters: Curvilinear velocity (VCL) Beta coefficients and 95% Confidence intervals	No association between MMP levels of 1.5–8.3 and Curvilinear velocity (VCL) in men of reproductive age (b=-1.54 95%CI: -4.31, 1.24, 3 studies, no participant data noted) No association between MMP levels of 8.3–278.1 and Curvilinear velocity (VCL) in men of reproductive age (b=.18 95%CI: -3.39, 3.74, 3 studies, no participant data noted)	No subgroup analysis	
				Sperm motion parameters: Linearity (LIN) Beta coefficients and 95% Confidence intervals	No association between MMP levels of 1.5–8.3 and Linearity (LIN) in men of reproductive age (b=0.99 95%CI: -0.17, 2.14, 3 studies, no participant data noted) No association between MMP levels of 8.3–278.1 and Linearity (LIN)in men of reproductive age (b=.93 95%CI: -0.61, 2.47, 3 studies, no participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Comet Assay Parameters: Comet extent Beta coefficients and 95% Confidence intervals	No association between MMP (IQR 8.85UG/l) and Comet extent in men of reproductive age (b=-02.08 95%CI: -10.89, 6.73, 2 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Percent DNA in tails Beta coefficients and 95% Confidence intervals	No association between MMP (IQR 8.85UG/l) and Percent DNA in tailin men of reproductive age (b=-2.44 95%CI: -7.16, 2.29, 2 studies, no participant data noted)	No subgroup analysis	
				comet assay parameters: Tail distributed moment Beta coefficients and 95% Confidence intervals	No association between MMP (IQR 8.85UG/l) and Tail distributed momentin men of reproductive age (b=0.31 95%CI: -1.23, 1.84, 2 studies, no participant data noted)	No subgroup analysis	
			Type MEP	Sperm Concentration OR and (95% CI)	No association between MEP levels of 3.3-49.8µg/L and reduced sperm concentration in males of reproductive age 0.84 (95% CI:0.43–1.63, 6 studies no participant data noted) No association between MEP levels of 77.2-11371µg/L and low sperm concentration in	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					males of reproductive age 1.42 (95% CI:0.84–2.42, 6 studies no participant data noted)		
				Sperm motility OR and (95% CI)	No association between MEP levels of 3.3-49.8µg/L and low sperm Motility in males of reproductive age 0.77 (95% CI:0.30–1.96, 6 studies no participant data noted) No association between MEP levels of 77.2-11371µg/L and low sperm Motility in males of reproductive age 0.89 (95% CI:0.59–1.32, 6 studies no participant data noted)	No subgroup analysis	
				Sperm Morphology OR and (95% CI)	No association between MEP levels of 3.3-49.8µg/L and low sperm Morphology in males of reproductive age0.88 (95% CI:0.44–1.75, 6 studies no participant data noted) No association between MEP levels of 77.2-11371µg/L and low sperm Morphology in males of reproductive age1.21 (95% CI:0.42–	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					3.42, 6 studies no participant data noted)		
				Sperm motion parameters: Straight-Line velocity (VSL) Beta coefficients and 95% Confidence intervals	No association between MEP levels of 59.6–979.5 and Straight-line velocity (VSL) in men of reproductive age (b= 0.12 95%CI: -0.88, 1.12, 3 studies, no participant data noted) Exposure to MEP levels of 979.5–11,371.0 was associated with Straight-line velocity (VSL) in men of reproductive age (b=2.36 95%CI:0.28, 4.45, 3 studies, no participant data noted)	No subgroup analysis	
				Sperm motion parameters: Curvilinear velocity (VCL) Beta coefficients and 95% Confidence intervals	No association between MEP levels of 59.6–979.5 and Curvilinear velocity (VCL)in men of reproductive age (b= -0.21 95%CI: -1.80, 1.38, 3 studies, no participant data noted) Exposure to MEP levels of 979.5–11,371.0 was associated with Curvilinear velocity (VCL) in men of reproductive age (b= 5.23 95%CI:1.67, 8.80, 3 studies, no participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm motion parameters: Linearity (LIN) Beta coefficients and 95% Confidence intervals	No association between MEP levels of 59.6–979.5 and Linearity (LIN) in men of reproductive age (b=0.01 95%CI: -0.82, 0.85, 3 studies, no participant data noted) No association between MEP levels of 979.5–11,371.0 and Linearity (LIN) in men of reproductive age (b= -0.44 95%CI: -1.94, 1.04, 3 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Comet extent Beta coefficients and 95% Confidence intervals	Exposure to MEP (IQR 449.4UG/l) was associated with Comet extent in men of reproductive age (b=4.22 95%CI:1.66, 6.77, 2 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Percent DNA in tails Beta coefficients and 95% Confidence intervals	No association between MEP (IQR 449.4UG/l) and Percent DNA in tailin men of reproductive age (b=-0.18 95%CI: -0.79, 0.44, 2 studies, no participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				comet assay parameters: Tail distributed moment Beta coefficients and 95% Confidence intervals	Exposure to MEP (IQR 449.4UG/l) was associated with Tail distributed momentin men of reproductive age (b=1.64 95%CI:0.24, 3.03, 2 studies, no participant data noted)	No subgroup analysis	
			Type MEHP	Sperm Concentration OR and (95% CI)	No association between MEHP levels 0.4–1.9µg/L and reduced sperm concentration in males of reproductive age 8.00 (95% CI:1.00–60.30, 6 studies no participant data noted) No association between 3.8–875.8µg/L and low sperm concentration in males of reproductive	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					age 0.99 (95% CI:0.64–1.54, 6 studies no participant data noted). Using Beta coefficients, no associations between (MEHP-no levels listed) and sperm concentration in males of reproductive age (b= -001 95% CI: -017,0.17, 3 studies, no participant data noted)		
				Sperm Motility OR and (95% CI)	No association between MEHP levels of 0.4–1.9µg/L and low sperm Motilityin males of reproductive age 0.70 (95% CI:0.20–2.00, 6 studies no participant data noted) No association between MEHP levels of 3.8–875.8µg/L and low sperm Motility in males of reproductive age 1.17 (95% CI:0.78–1.76, 6 studies no participant data noted) Using beta coefficients no association between MEHP (no levels listed)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					and sperm motility in males of reproductive age b= 94.62 (95%CI: -176.54, 365.77, 3 studies, no participant data noted)		
				Sperm Morphology OR and (95% CI)	No association between 3.8–875.8µg/L and low sperm Morphology in males of reproductive age 1.00 (95% CI:0.66–1.51, 6 studies no participant data noted) No other levels reported for sperm morphology Using beta coefficients no association between MEHP (no levels listed) and low sperm morphology in males of reproductive age b= 0.19 (95%CI: -0.40, 0.79, 3 studies, no participant data noted)	No subgroup analysis	
				Sperm motion parameters: Straight-Line velocity (VSL) Beta coefficients and 95% Confidence intervals	Exposure to MEHP levels of 3.1–208.1 was associated with Straight-line velocity (VSL) in men of reproductive age (b=-1.06 95%CI: -1.99, -0.12, 3 studies, no participant data noted) No association between MEHP levels of 208.1–875.8 and Straight-line	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					velocity (VSL) in men of reproductive age (b= -1.76 95%CI: -3.83, 0.31, 3 studies, no participant data noted)		
				Sperm motion parameters: Curvilinear velocity (VCL) Beta coefficients and 95% Confidence intervals	No association between MEP levels of 3.1–208.1 and Curvilinear velocity (VCL)in men of reproductive age (b=-1.48 95%CI: -2.99, 0.03, 3 studies, no participant data noted) No association between MEHP levels of 208.1–875.8 and Curvilinear velocity (VCL)in men of reproductive age (b=-2.41 95%CI: -5.96, 1.15, 3 studies, no participant data noted)	No subgroup analysis	
				Sperm motion parameters: Linearity (LIN) Beta coefficients and 95% Confidence intervals	Exposure to MEHP levels of 3.1–208.1 was associated with Linearity (LIN) in men of reproductive age (b=-0.43 95%CI: -0.80, -0.06, 3 studies, no participant data noted) No association between MEHP levels of 208.1–875.8 and Linearity (LIN) in men of reproductive age (b=-0.43 95%CI: -	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					1.90, 1.05, 3 studies, no participant data noted)		
				Comet Assay Parameters: Comet extent Beta coefficients and 95% Confidence intervals	No association between MEHP (IQR 14.35UG/l) and Comet extent in men of reproductive age (b=-0.16 95%CI: -1.45, 1.13, 2 studies, no participant data noted)	No subgroup analysis	
				Comet Assay Parameters: Percent DNA in tails Beta coefficients and 95% Confidence intervals	No association between MEHP (IQR 14.35UG/l) and Percent DNA in tailin men of reproductive age (b=1.40 95%CI: -1.60, 4.40, 2 studies, no participant data noted)	No subgroup analysis	
				comet assay parameters: Tail distributed moment Beta coefficients and 95% Confidence intervals	No association between MEHP (IQR 14.35UG/l) and Tail distributed momentin men of reproductive age (b=0.01 95%CI: -0.53, 0.54, 2 studies, no participant data noted)	No subgroup analysis	
			Type MEOHP	Sperm Concentration OR and (95% CI)	No association between MEOHP levels of 1.9–30.6µg/L and reduced sperm concentration in males of reproductive age 1.66 (95% CI:0.50–5.50, 6 studies no participant data noted) No association between MEOHP levels of 32.1–	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					3063.0µg/L and low sperm concentration in males of reproductive age 1.30 (95% CI:0.45–3.75, 6 studies no participant data noted)		
				sperm motility OR and (95% CI)	No association between MEOHP levels of 1.9–30.6µg/L and low sperm Motility in males of reproductive age 0.84 (95% CI:0.47–1.50, 6 studies no participant data noted) No association between MEOHP levels of 32.1–3063.0µg/L and low sperm Motility in males of reproductive age 0.66 (95% CI:0.33–1.31, 6 studies no participant data noted)	No subgroup analysis	
				Sperm Morphology OR and (95% CI)	No association between MEOHP levels of 1.9–30.6µg/L and low sperm Morphology in males of reproductive age1.40 (95% CI:0.50–3.70, 6 studies no participant data noted) No association between MEOHP levels of 32.1–3063.0µg/L and low sperm Morphology in males of reproductive	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					age0.59 (95% CI:0.26–1.33, 6 studies no participant data noted)		
			Type MEHP AND MEOHP	Sperm Concentration OR and (95% CI)	No association between MEHP, MEOHP levels of 2.2–84.2µg/L and reduced sperm concentration in males of reproductive age 1.16 (95% CI:0.67–2.03, 6 studies no participant data noted) No association between MEHP, MEOHP levels of 93.9–3938.8µg/L and reduced sperm concentration in males of reproductive age 0.94 (95% CI:0.48–1.81, 6 studies no participant data noted)	No subgroup analysis	
				sperm motility OR and (95% CI)	No association between MEHP, MEOHP levels of 2.2–84.2µg/L and low sperm Motility in males of reproductive age 0.94 (95% CI:0.62–1.43, 6 studies no participant data noted) No association between MEHP, MEOHP levels of 93.9–3938.8µg/L and low sperm Motility in males of reproductive age 0.99 (95% CI:0.62–1.60, 6	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					studies no participant data noted)		
				Sperm Morphology OR and (95% CI)	No association between MEHP, MEOHP levels of 2.2–84.2µg/L and low sperm Morphology in males of reproductive age1.01 (95% CI:0.56–1.81, 6 studies no participant data noted) No association between MEHP, MEOHP levels of 93.9–3938.8µg/L and low sperm Morphology in males of reproductive age 0.70 (95% CI:0.41–1.20, 6 studies no participant data noted)	No subgroup analysis	
			Type DBP	Sperm Motility (from semen levels) Beta coefficients and 95% Confidence intervals	Exposure to DBP was negatively associated with sperm motility (b= -0.19, 95%CI: -0.28 to -0.1; 2 studies, no participant data noted)	No subgroup analysis	
			Type DEHP and DEHP metabolites	Sperm Concentration OR and (95% CI)	No association between DEHP metabolite levels of 23.2–79.5µg/L and low sperm concentration in males of reproductive age 1.20 (95% CI:0.74–1.94, 6 studies no participant data noted) No association between DEHP metabolite levels of 79.5–8744.8µg/L and	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					low sperm concentration in males of reproductive age 1.32 (95% CI:0.62–2.80, 6 studies no participant data noted)		
				Sperm Motility OR and (95% CI)	No association between DEHP metabolite levels of 23.2–79.5µg/L and low sperm Motility in males of reproductive age 1.01 (95% CI:0.57–1.78, 6 studies no participant data noted) No association between DEHP metabolite levels of 79.5–8744.8µg/L and low sperm Motility in males of reproductive age 0.88 (95% CI:0.57–1.37, 6 studies no participant data noted)	No subgroup analysis	
				Sperm Motility (from semen levels) Beta coefficients and 95% Confidence intervals	Exposure to DEHP was negatively associated with sperm motility (b= -0.21, 95%CI: -0.3 to -0.12; 2 studies, no participant data noted)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Sperm Morphology OR and (95% CI)	No association between DEHP metabolite levels of 23.2–79.5µg/L and low sperm Morphology in males of reproductive age 1.28 (95% CI:0.85–1.93, 6 studies no participant data noted) No association between DEHP metabolite levels of 79.5–8744.8µg/L and low sperm Morphology in males of reproductive age 1.10 (95% CI:0.54–2.25, 6 studies no participant data noted)	No subgroup analysis	
Dorman 2018- Systematic reviews and meta-analyses of human and animal evidence of prenatal diethylhexyl phthalate exposure and changes in male anogenital distance- No COIs declared							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Oct-14 **Study types** observational prospective cohort studies **Included studies in the review =** 6; however, only 5 included in meta-analysis as only 1 study used AGD index **Included studies in the meta-analysis =** 6	OHAT RoB tool (NTP 2015). Elements were rated as definitely low RoB, probably low RoB, probably high RoB, definitely high RoB, or not reported (NR). A rating of NR was considered equivalent to probably high-risk RoB. Most studies scores probably low risk to definitely low risk of bias in their evaluation. Bar Suzuki et al. 2012 which was reported to have a high risk of bias as the reviewers could not be confident of their outcome assessments.	male infants: No further information about included participants were reported N = unspecified	**Type** diethylhexyl phthalate (DEHP) **Route** Unspecified **Measure** maternal urine ng/ml **Exposure time** In utero between 1st and 3rd trimester	anogenital distance (AGD). beta coefficient w 95% CI	Exposure to DEHP was associated with a change in AGD −4.07 (95% CI: −6.49, −1.66; 5 studies, no participant data noted) per log10 rise in urinary DEHP metabolite concentrations	no human subgroup analysis The human present a consistent pattern of findings that foetal exposure to DEHP is associated with reduced AGD in male offspring. Changes in AGD are considered an adverse effect. Under the OHAT method, a combination of a moderate level of human evidence leads to the conclusion that DEHP is presumed to be a reproductive hazard to humans on the basis of effects on AGD.	8
Fu 2020 - The association between environmental endocrine disruptors and cardiovascular disease: A systematic review and meta-analysis - No COIs reported							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Jan-19 **Study types** Cross sectional (n=17) Retrospective cohort (n=7) Prospective cohort (n=4) Case control (n=1) **Included studies in the review =** 29 **Included studies in the meta-analysis =** 5	Newcastle-Ottawa Scale. The authors only provide the final score per study with the following statement "The literatures were considered as high quality, medium quality, and low quality with the corresponding scores of ≥7, 5–7, and<5."	Anybody in whom EED (environmental endocrine disruptor) exposure was pre-determined. No age limitations. N = 41854	**Type** Any phthalate **Route** Unspecified **Measure** urine **Exposure time** Unspecified	Incidence of cardiovascular disease (CVD) OR and 95%CI No logistic regression		Subgrouping conducted based on phthalate subtype. No association between MBzP exposure and incidence of CVD (OR=1.18, 95%CI:0.93, 1.51; 4 studies, 9,261 participants). No association between MBP exposure and incidence of CVD OR=1.02, 95%CI:0.78, 1.32; 4 studies 9,261 participants). No association between MECCP and incidence of CVD (OR=1.15, 95%CI:0.94, 1.41; 4 studies 9,261 participants). No association between MEHHP exposure and incidence of CVD (OR=1.08, 95%CI:0.95,1.23; 4 studies 9,261 participants). No association between MEHP exposure and incidence of CVD (OR=1.05, 95%CI:0.97, 1.13; 4 studies 9,261 participants). No association between MEOHP exposure and incidence of CVD (OR=1.09, 95%CI:0.93, 1.26; 4 studies 9,261 participants). No association between MEP exposure and incidence of CVD (OR=1.15, 95%CI:0.99,1.34; 4 studies 9,261 participants). No association between MiBP exposure and CVD (OR=1.18, 95%CI:0.99,1.38; 4 studies 9,261 participants). EED exposure is a risk factor for CVD. PCBs, BPA, OCPs and PAEs have a	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						great impact on the development and progression of CVD. No statistical significance was found in the pooled OR value between the eight metabolites. However, the pooled OR value of total PAEs was 1.11	
Golestanzadeh 2020 - Association of phthalate exposure with precocious and delayed pubertal timing in girls and boys: a systematic review and meta-analysis - No COIs declared							
Last search Jul-19 **Study types** Case control (n=13) Cohort (n-17) Cross sectional (n=9) **Included studies in the review =** 39 **Included studies in the meta-analysis =** 4	The STROBE checklist was used to evaluate the methodology quality of the included papers. Discussion of appraisal was limited to "most of the included papers entered in this systematic review were high-quality papers based on the STROBE checklist".	Adolescent boys and girls, age ranging from 7 years (min) to 19 years (max). N = 10,524	**Type** Monoethyl phthalate (MEP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal breast development age (Early breast development defined as before the age of 8) (Delayed breast development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size."	No association between MEP exposure and abnormal breast development age (OR=0.82, 95%CI: 0.6, 1.05; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted. This systematic review and meta-analysis provided findings on a moderate association between exposure to different phthalates including LMWPs and HMWPs and pubertal timing and status of puberty for both genders. Exposure to phthalates may alter physiological development of humans such as pubic hair and breast development, menarche, production rates of hormones, as well as the size of ovaries, uterus and testicles.	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Monoethyl phthalate (MEP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (girls) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEP exposure and abnormal pubic hair development age (OR =0.99, 95%CI: 0.81, 1.17; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Monoethyl phthalate (MEP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure**	Abnormal age of menarche (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly	No association between MEP exposure and an abnormal age of menarche (OR=0.89, 95%CI: 0.62, 1.16, 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified **Exposure time** Unspecified	correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Monoethyl phthalate (MEP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (boys) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEP exposure and abnormal pubic hair development age (OR=1.02, 95%CI: 0.85, 1.19; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Monoethyl phthalate (MEP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Testicle volume (authors have not described how this variable has been categorised) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEP exposure and testicle volume (OR = 0.99, 95%CI: 0.77, 1.21; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono-methyl phthalate (MMP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified	Abnormal breast development age (Early breast development defined as before the age of 8) (Delayed breast development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a	No association between MMP exposure and abnormal breast development age (OR = 0.84, 95%CI: 0.67, 1.01; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Exposure time Unspecified	linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono-methyl phthalate (MMP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (girls) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MMP exposure and abnormal pubic hair development age (OR = 0.95, 95% CI: 0.77, 1.14; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-methyl phthalate (MMP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of menarche (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MMP exposure and an abnormal age of menarche (OR= 0.89, 95%CI: 0.68, 1.10; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono-methyl phthalate (MMP) **Route** Unspecified. But exposure measured through blood or urine analysis	Abnormal age of pubic hair development (boys) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly	No association between MMP exposure and abnormal pubic hair development age (OR = 0.63, 95% CI: 0.23, 1.03; 4 studies, 727 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Measure Unspecified **Exposure time** Unspecified	correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono-methyl phthalate (MMP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Testicle volume (authors have not described how this variable has been categorised) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MMP exposure and testicle volume (OR=1.01, 95%CI: 0.59, 1.44; 3 studies, 505 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type MnBP (Abbreviation not explained)	Abnormal breast development age (Early breast development defined as before the age of 8)	No association between MnBP exposure and abnormal breast development age (OR = 1.03, 95%CI: 0.27, 1.79; 2	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Route Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	(Delayed breast development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	studies, 423 participants).		

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MnBP (Abbreviation not explained) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (girls) (Early development before the age of 8) (Delayed development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size.	No association between MnBP exposure and anormal age of pubic hair development (OR =0.88, 95% CI: 0.59, 1.16, 2 studies, 423 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MnBP (Abbreviation not explained) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of menarche (Early development before the age of 8) (Delayed development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MnBP exposure and an abnormal age of menarche (OR=1.01, 95%CI: 0.06, 1.96; 2 studies, 423 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type MnBP (Abbreviation not explained) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure**	Abnormal age of pubic hair development (boys) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a	MnBP exposure was associated with a decreased odds of abnormal pubic hair development age (OR=0.66, 95%CI: 0.39, 0.93; 2 studies, 423 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified **Exposure time** Unspecified	linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono-ethylhexyl phthalate (MEHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal breast development age (Early breast development defined as before the age of 8) (Delayed breast development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHP exposure and abnormal breast development (OR = 1.16, 95%CI: 0.73, 1.59; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-ethylhexyl phthalate (MEHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (girls) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHP exposure and abnormal pubic hair development age (OR =0.91, 95CI: 0.74, 1.08, 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono-ethylhexyl phthalate (MEHP) **Route** Unspecified. But exposure measured through blood or urine analysis	Abnormal age of menarche (Early development before the age of 8) (Delayed development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a	No association between MEHP exposure and an abnormal age of menarche (OR=0.89, 95%CI: 0.66, 1.11; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Measure Unspecified **Exposure time** Unspecified	linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono-ethylhexyl phthalate (MEHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (boys) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHP exposure and abnormal pubic hair development age (OR=0.89, 95%CI: 0.62, 1.16; 3 studies, 609 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-ethylhexyl phthalate (MEHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Testicle volume (authors have not described how this variable has been categorised) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHP exposure and testicle volume (OR=1.13, 95%CI: 0.88, 1.37; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure**	Abnormal breast development age (Early breast development defined as before the age of 8) (Delayed breast development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a	Exposure to MEHHP was associated with an increased odds of abnormal breast development age (OR = 1.48, 95%CI: 1.11, 1.85; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified **Exposure time** Unspecified	linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of pubic hair development (girls) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHHP and abnormal pubic hair development age (OR = 0.96, 95% CI: 0.59, 1.13; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of menarche (Early development before the age of 8) (Delayed development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHHP exposure and an abnormal age of menarche (OR=1.07, 95%CI: 0.14, 2.01; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure**	Abnormal age of pubic hair development (boys) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a	Exposure to MEHHP was associated with a decreased odd of an abnormal pubic hair development age (OR = 0.61, 95%CI: 0.32, 0.91; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified **Exposure time** Unspecified	linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Testicle volume (authors have not described how this variable has been categorised) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEHHP exposure and testicle volume (OR=0.79, 95%CI: 0.44, 1.14; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)	Abnormal breast development age (Early breast development defined as before the age of 8) (Delayed breast	Exposure to MEOHP was associated with an increased odds of abnormal breast development age (OR = 1.52, 95%CI: 1.15, 1.88; 2	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Route Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	studies, 387 participants).		
			Type Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time**	Abnormal age of pubic hair development (girls) (Early development before the age of 8) (Delayed development defined as after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into	No association between MEOHP and abnormal pubic hair development age (OR = 0.95 95% CI: 0.66, 1.23; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified	correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			
			Type Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Abnormal age of menarche (Early development before the age of 8) (Delayed development after the age of 13) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEOHP exposure and an abnormal age of menarche (OR=1.08 95% CI:0.19, 1.98, 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	
			Type Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) **Route**	Abnormal age of pubic hair development (boys) (Early development before the age of 8) (Delayed development defined as after the age of 13)	Exposure to MEOHP was associated with a decreased odd for an abnormal pubic hair development age (OR = 0.61, 95%CI: 0.26, 0.97; 2 studies, 387 participants).	No further subgrouping or sensitivity analysis conducted.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size			

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) **Route** Unspecified. But exposure measured through blood or urine analysis **Measure** Unspecified **Exposure time** Unspecified	Testicle volume (authors have not described how this variable has been categorised) OR and 95%CI "If the regression coefficient remains in the interval +0.5 then correlation and regression coefficients are highly correlated (r=0.84) in a linear way. Therefore, extracted beta coefficients were transformed into correlation and then z Fisher transformation of correlation with the corresponding standard error was considered as desired effect size	No association between MEOHP exposure and testicle	No further subgrouping or sensitivity analysis conducted.	
Golestanzadeh 2019- Association of exposure to phthalates with cardiometabolic risk factors in children and adolescents: a systematic review and meta-analysis. No COI declared.							
Last search Dec-18 **Study types** cohort (n=17) cross sectional	STROBE checklist. ****Note this is a reporting guideline not a critical appraisal tool. ****The quality of the included observational	Children (≤ 18 years) N = 24,943	**Type** Phthalates **Route** Unspecified **Measure**	Birth weight Beta coefficient and 95% CI		For LMWP: Exposure to MEP was negatively associated with birthweight (z= -10.1, 95%CI: − 18.57, − 1.6; 3 studies, 4775 participants) but not for MMP (z= -0.05, 95%CI: -20.99, 20.90; 2 studies,4476 participants), MBP (z= 0.05, 95%CI: -0.51, 0.62; 4 studies,	5

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
(n=15) case control (n=3) **Included studies in the review =** 35 **Included studies in the meta-analysis =** 23	studies was good and most of them gained a high score.		Urine and serum (units unspecified) **Exposure time** Prenatal			5296 participants) and MiBP (z= -0.11, 95%CI: -0.87, 0.65; 2 studies, 820 participants). For HMWP: No significant associations with birth weight in the subgroup analysis of HMWPs; MECPP (z= 16.15,95%CI:−18.3, 50.58; 3 studies, 1822 participants), MEHHP (z= − 0.16, 95%CI:−1.27, 0.9; 5 studies, 5424 participants), MEOHP (z= − 0.39, 95%CI:−12.9, 12.13; 5 studies, 5424 participants), MEHP (z = − 0.79, 95%CI:− 3.84 2.62; 4 studies, 4461 participants), MBzP (z= − 2.38, 95%CI:− 9.20 3.53; 3 studies, 4294 participants), DEHP z= 3.85, 95%CI: −17.8, 25.6; 4604 participants). This meta-analysis shows positive associations between phthalate exposure and some cardiometabolic risk factors (BMI, BMI z score and systolic blood pressure) in children and adolescents. Therefore, prevention of exposure to phthalates and reduction of their use should be underscored in strategies for primordial prevention of cardiovascular diseases.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				BMI Beta coefficient and 95% CI		ForLMWP: Exposure to MiBP was positively associated with BMI (z= 0.18, 95%CI: 0.002, 0.35; 3 studies, 950 participants) but not for MMP (z=0.09, 95%CI:−0.08, 0.26; 6 studies, 1695 participants), MEP (z= 0.19, 95%CI:− 0.09, 0.46; 6 studies, 2545 participants), For HMWP: Exposure to MEHHP was positively associated with BMI (z= 0.18, 95%CI: 0.04, 0.31; 9 studies, 2490 participants) but not for MEHP (z= 0.15,95%CI: − 0.10 0.39; 9 studies, 3195 participants), MEOHP (z= − 0.001, 95%CI:− 0.09, 0.09; 9 studies, 2490 participants), MBzP (z= 0.17,95%CI: − 0.09, 0.43; 3 studies, 905 participants), MCOP (z= 0.05,95%CI: − 0.06, 0.17; 1 study, 276 participants), MCPP (z 0.15, 95%CI:− 0.10 0.41; 2 studies, 663 participants), and MECPP (z= − 0.12,95%CI: − 0.27, 0.03; 4 studies, 1059 participants).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				BMI z-score Beta coefficient and 95% CI		Exposure to LMWP metabolites and BMI z-score was positively associated in all subgroups; Mono-butyl phthalate (MBP) (z=0.11, 95%CI: 0.06, 0.16; 5 studies, 3991 participants), monoethylphthalate (MEP) (z=0.11, 95%CI: 0.05, 0.17, 4 studies, 3774 participants), monoisobutylphthalate (MiBP) (z=0.11, 95%CI: 0.08, 0.17, 4 studies, 3774 participants). Exposure to HMWP metabolites was associated with a higher BMI z-score; monobenzylphthalate (MBzP) (z=0.09, 95%CI: 0.01, 0.16; 4 studies, 1154 participants), mono(3-carboxyprpoyl)phthalate (MCPP) (z=0.06, 95%CI: 0.01, 0.11; 3 studies, 912 participants), monocarboxyoctylphthalate (MCOP) (z=0.11, 95%CI: 0.06, 0.16; 1 study, 345 participants) and di-2-ethylhexylphthalate (DEHP subgroups) (z= 0.07, 95%CI: 0.01, 0.13; 4 studies, 3774 participants), but not for MEHP (z= 0.16, 95%CI:− 0.06, 0.15; 2 studies, 629 participants), MEHHP (z= 0.20, 95%CI:− 0.08, 0.48; 2 studies, 629 participants), MEOHP (z= 0.12, 95%CI: − 0.02, 0.26; 2 studies, 629 participants).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Waist circumference Beta coefficient and 95% CI		For LMWP: No associations were found for MMP (z= 0.06, 95%CI: − 0.06, 0.18; 3 studies, 777 participants), MEP (z= 0.17, 95%CI: − 0.18, 0.52; 3 studies, 922 participants), MBP (z= 0.19, 95%CI: − 0.19 0.58; 4 studies, 1043 participants) and MiBP (z= − 0.33, 95%CI: − 1.11, 0.45; 2 studies, 646 participants). Exposure to the HMWP metabolites was associated with waist circumference; mono(2-ethylhexyl)phthalate (MEHP) (z=0.13, 95%CI: 0.04, 0.21; 5 studies, 1301 participants), mono(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP) (z=0.28, 95%CI: 0.09, 0.47, 5 studies, 1301 participants) and monobenzylphthalate (MBzP) (z=0.12, 95%CI: 0.02, 0.22, 3 studies, 905 participants) but not for MEOHP (z=0.05, 95%CI:− 0.02, 0.13; 5 studies, 1301 participants), MCOP (z=0.02, 95%CI:− 0.10, 0.14; 1 study, 276 participants), MCPP (z= − 0.46, 95%CI: − 1.42, 0.51; 2 studies, 663 participants), and MECPP (z= − 0.11, 95%CI: − 0.24, 0.03: 4 studies, 1059 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Blood pressure (systolic) Beta coefficient and 95% CI		Exposure to the phthalate metabolites was associated with increased systolic blood pressure; MEHHP (z= 0.16, 95%CI: 0.09, 0.23; 3 studies, 761 participants), mono(2-ethyl-5-oxohexyl)phthalate (MEOHP) (z= 0.12, 95%CI: 0.01, 0.24; 3 studies, 761 participants) but not MMP (z= 0.09, 95%CI:− 0.03, 0.20: 2 studies, 518 participants), MEHP (z= 0.13, 95%CI:− 0.02, 0.28; 3 studies, 731 participants) and MBzP (z= 0.09, 95%CI:− 0.11, 0.29; 3 studies, 518 participants).	
				Blood pressure (diastolic) Beta coefficient and 95% CI		No association between phthalate metabolites and diastolic blood pressure; MMP (z= 0.02, 95%CI: − 0.06, 0.11; 2 studies, 518 participants), MEHP (z= − 0.01, 95%CI: − 0.09, 0.08; 2 studies, 518 participants), MEHHP (z= 0.07, 95%CI: − 0.02, 0.15; 2 studies, 518 participants), MEOHP (z= 0.03, 95%CI: − 0.06, 0.12;2 studies, 518 participants) and MBzP (z= 0.04, 95%CI: − 0.05, 0.12; 2 studies, 518 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				HDL (lipid) Beta coefficient and 95% CI		Exposure to the phthalate MEOHP was associated with HDL (z=0.31, 95%CI: 0.25, 0.37; 2 studies, 485 participants) but not MEHP (z= −0.20, 95%CI:− 0.42, 0.03; 3 studies, 622 participants), MBP (z=− 0.15, 95%CI: − 0.88, 0.58; 2 studies, 397 participants), MEHHP (z= 0.20, 95%CI:− 0.23, 0.63; 2 studies, 485 participants), MBzP (z= − 0.11, 95%CI:− 0.47, 0.26; 3 studies, 1400 participants), MCPP (z= 0.11, 95%CI: − 0.10, 0.33; 2 studies, 1158 participants) and DEHP subgroups (z= 0.09, 95%CI:− 0.26, 0.44; 4 studies, 3231 participants	
				Triglyceride (Lipids) Beta coefficient and 95% CI		No association between phthalate metabolites and triglycerides; MEHP (z= 0.2, 95%CI:− 0.06, 0.47; 3 studies, 787 participants), MBP (z= 0.08, 95%CI: − 0.18, 0.34; 2 studies, 397 participants), MEHHP (z= 0.01, 95%CI:− 0.05, 0.07; 2 studies, 485 participants), MEOHP (z= − 0.06, (%%CI: − 0.19, 0.06; 2 studies, 485 participants), MBzP (z=0.14, 95%CI:− 0.10, 0.37; 3 studies, 1400 participants), MCPP (z=− 0.04, 95%CI:− 0.09, 0.02; 2 studies, 1158 participants) and DEHP subgroups (z=− 0.11, 95%CI:− 0.31, 0.08; 4 studies, 3907 participants)	
Kim 2019b - Association Between Diethylhexyl Phthalate Exposure and Thyroid Function: A Meta-Analysis - No COI declared							
Last search Oct-17	None reported	Children (neonates	**Type**	Thyroid function (free thyroxine [fT4])	No association found between MEHP and fT4	**Children**: No association found between MEHP and fT4 levels	5

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Study types Cross sectional, case control and cohort (numbers not reported) **Included studies in the review =** 13 **Included studies in the meta-analysis =** 13		excluded) and adolescents (aged < 18 years); pregnant women, adults (aged ≥ years), and general population N = 12,674	Diethylhexyl phthalate (DEHP) - metabolite (monoethylhexyl phthalate [MEHP]) **Route** Unspecified **Measure** Urinary **Exposure time** Unspecified	Pearson's correlation coefficient (r)	levels (r=-0.02, 95%CI: -0.05,0.00, 10 studies, 4673 participants)	(r=0.03, 95%CI: -0.01,0.08, 6 studies, 1832 participants)	
						Pregnant Women: No association found between MEHP and fT4 levels (r=-0.04, 95%CI: -0.07,0.00, 4 studies, 2841 participants)	
						Adults: No association found between MEHP and fT4 levels (r=-0.03, 95%CI: -0.14,0.07, 2 studies, 1829 participants)	
				Thyroid function (total free thyroxine [TT4]) Pearson's correlation coefficient (r)	No association found between MEHP and TT4 levels (r=0.01, 95%CI: -0.03, 0.06, 13 studies, 5097 participants)	**Children**: No association found between MEHP and TT4 levels (r=0.02, 95%CI -0.04,0.07, 7 studies, 2061 participants)	
						Pregnant Women: No association found between MEHP and TT4 levels (r=-0.01, 95%CI: -0.13,0.11, 4 studies, 2841 participants)	
						Adults: No association found between MEHP and TT4 levels (r=-0.04, 95%CI: -0.08,0.01, 4 studies, 2024 participants)	
				Thyroid function (thyrotropin [TSH]) Pearson's correlation coefficient (r)	No association found between MEHP and TSH levels (r=-0.03, 95%CI: -0.07,0.01, 13 studies, 5096 participants)	**Children**: No association found between MEHP and TSH levels (r=-0.01, 95%CI: -0.05,0.04, 7 studies, 2060 participants)	
						Pregnant Women: No association found between MEHP and TSH levels (r=0.00, 95%CI: -0.13,0.14, 4 studies, 2841 participants)	
						Adults: No association found between MEHP and TSH levels (r=-	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						0.04, 95%CI: -0.08,0.01, 4 studies, 2024 participants)	
			Type Diethylhexyl phthalate (DEHP) - metabolite (2-ethyl-5-hydroxyhexyl) phthalate [MEHHP])	Thyroid function (free thyroxine [fT4]) Pearson's correlation coefficient (r)	MEHHP was associated with fT4 levels (r=-0.03, 95%CI: -0.05, -0.01, 10 studies, 10,601 participants)	**Children**: MEHHP was associated with fT4 levels (r=0.06, 95%CI: 0.01,0.10, 6 studies, 1832 participants)	
						Pregnant Women: No association found between MEHHP and fT4 levels (r=-0.04, 95%CI: -0.08,0.00, 3 studies, 2766 participants)	
						Adults: Association found between MEHHP and fT4 levels (r=-0.08, 95%CI: -0.14, -0.01, 3 studies, 7832 participants)	
				Thyroid function (total free thyroxine [TT4]) Pearson's correlation coefficient (r)	No association found between MEHHP and TT4 levels (r=0.03, 95%CI: -0.01,0.08, 11 studies, 10,830 participants)	**Children**: No association found between MEHHP TT4 levels (r=0.04, 95%CI: 0.00,0.09, 7 studies, 2061 participants)	
						Pregnant Women: No association found between MEHHP and TT4 levels (r=-0.00, 95%CI: -0.19,0.19, 3 studies, 2766 participants)	
						Adults: No association found between MEHHP and TT4 levels (r=0.00, 95%CI: -0.02,0.03, 3 studies, 7832 participants)	
				Thyroid function (thyrotropin [TSH])	No association found between MEHHP and TSH levels (r=-0.02, 95%CI -0.07,0.03, 10	**Children**: No association found between MEHHP and TSH levels (r=-0.00, 95%CI: -0.05,0.05, 7 studies, 2060 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Pearson's correlation coefficient (r)	studies, 4826 participants)	**Pregnant Women**: No association found between MEHHP and TSH levels (r=-0.00, 95%CI: -0.20,0.19, 3 studies, 2766 participants)	
						Adults: No association found between MEHHP and TSH levels (r=-0.04, 95%CI: -0.09,0.00, 2 studies, 1829 participants)	
			Type Diethylhexyl phthalate (DEHP) - mono (2-ethyl-5-oxohexyl) phthalate [MEOHP])	Thyroid function (free thyroxine [fT4]) Pearson's correlation coefficient (r)	No association found between MEOHP and fT4 levels (r-0.01, 95%CI: -0.03,0.01, 10 studies, 10,601 participants)	**Children**: No association found between MEOHP and fT4 levels (r=0.05, 95%CI: 0.00,0.10, 6 studies, 1832 participants)	
						Pregnant Women: No association found between MEOHP and fT4 levels (r=0.02, 95%CI: -0.05,0.10, 3 studies, 2766 participants)	
						Adults: No association found between MEOHP and fT4 levels (r=-0.05, 95%CI: -0.10,0.01, 3 studies, 7832 participants)	
				Thyroid function (total free thyroxine [TT4]) Pearson's correlation coefficient (r)	MEOHP was not associated with TT4 levels (r=0.02, 95%CI: 0.00,0.04, 11 studies, 10,830 participants)	**Children**: MEOHP was associated with TT4 levels (r=0.05, 95%CI: 0.01,0.10, 7 studies, 2061 participants)	
						Pregnant Women: No association found between MEOHP and TT4 levels (r=-0.03, 95%CI: -0.13,0.08, 3 studies, 2766 participants)	
						Adults: No association found between MEOHP and TT4 levels (r=0.01, 95%CI: -0.01,0.03, 3 studies, 7832 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Thyroid function (thyrotropin [TSH]) Pearson's correlation coefficient (r)	No association found between MEOHP and TSH levels (r-0.02, 95%CI: -0.07,0.03, 10 studies, 4826 participants)	**Children**: No association found between MEOHP and TSH levels (r=0.00, 95%CI -0.04,0.05, 7 studies, 2060 participants)	
						Pregnant Women: No association found between MEOHP and TSH levels (r=0.03, 95%CI: -0.16,0.20, 3 studies, 2766 participants)	
						Adults: No association found between MEOHP and TSH levels (r=-0.10, 95%CI: -0.221,0.03, 2 studies, 1829 participants)	
Lee 2018 - Prenatal and postnatal exposure to di-(2-ethylhexyl) phthalate and neurodevelopmental outcomes: A systematic review and meta-analysis - No COI declared							
Last search Sep-17 **Study types** Cross sectional (n=2); Observational (n=8) **Included studies in the review =** 10 **Included studies in the meta-analysis =** 10	Newcastle-Ottawa quality assessment scale (NOS) - low quality (0−3), moderate quality (4−6), or high quality (7−9). Scores of the cohort studies (n = 8) ranged from 7 to 8, and the cross-sectional studies (n = 2) both scored at 8.	Age: 6 months to 12 years N = 2,496	**Type** Di-(2-ethylhexyl) phthalate (DEHP) **Route** prenatal **Measure** prenatal maternal urine (n=8); child's urine (n=2); both (n=3) -	Neurodevelopment measured with Weschsler Intelligence Scale for Children (WISC) and Bayley Scales of Infant Development (BSID) beta coefficient (b)	Longitudinal data: No association found between DEHP and neurodevelopment (WISC/BSID/MDI/FSIQ) in children (b=-0.14, 95%CI: -0.705, 0.41, 8 studies, 1625 participants).	Longitudinal data: No association found between DEHP and neurodevelopment (components of BSID; Mental Development Index [MDI] in children (b= -0.36 95%CI -1.05,0.32, 5 studies, 871 participants).	7
						Longitudinal data: Exposure to DEHP was negatively associated with neurodevelopment (components of BSID; Psychomotor Developmental index [PDI]) in children (b= -0.80, 95%CI -1.48, -0.12, 5 studies, 871 participants).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Exposure time Unspecified		Cross-sectional data: Exposure to DEHP was negatively associated with neurodevelopment (WISC/ FSIQ/cognitive) in children (b= -1.03, 95%CI -1.88, -0.18, 5 studies, 1462 participants).	No subgroup analysis conducted	
Li 2017- Phthalate esters and childhood asthma: A systematic review and congener-specific meta-analysis. No COI declared.							
Last search Oct-16 **Study types** Case control (n=3) cross sectional (n=4) cohort (n=2)	Newcastle-Ottawa scale. The score of the included cohort or case-control studies ranged from 6 to 8, and 7 to 9 for cross-sectional studies (moderate to high quality).	Children (≤18 years) N = 3,406	**Type** Phthalates **Route** Pre and postnatal exposure **Measure** Urine and Dust (units	Childhood asthma risk OR and 95%CI; Test unspecified, logistic regression unspecified		.	9

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the review = 9 **Included studies in the meta-analysis =** 9			unspecified) **Exposure time** Unspecified				
			Type DEP			No association between postnatal DEP and childhood asthma (OR 1.09 95%CI: 0.75 to 1.58; 4 studies, participants unspecified)	
			Type DnBP			No association between prenatal urinary DnBP levels and childhood asthma (OR 0.83, 95%CI: 0.12 to 5.77; 2 studies, participants unspecified) and postnatal urinary DnBP metabolites and childhood asthma (OR 0.72, 95%CI: 0.48 to 1.10; 5 studies, participants unspecified)	
			Type DIBP			No association between postnatal urinary DIBP metabolites and childhood asthma (OR 1.06, 95%CI: 0.67 to 1.66; 3 studies, participants unspecified)	
			Type BBzP			There is an association between prenatal urinary BBzP levels and increased risk in childhood asthma (OR 1.38, 95%CI: 1.09 to 1.75); 3 studies, participants unspecified) but not with postnatal urinary BBzP levels (OR 1.19, 95%CI: 0.79 to 1.80; 5 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type DEHP			No association between prenatal urinary DEHP levels and childhood asthma (OR 1.17, 95%CI: 0.90 to 1.52; 3 studies, participants unspecified) No association between prenatal (OR 1.11, 95%CI: 0.97 to 1.26; 3 studies, participants unspecified) and postnatal (OR 0.76, 95%CI: 0.32 to 1.79; 5 studies, participants unspecified) urinary DEHP metabolites and childhood asthma	
			Type DiNP			No association between postnatal DiNP and childhood asthma (OR 1.21, 95%CI: 0.48 to 3.05; 2 studies, participants unspecified)	
Radke 2020 - Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence - No COIs reported							
Last search Mar-19 **Study type** Prospective Cohort (n=25) Case control (n=1) However, different values provided in the review that do not align. These values have been taken from Table 2.	ROBINS-I tool. Four studies were classified as high confidence; ten studies were classified as medium confidence and three were classified as low confidence.	With one exception, all the included studies are birth cohorts with follow-up infancy to childhood (newborns to age 11 years), ranging in sample size between 135-657 children. The remaining study was a cohort of children admitted to the paediatric intensive care	**Type** di(2-ethylhexyl) phthalate (DEHP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** nmol/mL ng/mL µg/g	Mental Development Index (MDI) Beta-coefficient effect size (natural units of the Bayley Scales of Infant Development)	No association between DEHP exposure and MDI (b= -0.1, 95%CI: -0.8, 0.5); 7 studies, 2536 participants).	No association between DEHP exposure and MDI in: Girls β −0.5, 95%CI: −2.2 to 1.2; studies and participants unspecified Boys β 0.1, 95%CI: −1.2 to 1.3; studies and participants unspecified	8

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the review = 26 **Included studies in the meta-analysis =** 7		unit and followed at 4 years post-admission. All children included in meta-analysis were 4 years of age or younger. N = 5,573	**Exposure time** Unspecified				
			Type di(2-ethylhexyl) phthalate (DEHP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** nmol/mL ng/mL µg/g	Psychomotor Development Index (PDI) Beta-coefficient effect size (natural units (natural units of the Bayley Scales of Infant Development)	No association between DEHP exposure and PDI (b= -0.4, 95%CI: -1.4, 0.7); 6 studies, 2106 participants).	No association between DEHP exposure and PDI in: Girls β 0.2, 95%CI: −0.8 to 1.3; studies and participants unspecified Boys β 0.1, 95%CI: −1.1 to 1.3; studies and participants unspecified	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Exposure time Unspecified				
			Type butyl benzyl phthalate (BBP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified	Mental Development Index (MDI) Beta-coefficient effect size (natural units of the Bayley Scales of Infant Development)	No association between BBP exposure and MDI (b= -0.1, 95%CI: -0.8, 0.5); 6 studies, 2119 participants).	No association between BBP exposure and MDI in: Girls β −0.7, 95%CI: −1.6 to 0.2; studies and participants unspecified Boys β 0.8, 95%CI: −0.3 to 1.9; studies and participants unspecified	
			Type butyl benzyl phthalate (BBP) **Route** Unspecified, but exposure level measured in urine or plasma	Psychomotor Development Index (PDI) Beta-coefficient effect size (natural units (natural units of the Bayley Scales of Infant Development)	No association between BBP exposure and PDI (b= -0.7, 95%CI: -1.4, 0.0); 6 studies, 2119 participants).	There is an association between BBP exposure and PDI in girls β −1.6, 95%CI: −2.6 to −0.6; studies and participants unspecified No association between BBP exposure and MDI in boys β 0.8, 95%CI: −0.2 to 1.9; studies and participants unspecified	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified				
			Type dibutyl phthalate (DBP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified	Mental Development Index (MDI) Beta-coefficient effect size (natural units of the Bayley Scales of Infant Development)	No association between DBP exposure and MDI (b= -0.2, 95%CI: -0.7, 0.4); 7 studies, 2536 participants).	No association between DBP exposure and MDI in: Girls β −0.8, 95%CI: −2.2 to 0.6; studies and participants unspecified Boys β 0.4, 95%CI: −0.8 to 1.6; studies and participants unspecified	
			Type dibutyl phthalate (DBP) **Route**	Psychomotor Development Index (PDI) Beta-coefficient effect size (natural units (natural units of the Bayley Scales of Infant Development)	No association between DBP exposure and PDI (b= -0.5, 95%CI: -1.5, 0.5); 6 studies, 2119 participants).	No association between DBP exposure and PDI in: Girls β −0.7, 95%CI: −1.8 to 0.3; studies and participants unspecified	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified			Boys β 0.0, 95%CI: −1.7 to 1.8; studies and participants unspecified	
			Type Diethyl phthalate (DEP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified	Mental Development Index (MDI) Beta-coefficient effect size (natural units of the Bayley Scales of Infant Development)	No association between DEP exposure and MDI (b=0.3, 95%CI: -0.3, 0.9); 5 studies, 1791 participants).	No association between DEP exposure and MDI in: Girls β 0.3, 95%CI: −0.8 to 1.4; studies and participants unspecified Boys β 0.0, 95%CI: −1.1 to 1.2; studies and participants unspecified	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Diethyl phthalate (DEP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified	Psychomotor Development Index (PDI) Beta-coefficient effect size (natural units (natural units of the Bayley Scales of Infant Development)	No association between DEP exposure and PDI (b= 0.0, 95%CI: -0.6, 0.6); 4 studies, 1361 participants).	No association between DEP exposure and PDI in: Girls β 0.4, 95%CI: −0.5 to 1.4; studies and participants unspecified Boys β 0.4, 95%CI: −0.5 to 1.4; studies and participants unspecified	
			Type diisobutyl phthalate (DIBP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study	Mental Development Index (MDI) Beta-coefficient effect size (natural units of the Bayley Scales of Infant Development)	No association between DIBP exposure and MDI (b= -0.1, 95%CI: -0.6, 0.4); 4 studies, 1361 participants).	No association between DIBP exposure and MDI in: Girls β −0.8, 95%CI: −2.1 to 0.6; studies and participants unspecified Boys β 0.8, 95%CI: −0.3 to 1.8; studies and participants unspecified	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Measure ng/mL µg/g **Exposure time** Unspecified				
			Type diisobutyl phthalate (DIBP) **Route** Unspecified, but exposure level measured in urine or plasma Varies between included study **Measure** ng/mL µg/g **Exposure time** Unspecified	Psychomotor Development Index (PDI) Beta-coefficient effect size (natural units (natural units of the Bayley Scales of Infant Development)	No association between DIBP exposure and PDI (b= -0.4, 95%CI: -1.1, 0.3); 5 studies, 1689 participants).	No association between DIBP exposure and PDI in: Girls β −0.5, 95%CI: −1.9 to 0.9; studies and participants unspecified Boys β −0.1, 95%CI: −1.4 to 1.2; studies and participants unspecified	
Ribeiro 2019 - Association between the exposure to phthalates and adiposity: A meta-analysis in children and adults - No COIs reported (Funding body acknowledged)							
Last search Aug-19 **Study types**	The STROBE checklist was used to evaluate the methodological quality of the included studies. In	Children and adults, no apparent age limiters used. Adults (n=16075)	**Type** Mono-butyl phthalate (MBP) **Route**	BMI Beta-coefficient effect size (transformed z-score)	No association between exposure to MBP and BMI **in children** (b= 0.00, 95%CI: -0.11, 0.12; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Cross sectional (n=25) Prospective cohort study (n=1) Case control (n=3) **Included studies in the review =** 29 **Included studies in the meta-analysis =** 8	children the paper with the lowest quality level was Shoaff with 14.8/22points, but for adults we found 3 papers with low quality: Peck (11.7/22), Milosevic (12.7/22) and Stojanoska (12.9/22). However, since all are above 11, it was considered as acceptable methodological quality, and they were eligible for the systematic review and meta-analysis. The three papers with the lowest quality score were included in meta-analysis but they had the lowest weight in the overall estimate.	Children (n=10893) N = 26,968	Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time** Combined post and prenatal exposure			In general, studies presented positive associations, both in children and adults, however, most of the studies did not reach statistical significance. Meta-analyses were performed for seven compounds, seven for BMI, five for WC and four for obesity (categorical BMI). Regarding adults, summary estimates indicate a negative association for MEHP and a positive association for MEP and MECPP but only for MECPP statistical significance was reached. In children, overall estimates were null for MBP; negative for MiBP, MbzP and MCPP and positive for MEP but none showed a statistically significant association. The inconsistency in the results and the fact that most of them reported associations that were not statistically significantly require some putative explanations, such as: 1) the study design and the short-half-life of phthalates, 2) the lipophilic capacity of phthalates, 3) gender and age differences.	
				Waist Circumference Beta-coefficient effect size (cm)	No association between exposure to MBP and waist circumference **in children** (b=0.13cm, 95%CI: -0.86, 1.13; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-(2-ethylhexyl) phthalate (MEHP) **Route** Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time** Combined post and prenatal exposure	BMI Beta-coefficient effect size (kg/m2)	No association between exposure to MEHP and BMI **in adults** (b= -0.05kg/m2, 95%CI: -0.15, 0.05; 3 studies, 1298 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the child population	
				Obesity (categorised using BMI) OR and (95% CI) No logistic regression	No association between exposure to MEHP and obesity **in adults** (OR = 0.91, 95%CI: 0.66, 1.27; 3 studies, 2432+ participants).	Children and adult data were split from the outset and no test for subgroup differences was performed.	
				Waist Circumference Beta-coefficient effect size (cm)	Positive association between exposure to MEHP and waist circumference (b= 0.58cm, 95%CI: 0.55, 0.62cm; 3 studies,2435 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the child population	
				Obesity (categorised using BMI) OR and (95% CI) No logistic regression	No association between exposure to MEHP and obesity **in children** (OR = 0.78, 95%CI: 0.47, 1.29; 3 studies, 773+ participants).	Children and adult data were split from the outset and no test for subgroup differences was performed.	
			Type Monoethyl phthalate (MEP) **Route** Unspecified **Measure**	BMI Beta-coefficient effect size (kg/m2)	No association between exposure to MEP and BMI **in adults** (b=0.05kg/m2, 95%CI: -0.06, 0.16; 4 studies, 512 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the child population	
				Obesity (categorised using BMI)	No association between exposure to MEP and Obesity **in adults** (OR =	Children and adult data were split from the outset and no test for subgroup differences was	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified only regression coefficients reported **Exposure time** Combined post and prenatal exposure	OR and (95% CI) No logistic regression	1.22, 95%CI: 0.94, 1.5; 4 studies, 3701+ participants).	performed. There was no meta-analysis performed on this outcome in the child population	
				BMI Beta-coefficient effect size (transformed z-score)	No association between exposure to MEP and BMI score **in children** (b= 0.02, 95%CI: -0.06, 0.10; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	
				Waist Circumference Beta-coefficient effect size (cm)	No association between exposure to MEP and waist circumference **in children** (b= 0.47cm, 95%CI: -0.23, 1.17; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	
			Type Mono-iso-butyl phthalate (MiBP) **Route** Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time** Combined post and prenatal exposure	BMI Beta-coefficient effect size (transformed z-score)	No association between exposure to MiBP and BMI **in children** (b= -0.01, 95%CI: -0.10, 0.07; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	
				Waist Circumference Beta-coefficient effect size (cm)	No association between exposure to MiBP and Waist Circumference **in children** (b=-0.62cm, 95%CI: -1.6, 0.37; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-benzyl phthalate (MBzP) **Route** Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time** Combined post and prenatal exposure	BMI Beta-coefficient effect size (transformed z-score)	No association between MBzP and BMI **in children** (b=-0.06, 95%CI: -0.15, 0.04; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	
				Waist Circumference Beta-coefficient effect size (cm)	No association between MBzP and Waist circumference **in children** (b=-0.35cm, 95%CI: -1.16, 0.48cm; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	
			Type Mono-(3-carboxypropyl) phthalate (MCPP) **Route** Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time**	BMI Beta-coefficient effect size (transformed z-score)	No association between MCPP and BMI **in children** (b=-0.12, 95%CI: -0.24, 0; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	
				Waist Circumference Beta-coefficient effect size (cm)	No association between MCPP and waist circumference **in children** (b=-0.73, 95%CI -1.74, 0.28; 3 studies, 820 participants).	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the adult population	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Combined post and prenatal exposure				
			Type Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) **Route** Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time** Combined post and prenatal exposure	Obesity (categorised using BMI) OR and (95% CI) No logistic regression	Positive association between exposure to MECPP and odds of obesity **in adults** (OR = 1.67, 95%CI: 1.3,2.16; 3 studies, 3599+ participants)	Children and adult data were split from the outset and no test for subgroup differences was performed. There was no meta-analysis performed on this outcome in the children population	
Shoshtari-Yeganeh 2019 - Systematic review and meta-analysis on the association between phthalates exposure and insulin resistance - No COI reported							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Jan-18 **Study types** Cross sectional **Included studies in the review =** 8 **Included studies in the meta-analysis =** 8	The authors have stated that they used assessed the quality of all included studies using the "Cochrane checklist" the results of this assessment are not provided in the manuscript or as supplementary material.	Participants aged from 12-79 years in the included studies. 3 studies from North American, 4 studies from Asia, 1 study from Europe N = 13,808	**Type** Any type of phthalate **Route** Unspecified **Measure** Unspecified only regression coefficients reported **Exposure time** Unspecified	Homeostatic model assessment - Insulin Resistance (HOMA-IR) Beta-coefficient effect size (transformed z-score)		Subgrouping occurred based on phthalate compound. Positive associations were found for insulin resistance and the following compounds: Mono-butyl phthalate (MBP) (b=0.13, 95%CI 0.07,0.19; 6216 participants) Mono-benzyl phthalate (MBzP) (b=0.05, 95CI: 0.01, 0.10; 5 studies, 11439 participants) Mono-(3-carboxypropyl) phthalate (MCCP) (b=0.15, 95%CI: 0.03,0.28; 3 studies, 1908 participants) Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) (b=0.16, 95%CI: 0.05, 0.27; 2 studies, 1122 participants) Mono-(2-ethylhexyl) phthalate (MEHP) (b=0.08, 95%CI: 0.03, 0.12; 7 studies,13248 participants) Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) (b=0.10, 95%CI: 0.01, 0.19; 5 studies, 7795 participants) Mono-iso-butyl phthalate (MiBP) (b=0.10, 95%CI: 0.03, 0.17; 4 studies, 6569 participants) MnBP (Abbreviation not explained) (b= 0.13, 95%CI: 0.06, 0.2; 3 studies,5783 participants) T.DEHP (Abbreviation not explained) (b=0.26, 95%CI 0.15, 0.38; 2 studies 4997 participants). No association were found for insulin resistance and the following	4

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						compounds: Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) (b=0.09 95%CI -0.01, 0.18; 5 studies, 7795 participants) Monoethyl phthalate (MEP) (b=0.02, 95%CI: -0.04, 0.08; 6 studies, 12455 participants) Mono-methyl phthalate (MMP) (b=0.02, 95%CI: -0.06, 0.11; 3 studies, 2158 participants)	
Song 2016- Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. No COI declared.							
Last search Mar-14 **Study type** cross sectional (n=41) cohort (n=8) **Included studies in the review =** 49 **Included studies in the meta-analysis =** 7	NR	adults N = 55,774	**Type** Phthalates **Route** NR **Measure** Urinary (ng/mL) **Exposure time** NR	Type 2 diabetes RR and 95%CI; Highest versus Lowest exposure categories; MEP > 17.5 ng/mL) with lowest (MEP ≤7.2 ng/mL)	No association between phthalates and type 2 diabetes (RR=1.48, 95%CI: 0.98, 2.25; 4 studies, 5307 participants).	Higher concentrations of monoethyl phthalate (MEP) was associated with increased risk of type 2 diabetes (RR=1.39, 95%CI: 0.55, 3.48; 4 studies and participants NR). Higher concentrations of Mono-iso-butyl phthalate (MiBP) was associated with increased risk of type 2 diabetes (RR=1.90, 95%CI: 1.17, 3.09; no. studies and participants NR) The present systematic review from different populations (including white, black Hispanic, Asian and Native American) indicates that serum concentrations of persistent endocrine disrupting-chemicals and urinary concentrations of non-	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						persistent endocrine-chemicals may significantly affect type 2 diabetes risk.	
				Fasting glucose		Mean difference between highest and lowest concentration 0.98 mg/dL (95% CI 0.00–1.97 mg); 3 studies, 3926 participants	
				Homeostatic model assessment - Insulin Resistance (HOMA-IR)		Pooled WMD of all metabolites 0.71 (95% CI 0.30–1.12); 4 studies, 5396 participants	
Wen 2015 - Association of PAEs with Precocious Puberty in Children: A Systematic Review and Meta-Analysis - No COIs declared							
Last search Mar-15 **Study types** Case control **Included studies in the review =** 14 **Included studies in the meta-analysis =** 14	Newcastle Ottawa Scale. Among 14 included studies, except for seven studies were considered as moderate risk of bias scores of 5 and 6), the others were assessed as low risk of bias (scores of 7 and 8) (Table 2). All studies had adequate case and controls definition, and exposure assessment. No standard method was adopted in sampling, which would affect the representativeness	Female children aged 0.5-11.3 years acted as cases (precocious puberty) and compared against female children aged 2.2-12 years). N = 2,012	**Type** di(2-ethylhexyl) phthalate (DEHP) **Route** Unspecified **Measure** Concentration in the serum and urine (combined for MA) **Exposure time** Unspecified	Prevalence precocious puberty (PP) (the appearance of secondary sex characteristics before the age of eight years in girls). OR and 95%CI	There was a positive association between serum DEHP and the odds of PP (OR=4.09, 95%CI:2.3, 7.3; 7 studies, 1390 participants).	Subgrouping was conducted based on country of the study. Positive association were found for studies coming from China (OR= 3.58, 95%CI:1.97, 6.49; 6 studies, 1324 participants), and Puerto Rico (OR=9.37, 95%CI:3.01, 29.19 1 study, 76 participants). Our findings suggested that a potential statistical association between phthalate exposure and PP, particularly, the exposure of DEHP and DBP might be a potential risk for girls with PP. No associations were identified between PP with MEHP, MBP, MEOHP, MECPP, MMP, MBzP or MEP. Nevertheless, it would be not appropriate to claim that those phthalate metabolites had no role in PP progress given the moderate strength of the present study.	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
	of the cases. The controls were recruited from the same community as cases in only five studies. Seven just matched case and control by age without consideration of other confounding factors.			Serum concentration (mean and standard deviation) SMD and 95%CI	Serum concentration of DEHP was significantly greater in the PP group compared to the control group (SMD=1.73, 95%: 0.54, 2.91; 7 studies, 1564 participants).	Subgrouping was conducted based on country of the study. Greater serum concentrations of DEHP were found in the PP group compared to the control group for the studies from China (SMD=2.13, 95%0.86, 3.4; 6 studies, 1324 participants). However, for the study from Korea, the serum concentration of DEHP was significantly greater in the control group compared to the PP group (SMD=-0.7, 95%CI: -0.97, -0.43; 1 study; 240 participants).	
			Type dibutyl phthalate (DBP) **Route** Unspecified **Measure** Concentration in the blood and urine (combined for MA) **Exposure time** Unspecified	Prevalence precocious puberty (PP) (the appearance of secondary sex characteristics before the age of eight years in girls). OR and 95%CI	There was no association between serum DBP concentration and the odds of PP (OR=3.26, 95%CI:0.69, 15.42; 5 studies, 1159 participants).	Subgrouping was conducted based on country of the study. No associations were found for studies coming from China (OR= 2.74, 95%CI:0.51, 14.79, 4 studies, 1083), or Puerto Rico (OR=3.26, 95%CI: 0.69, 15.42 1 study, 76 participants).	
				Serum concentration (mean and standard deviation) SMD and 95%CI	Serum concentration of DBP was significantly greater in the PP group compared to the control group (SMD=4.31, 95%CI:2.67, 5.95; 5 studies, 1323 participants).	Subgrouping was conducted based on country of the study. For the studies from China, a greater serum concentration of DBP was found in the PP group compared to the control group (SMD=6.33, 95%CI: 4.09, 8.57; 4 studies, 1083 participants). For the studies from Korea, there was no difference in serum DBP was found between the PP and control group (SMD=-0.23, 95%CI: -0.49, 0.03; 1 study, 240 participants).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type Mono-ethylhexyl phthalate (MEHP) **Route** Unspecified **Measure** Concentration in the blood and urine (combined for MA) **Exposure time** Unspecified	Serum concentration (mean and standard deviation) SMD and 95%CI	There was no association in serum MEHP concentration between the PP and the control group (SMD=0.18, 95%CI: -0.99, 1.36; 4 studies, 895 participants).	Subgrouping was conducted based on country of the study. For the studies from China, there was no difference in serum MEHP concentrations between the groups (SMD=1.38, 95%CI:-1.35,4.11; 2 studies, 599 participants). However, for both studies from the USA and Korea, serum concentrations of MEHP were decreased in the PP group compared to the control group (USA: SMD=-1.31, 95%CI: -1.9, -0.73; 1 study, 56 participants) (Korea: SMD= -0.71, 95%CI: -0.98, -0.44; 1 study, 240 participants).	
				Urinary concentration SMD and 95%CI	There was no association between urinary MEHP concentration and odds of PP (SMD= -0.44, 95%CI: -1.18, 0.29; 3 studies, participants unspecified); Chinese studies only		
			Type Mono-butyl phthalate (MBP) **Route** Unspecified	Serum concentration (mean and standard deviation) SMD and 95%CI	There was no association in serum MBP concentration the PP and the control group (SMD=0.01, 95%CI: -0.3, 0.27; 3 studies, 784 participants)	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Measure Concentration in the blood and urine (combined for MA) **Exposure time** Unspecified	Urinary concentration SMD and 95%CI	There was no association between urinary MBP concentration and odds of PP (SMD= -0.11, 95%CI: -0.48, 0.26; 3 studies, participants unspecified); Chinese and Danish studies	There was no association between urinary MBP concentration and the odds of PP in a subgroup of Chinese studies (SMD= -0.21, 95%CI: -0.87, 0.46; 2 studies, participants unspecified)	
			Type MMP **Route** Unspecified **Measure** Concentration in the blood and urine (combined for MA) **Exposure time** Unspecified	Urinary concentration SMD and 95%CI	There was no association between urinary MMP concentration and the odds of PP (SMD= 0.27, 95%CI: -0.21, 0.76; 3 studies, participants unspecified); Chinese studies only		
			Type MBzP **Route** Unspecified **Measure** Concentration in the blood and urine (combined	Urinary concentration SMD and 95%CI	There was no association between urinary MBzP concentration and the odds of PP (SMD= 0.00, 95%CI: -0.43, 0.43; 4 studies, participants unspecified); Chinese and Danish studies	There was no association between urinary MBzP concentration and the odds of PP in a subgroup of Chinese studies (SMD= -0.004, 95%CI: -0.68, 0.59; 3 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			for MA) **Exposure time** Unspecified				
			Type MEP **Route** Unspecified **Measure** Concentration in the blood and urine (combined for MA) **Exposure time** Unspecified	Urinary concentration SMD and 95%CI	There was no association between urinary MEP concentration and the odds of PPPP (SMD= 0.73, 95%CI: -0.40, 1.86]; 3 studies, participants unspecified); Chinese and Danish studies	There was no association between MEP concentration between PP and the control group in a subgroup of Chinese studies (SMD= 0.16, 95%CI: -0.19, 0.50; 2 studies, participants unspecified)	
Wu 2020b - Association between phthalate exposure and asthma risk: A meta-analysis of observational studies - No COI declared							
Last search Jan-20 **Study types** Case control (n=2) Cohort (n=7) Cross sectional (n=5) **Included studies in the review =** 14	Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, and an adapted form of the NOS cohort scale for cross-sectional studies. The estimated quality ranged from 7 to 9 in the cohort studies, 7–8 in the case-control	Men and women of any age, the only unique characteristic was that phthalate metabolites had to measured using urine biomarkers *Note* Authors only provide the number of cases and not total participants in the studies.	**Type** MBzP (Mono-benzyl phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped	Asthma OR and 95%CI	There was a positive association between exposure to MBzP and asthma risk (OR=1.17, 95%CI: 1.06, 1.28; 15 studies)	The first subgroup was based on age. In children there was a positive association between MBzP exposure and asthma risk (OR=1.17, 95%CI: 1.05, 1.29; 12 studies). No association was found for adults (OR=1.17, 95%CI:0.94, 1.46; 3 studies). The second subgroup analysis was conducted based on location, positive associations were found for studies from Europe (OR=1.16, 95%CI:1.02, 1.32; 5 studies) and North American (OR=1.23, 95%CI:1.05, 1.44; 7 studies), but no	5

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the meta-analysis = 14	studies, and 6–8 in the cross-sectional studies, which indicated moderate to high quality in the included studies.	N (cases) = 1731 participants numbers are all unspecified for the accompanying meta-analyses.	based on prenatal or postnatal exposure			association was found for studies from Asia (OR=1.08, 95%CI:0.37,3.19; 4 studies). The third subgroup analysis was conducted based exposure time. A positive association was identified for postnatal exposure (OR=1.17, 95%CI:1.03, 1.33; 10 studies) but no association was identified for prenatal exposure (OR=1.15, 95%CI 1.01, 1.32, 6 studies). The fourth subgroup analysis was conducted based on gender. No associations were found for either male (OR=1.19, 95%CI 0.99,1.41; 5 studies) or female (OR=1.04, 95%CI: 0.77,1.42; 4 studies).	
			Type MnBP (Mono-n-butyl phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between exposure to MnBP and asthma risk (OR=1.03, 95%CI:0.85, 1.24; 11 studies)	The first subgroup analysis was conducted based on age. There was no association for children (OR=0.97, 95%CI:0.85, 1.09; 8 studies) or adults (OR=1.35, 95%CI:0.93, 1.96; 3 studies). The second subgroup analysis was conducted based on study location. There was no association for studies from Europe (OR=0.98,95%CI:0.74,1.29; 4 studies) and North America (OR=1.09, 95%CI: 0.89, 1.33; 7 studies). The third subgroup analysis was conducted based on exposure time. There was no association for postnatal (OR=0.95, 95%CI:0.78, 1.16; 7 studies) or prenatal exposure (OR=1.07, 95%CI:0.8, 1.42; 4	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						studies). The fourth subgroup analysis was conducted based on gender. No associations were found for males (OR=0.98, 95%CI:0.82, 1.16; 4 studies) or females (OR=0.84, 95%CI:0.56, 1.25; 3 studies).	
			Type MiBP (Mono-iso-butyl phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between exposure to MiBP and asthma risk (OR=1.05, 95%CI0.93, 1.19; 10 studies)	The first subgroup analysis was conducted based on age. There was no association for children (OR=1.04, 95%CI:0.91, 1.19; 7 studies) or adults (OR=1.11, 95%CI: 0.84, 1.47; 3 studies). The second subgroup was conducted based on study location. There was no association for studies from Europe (OR=1.05, 95%CI:0.90, 1.23; 4 studies) or North America (OR=1.06, 95%CI:0.87, 1.29; 6 studies). The third subgroup was conducted based on exposure time. There was no association between postnatal (OR=1.06, 95%CI:0.89,1.27; 7 studies) or prenatal exposure (OR=1.05, 95%CI: 0.88, 1.24; 3 studies). The fourth subgroup was conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						based on gender. There was no association between males (OR=1.08, 95%CI:0.88, 1.33; 4 studies) or females (OR=0.81, 95%CI:0.51, 1.29; 3 studies).	
			Type MEP (Monoethyl phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between exposure to MEP and asthma risk (OR=1.03, 95%CI: 0.96, 1.12; 13 studies)	The first subgroup analysis was conducted based on age. There was no association for children (OR=1.02, 95%CI:0.94, 1.11; 10 studies) or adults (OR=1.11, 95%CI:0.89, 1.39; 3 studies). The second subgroup analysis was conducted based location. There was no association for studies coming from Europe (OR=1.06, 95%CI:0.9, 1.24; 4 studies), North America (OR=1.03, 95%CI:0.93, 1.14; 7 studies) or Asia (OR=1.03, 95%CI: 0.86, 1.25; 3 studies). The third subgroup analysis was conducted based on exposure time. No association was found for postnatal (OR=1.08, 95%CI:0.95,1.23; 9 studies) or prenatal exposure (OR=1.02, 95%ci:0.93, 1.12; 5	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						studies). The fourth subgroup analysis was conducted based on gender. No association was found for males (OR=1.12, 95%CI 0.97. 1.31; 5 studies) or females (OR=0.94, 95%CI:0.58, 1.53; 3 studies).	
			Type MEHP (Mono-2-ethylhexyl phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or	Asthma OR and 95%CI	There was no association between exposure to MEHP and asthma risk (OR=1.04, 95%CI:0.89, 1.20;5 studies) in children	The first subgroup analysis was conducted based on location. No association was found for studies coming from Europe (OR=1.04, 95%CI:0.89, 1.21; 3 studies) or from Asia (OR=1.14, 95%CI:0.48, 2.71; 3 studies). The second subgroup analysis was conducted based on exposure time. These was no association for postnatal (OR=0.78, 95%CI:0.41, 1.48; 3 studies) or prenatal exposure (OR=1.06, 95%CI0.91, 1.23; 3 studies). The third subgroup analysis was conducted based on gender. No association was found for males (OR=0.99, 95%CI: 0.81, 1.19; 2	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			postnatal exposure			studies) or females (OR=1.04, 95%CI:0.10, 10.62; 1 study).	
			Type MEHHP (Mono-(2-ethyl-5-hydroxyhexul) phthala) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was a positive association between MEHHP exposure and asthmas risk (OR=1.13, 95%CI: 1.03, 1.24; 5 studies) in children.	The first subgroup analysis was conducted based on location. No association was found for studies from Europe (OR=1.11, 95%CI:0.94, 1.31; 3 studies) or for North America (OR=1.03, 95%CI:0.89, 1.20; 1 study). A positive association was found for studies from Asia (OR=1.33, 95%CI:1.11, 1.60; 1 study). The second subgroup analysis was conducted based on exposure time. A positive association was found for postnatal exposure (OR=1.30, 95%CI:1.09, 1.56; 2 studies), no association was found for prenatal exposure (OR=1.07, 95%CI:0.96, 1.20; 3 studies).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MEOHP (Mono-(2-ethyl-5-oxohexyl) phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between MEOHP exposure and asthma risk (OR=1.09, 95%CI:0.77, 1.53; 3 studies) in children.	Subgroup was conducted based on exposure time. No association was found for postnatal (OR=0.5, 95%CI:0.23, 1.31; 1 study) or prenatal exposure (OR=1.19, 95%CI: 0.88, 1.61; 2 studies).	
			Type MECPP (Mono-(2-ethyl-5-carboxypentyl) phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time**	Asthma OR and 95%CI	There was no association between MECPP exposure and asthma risk (OR=1.2, 95%CI: 1.0, 1.42; 3 studies) in children.	Subgroup analysis was conducted based on exposure time. There was no association for postnatal exposure (OR=0.59, 95%CI: 0.25, 1.41; 1 study). There was a positive association for prenatal exposure (OR=1.23, 95%CI: 1.03, 1.47; 2 studies).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Subgrouped based on prenatal or postnatal exposure				
			Type ΣDEHP ((Sum of all) Di-2-ethylhexyl phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between ΣDEHP exposure and asthma risk (OR=0.99, 95%CI:0.8, 1.22; 11 studies).	The first subgroup analysis was conducted based on age. No association was found for children (OR=0.87, 95%CI:0.67, 1.14; 8 studies) or adults (OR=1.27, 95%CI:0.99, 1.61; 3 studies). The second subgroup was conducted based on location. There was no association for studies from Europe (OR=1.16, 95%CI:1.0,1.34; 4 studies), North America, (OR=0.81, 95%CI:0.57, 1.17; 6 studies) and Asia (OR=1.89l, 95%CI:0.79, 4.53; 2 studies). No association for both postnatal (OR= 1.04, 95%CI: 0.71, 1.54; 7 studies) and prenatal exposure (OR= 1.08, 95%CI:0.92, 1.26; 5 studies)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MCNP (Mono-(carboxynonyl) phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between MCNP and asthma risk (OR=1.10, 95%CI:0.98, 1.24; 7 studies).	The first subgroup was conducted based on age. There was no association for children (OR=1.15, 95%CI:1,1.31; 5 studies) or adults (OR=1.0, 95%CI:0.8, 1.24; 2 studies). The second subgroup analysis was conducted based on location. A positive association was found for studies from Europe (OR=1.18, 95%CI:1.02,1.37; 2 studies). No association was found for studies from North America (OR=0.99, 95%CI:0.82, 1.19; 5 studies). The third subgroup analysis was conducted based on exposure time. There was no association for postnatal (OR=1.07, 95%CI:0.92, 1.26; 5 studies) or prenatal exposure (OR=1.14, 95%CI:0.96, 1.34; 2 studies). The fourth subgroup analysis was conducted based on gender. There was no association for males (OR=1.12, 95%CIL0.95, 1.33; 3 studies) or females (OR=1.02, 95%CI:0.73, 1.44; 2 studies).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MCPP (Mono-(3-carboxypropyl) phthalate) **Route** Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure	Asthma OR and 95%CI	There was no association between MCPP exposure and asthma risk (OR=1.04, 95%CI:0.91, 1.19; 8 studies).	The first subgroup analysis was conducted based on age. No association was found for children (OR=0.97, 95%CI:0.83, 1.13; 6 studies) or adults (OR=1.32, 95%CI:1.0, 1.75; 2 studies). The second subgroup analysis was conducted based on location. There was no association found for studies from Europe (OR=0.96, 95%CI:0.8, 1.15; 2 studies) or North America (OR=1.14, 95%CI: 0.94, 1.4; 6 studies). The third subgroup analysis was conducted based on exposure time. There was no association for postnatal (OR=1.09, 95%CI:0.91, 1.32; 5 studies) or prenatal exposure (OR=0.99, 95%CI: 0.81, 1.2; 3 studies). The fourth subgroup analysis was conducted based on gender. There was no association for males (OR=0.93, 95%CI:0.76, 1.14; 4 studies) or females (OR=1.36, 95%CI:0.98, 1.88; 3 studies).	
			Type MCOP (Monocarboxy-isooctyl phthalate) **Route**	Asthma OR and 95%CI	There was no association between MCOP exposure and asthma risk (OR=1.13, 95%CI:0.99, 1.28; 5 studies).	The first subgroup analysis was conducted based on age. There was a positive association for children (OR=1.19, 95%CI: 1.02, 1.37; 4 studies), but no association for adults (OR=0.96, 95%CI:0.73, 1.25; 1 study). The second subgroup analysis was conducted based on study location. There was no association for studies	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Unspecified **Measure** Concentration in urine (µg/L) **Exposure time** Subgrouped based on prenatal or postnatal exposure			from Europe (OR=1.13, 95%CI:0.95, 1.34; 2 studies) or North America (OR=1.10, 95%CI: 0.74, 1.64; 3 studies). The third subgroup analysis was conducted based on exposure time. There was no association for postnatal (OR=1.08, 95%CI:0.9, 1.31; 3 studies) or prenatal exposure (OR=1.17, 95%CI: 0.98, 1.41; 2 studies.	
Zhang 2020- Associations between phthalate exposure and risk of spontaneous pregnancy loss: A systematic review and meta-analysis- No COI declared							
Last search Apr-20 **Study types** n=4 was case control; n= 4 were prospective cohort studies **Included studies in the review =** 8 **Included studies in the meta-analysis =** 8	Newcastle-Ottawa Scale. All studies scored between 7-9 and deemed to be high quality by the authors.	Reproductive age women un-derwent spontaneous pregnancy loss). Reproductive loss occurred from conception to 27 weeks, however, n=3 studies were not limited by gestational week. Control group (defined as: reproductive age women without pregnancy loss) N = 4713 (651 cases and 4063 controls)	**Type** MMP **Route** In utero **Measure** Urinary phthalates levels (Measurements noted: µg/g, ng/mL, µg/L) **Exposure time** During pregnancy; non-specific about mothers' exposure.	Spontaneous pregnancy loss 0R with 95% CI	No relationship between MMP and spontaneous pregnancy loss with reproductive women OR: 1.54 (95% 0.91-2.60, 5 studies, participants unknown)	No subgroup analysis Findings indicate that phthalate exposure might be a risk factor for spontaneous pregnancy loss. Given indirect estimate of phthalate exposure by evaluating its metabolite levels, our results should be interpreted with caution.	8

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MBP **Route** In utero **Measure** Urinary phthalates levels (Measurements noted: µg/g, ng/mL, µg/L) **Exposure time** During pregnancy; non-specific about mothers' exposure.	Spontaneous pregnancy loss 0R with 95% CI	Exposure to MBP was positively significant associated with spontaneous pregnancy loss with reproductive women OR:1.34 (95%1.04-1.72 7 studies, participants unknown)	Subgroup analysis was conducted according to the study design. There was no relationship for cohort studies OR: 1.34 (95% CI: 0.82, 2.19, 4 studies, participants unknown) and case-control studies OR: 1.54 (95%CI:.084, 2.83, 3 studies, participants unknown). Pooled OR for cohort and case-controlled studies was OR: 1.40 (95%ci:.99, 1.96, 7 studies, participants unknown).	
			Type MEP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time** During pregnancy; non-	Spontaneous pregnancy loss 0R with 95% CI	No relationship between MEP and spontaneous pregnancy loss with reproductive women OR: 1.30(95% 0.84-2.03 7 studies, participants unknown)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			specific about mothers' exposure.				
			Type MiBP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time** During pregnancy; non-specific about mothers' exposure.	Spontaneous pregnancy loss 0R with 95% CI	No relationship between MiBP and spontaneous pregnancy loss with reproductive women OR: 1.31(95% 0.69-2.49 4 studies, participants unknown)	No subgroup analysis	
			Type MBzP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time**	Spontaneous pregnancy loss 0R with 95% CI	No relationship between MBzP and spontaneous pregnancy loss with reproductive women OR: 1.10 (95% 0.74-1.64 4 studies, participants unknown)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			During pregnancy; non-specific about mothers' exposure.				
			Type MEHP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time** During pregnancy; non-specific about mothers' exposure.	Spontaneous pregnancy loss 0R with 95% CI	Exposure to MEHP was positively significant associated with spontaneous pregnancy loss with reproductive women OR:1.57 (95% 1.29-1.90 7 studies, participants unknown)	Subgroup analysis was conducted according to the study design. There was a positive association with both cohort studies OR: 1.50 (95% CI: 1.10-2.04, 4 studies, participants unknown) and case-control studies OR: 1.61 (95% Cl:1.26-2.06, 3 studies, participants unknown). Pooled OR for cohort and case-control studies was OR: 1.57 (95%ci: 1.29, 1.90, 7 studies, participants unknown).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type MEHHP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time** During pregnancy; non-specific about mothers' exposure.	Spontaneous pregnancy loss 0R with 95% CI	Exposure to MEHHP was positively significant associated with spontaneous pregnancy loss with reproductive women OR:1.59 (95% 1.23-2.07 6 studies, participants unknown)	Subgroup analysis was conducted according to the study design. There was a positive association for cohort studies OR: 1.85 (95% CI: 1.33-2.58, 4 studies, participants unknown), but no associations for case-control studies OR: 1.24 (95% CI:0.82, 1.90, 2 studies, participants unknown. Pooled OR for cohort and case-control studies was positively associated OR:1.59 (95%CI: 1.23, 2.07, 6 studies, participants unknown).	
			Type MEOHP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time** During pregnancy; non-specific about	Spontaneous pregnancy loss 0R with 95% CI	Exposure to MEOHP was positively significant associated with spontaneous pregnancy loss with reproductive women OR:1.47 (95% 1.15-1.89 6 studies, participants unknown)	Subgroup analysis was conducted according to the study design. There was a positive association for cohort studies OR: 1.73 (95%CI: 1.24, 2.42, 4 studies, participants unknown). There was no association with case-control studies OR:1.19 (95%CI: 0.81, 1.74, 2 studies, participants unknown). The pooled OR of cohort and case-control studies was positively associated OR: 1.47 (95%ci:1.15, 1.89, 6 studies, participants unknown).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			mothers' exposure.				
			Type MECCP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted) **Exposure time** During pregnancy; non-specific about mothers' exposure.	Spontaneous pregnancy loss 0R with 95% CI	No relationship between MECCP and spontaneous pregnancy loss with reproductive women OR: 1.08 (95% 0.80-1.46 3 studies, participants unknown)	Insufficient studies for subgroup analysis	
			Type ΣDEHP **Route** In utero **Measure** Urinary phthalates levels (Measurements not noted)	Spontaneous pregnancy loss 0R with 95% CI	Exposure to ΣDEHP (metabolite included: MEHP, MEHHP, MEOHP & MECPP) was positively significant associated with spontaneous pregnancy loss with reproductive women OR:1.79 (95% 1.27-2.53 3 studies, participants unknown)	No subgroup analysis	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Exposure time During pregnancy; non-specific about mothers' exposure.				

APPENDIX 8 – TABLE OF CHARACTERISTICS OF INCLUDED REVIEWS AND POOLED ANALYSES ON FLAME RETARDANTS

Table 8.1: Characteristics of included reviews and pooled analyses on flame retardants

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Cano-Sancho 2019- Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis. No COI declared.							
Last search Aug-18 **Study types** Case control (n=16) cohort (n=1) **Included studies in the review =** 17 **Included studies in the meta-analysis =** 9	Adapted National Toxicology Program/ Office of Health Assessment and Translation (NTP/OHAT) Risk of Bias Rating Tool for Human and Animal Studies. Overall, most studies were classified as tier 1 or tier 2 indicating the presence plausible bias that may raise some doubt about the results.	Unclear study states all ages, body mass index, and/or life-stage at exposure or outcome (assume women) N = 32,743	**Type** Polychlorinated biphenyl (PCB) **Route** NR **Measure** Serum (units NR) **Exposure time** NR	Endometriosis risk log OR and 95%Cis; High versus low percentiles	Exposure to PCB was associated with increased odds in developing endometriosis (log OR=0.53, 95%CI: 0.18, 0.57; 9 studies, 31041 participants) corresponding to an OR= 1.70, 95%CI: 1.20, 2.39). There was considerable heterogeneity (I2=78%)	Subgroup by sample revealed an associated risk in serum samples (OR 2.02, 95%CI; 1.20 to 3.40; 6 studies, 2,271 participants) but not in adipose tissues samples (OR 1.42, 95%CI: 0.91 to 2.21; 3 studies, 28,770 participants). Subgroup by region revealed an associated risk in studies in Europe (OR 2.35, 95%CI: 1.44 to 3.82; 4 studies, 385 participants) but not in the US (OR 1.08, 95%CI: 0.93 to 1.26; 5 studies, 30,656 participants) Subgroup by population sample revealed an associated risk among operative case-control population (OR 2.08, 95%CI: 1.40 to 3.08; 6 studies, participants unspecified) but not the population-based group (OR 1.14, 95%CI: 0.88 to 1.48; 3 studies, participants unspecified).	8

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						Subgroup by the type of outcome revealed an associated risk whether deep endometriosis (OR 1.76, 95%CI: 1.35 to 2.28, 2 studies, participants unspecified) or total endometriosis (OR 1.73, 95%CI: 1.08 to 2.76; 7 studies, participants unspecified).	
						Other subgroup findings: Subgroup by exposure contract: Continuous (OR 1.51, 95%CI: 0.89 to 2.57; 4 studies, participants unspecified); categorical (OR 1.86, 95%CI: 1.21 to 2.86; 5 studies, participants unspecified) Subgroup by risk of bias: Tier 2 (OR 1.57, 95%CI: 1.18 to 2.09; 4 studies, participants unspecified); Tier 1 (OR 1.78, 95%CI: 1.02 to 3.12; 5 studies, participants unspecified) Subgroup by laparoscopy among controls: With laparoscopy (OR 1.78, 95%CI: 1.02 to 3.13; 5 studies, participants unspecified); No laparoscopy (OR 1.57, 95%CI: 1.18 to 2.09; 4 studies, participants unspecified)	
Catalani 2019- Occupational and environmental exposure to polychlorinated biphenyls and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis of epidemiology studies. No COI declared.							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Mar-18 **Study types** Cohort (n=12) case control (n=18) **Included studies in the review =** 30 **Included studies in the meta-analysis =** 30	Newcaste-Ottawa Scale. No interpretation provided by authors	Workers occupationally exposed to PCBs (telecommunication workers, electrical workers and transformer and capacitor workers) or populations living in areas with reported PCB exposure. N = 309,975	**Type** Polychlorinated biphenyl (PCB) **Route** Occupational, food contamination or residents in polluted areas **Measure** Unspecified **Exposure time** 1920-2008	Non-Hodgkin's lymphoma risk RR and 95%CI; Highest versus lowest quartile	No association between PCB 118 and non-Hodgkin's lymphoma RR 0.82, 95%CI: 0.53 to 1.10; 8 studies, 1,571 participants No association between PCB 138 and non-Hodgkin's lymphoma RR 0.93, 95%CI: 0.59 to 1.27; 8 studies, 1,571 participants No association between PCB 153 and non-Hodgkin's lymphoma RR 1.10 95%CI: 0.68 to 1.53; 8 studies, 1,571 participants	No association found in retrospective studies (RR 0.98, 95%CI: 0.58 to1.38; 8 studies, 1,106 participants)	6
					No association between PCB 180 and non-Hodgkin's lymphoma RR 1.07, 95%CI: 0.67 to 1.47; 7 studies, 954 participants		

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					No association between PCB 170 and non-Hodgkin's lymphoma RR 0.89, 95%CI: 0.58 to 1.21: 5 studies, 984 participants		
Fu 2020 - The association between environmental endocrine disruptors and cardiovascular disease: A systematic review and meta-analysis - No COI reported							
Last search Jan-19 **Study types** Cross sectional (n=17) Retrospective cohort (n=7) Prospective cohort (n=4) Case control (n=1) **Included studies in the review =** 29 **Included studies in the meta-analysis =** 11	Newcastle-Ottawa Scale. The authors only provide the final score per study with the following statement "The literatures were considered as high quality, medium quality, and low quality with the corresponding scores of ≥7, 5–7, and<5."	Anybody in whom EED (environmental endocrine disruptor) exposure was pre-determined. No age limitations. N = 41854	**Type** Polychlorinated biphenyl (PCBs) **Route** Unspecified **Measure** Unspecified **Exposure time** Unspecified	Prevalence cardiovascular disease (CVD) (categorisation unspecified) OR and 95%CI No logistic regression	Positive association between PCB exposure and incidence of CVD (OR=1.28, 95%CI:1.17, 1.39; 11 studies, 86296 participants).	Subgroup conducted based on PCB subtype. Positive association between PCB 138 exposure and incidence of CVD (OR=1.35, 95%CI:1.10, 1.66; 7 studies, 13409 participants). Positive association between PCB 153 and incidence of CVD (OR=1.35, 95%CI:1.13,1.62; 10 studies, 49326 participants). No association between exposure to PCB 180 and incidence of CVD (OR=1.19, 95%CI:0.98, 1.45; 9 studies,14735 participants). No association between exposure to total PCBs and incidence of CVD (1.32, 95%CI:0.97, 1.78; 4 studies, 8826 participants).	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Govarts 2012- Birth Weight and Prenatal Exposure to Polychlorinated Biphenyls (PCBs) and Dichlorodiphenyldichloroethylene (DDE): A Meta-analysis within 12 European Birth Cohorts. No COI declared.							
Last search Unspecified **Study types** Cohort **Included studies in the meta-analysis =** 12	unspecified	Infant-mother pairs N = 7,762	**Type** Polychlorinated biphenyl (PCB) **Route** Maternal/prenatal **Measure** Cord plasma or serum/ maternal serum or blood/breast milk (ng/L or ng/g fat) **Exposure time** Prenatal	Birth weight Beta coefficient and 95% CI	Exposure to PCBs was associated with lower birth weight (b= -0.15, -0.24, -0.05; 12 studies, 7666 participants).	No association between PCB exposure and lower birth weight was found in nulliparous women (b= -152g/µg PCB 153, 95%CI: -341, 37; 12 studies, 3856 participants	3
Gascon 2014- Prenatal Exposure to DDE and PCB 153 and Respiratory Health in Early Childhood: A Meta-Analysis. No COI declared.							
Last search Unspecified **Study types**	unspecified	Mother-children pairs N = 4,608	**Type** Polychlorinated biphenyl (PCB)-153	Bronchitis and/or wheeze (<18 months age)	No association between PCBs and presence of bronchitis and/or wheeze in infants < 18 months old (RR=1.02, 95%CI:	No subgroup analysis conducted	3

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Cohort **Included studies in the review =** NA **Included studies in the meta-analysis =** 10			**Route** Maternal/prenatal **Measure** Maternal whole blood or serum/ cord plasma or serum/breast milk (ng/L or ng/g lipid) **Exposure time** Prenatal	RR and 95%CI (continuous per log, ng/L); logistic regression	0.96, 1.08; 9 studies, 4394 participants)		
				Bronchitis (<18 months age) RR and 95%CI (continuous per log, ng/L); logistic regression	No association between PCBs and presence of bronchitis in infants < 18 months old (RR=1.06, 95%CI: 1.01, 1.12; 7 studies, 2990 participants) (P=0.89)	No subgroup analysis conducted	
				wheeze (<18 months age) RR and 95%CI (continuous per log, ng/L); logistic regression	No association between PCBs and presence of wheeze in infants < 18 months old (RR=1.01, 95%CI: 0.94, 1.09; 8 studies, 3675 participants)	No subgroup analysis conducted	
				Wheeze (>18 months age) RR and 95%CI (continuous per log, ng/L); logistic regression	No association between PCBs and presence of wheeze in children > 18 months old (RR=1.06, 95%CI: 0.98, 1.15; 6 studies, 1754 participants)	No subgroup analysis conducted	
Lam 2017 - Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis - No COIs declared							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last Search Sep-16 **Study types** Cross sectional (n=1) Prospective Cohort (n=13) Case Control (n=1) **Included studies in the review =** 15 **Included studies in the meta-analysis =** 4	We evaluated risk of bias for each of the included studies using a modified instrument based on the Cochrane Collaboration's "Risk of Bias" tool and the Agency for Healthcare Research and Quality's (AHRQ) domains (i.e., selection bias, confounding, performance bias, attrition bias, detection bias, and reporting bias) (Higgins and Green 2011; Viswanathan et al. 2012). Risk of bias for studies of IQ was generally "low" or "probably low" across studies and domains. Studies that received	The authors state "humans", however, reading this can be simplified to mother-child pairs studied during late-pregnancy. However, the only synthesised effect estimate presented is a comparison of prenatal PBDE exposure and IQ on children 48-84 months. N = 2,884	**Type** Polybrominated diphenyl ethers (PBDE) **Route** Unspecified, but detection limited to umbilical cord blood or maternal serum during gestation or at birth **Measure** Authors present [PBDE] in ln(10)-units. Verbatim from author "…overall pooled estimates from RE model per 10-fold increase (in other words, times 10) in PBDE exposure	IQ Beta-coefficient effect size (ln (10)). All primary studies provided lipid-adjusted estimates.	Prenatal exposure to PBDE was associated with a decrease in IQ points per 10-fold increase in PBDE concentration (lipid adjusted) (b = -3.7 points, 95% CI: -6.56, -0.83 points, (p-value not specified); 4 studies; 595 participants).	No subgroup or sensitivity analysis conducted	11

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
	"probably high ratings" evaluated outcomes related to IQ, such as infant/toddler assessments of intelligence (i.e., Bayley Scales), and these studies were not included in the meta-analysis that informed our final decision. As such, we agreed that these limitations within certain studies were not strong enough to warrant downgrading for risk of bias across all studies.		**Exposure time** Unspecified But exposure was prenatal				
Leng 2016 - Polychlorinated biphenyls and breast cancer: A congener-specific meta-analysis - No COIs declared							
Last search Jan-15 **Study types** Case control (n=11);	Newcastle-Ottawa Scale (NOS) - 5/8 (n=2); 6/8 (n=5); 7/8 (n=1)	Female; evidence of exposure to any one of 209 PCB congeners N = 7,041	**Type** polychlorinated biphenyls (PCB) - PCB 187 **Route**	Breast Cancer Adjusted OR and 95%CI - (25th, and 75th percentiles)	Exposure to PCB 187 was associated with an increased odds in developing breast cancer in women (OR=1.18, 95%CI: 1.01,1.39; 7 studies, 1456 participants)	No subgroup analysis conducted	8

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Nested case control (n=5) **Included studies in the review =** 16 **Included studies in the meta-analysis =** 13			Unspecified **Measure** serum (n=9); adipose tissue (n=7) - ng/g **Exposure time** Unspecified				
			Type polychlorinated biphenyls (PCB) - PCB 118		No association between PCB 118 and risk of breast cancer in women (OR=1.32, 95%CI: 0.98, 1.78; 9 studies, 2,446 participants)	Subgroup based on sample size Cases≥100 No association OR 1.07, 95%CI: 0.87 to 1.32; 7 studies, 2,346 participants Cases<100 There is an association OR 3.72, 95%CI:2.16 to 6.42; 2 studies, 100 participants	
			Type polychlorinated biphenyls (PCB) - PCB 138		No association between PCB 138 and risk of breast cancer in women (OR=1.08, 95%CI: 0.99, 1.17; 11 studies, 2,911 participants)	No subgroup analysis conducted	
			Type polychlorinated biphenyls (PCB) - PCB 156		No association between PCB 156 and risk of breast cancer in women (OR=1.19, 95%CI: 0.85, 1.67; 6	Subgroup based on statistical method (variable type) PCB as categorical variable There is an association OR 1.35,	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					studies, 1,506 participants	95%CI: 1.02 to 1.78; 5 studies, 1,202 participants	
			Type polychlorinated biphenyls (PCB) - PCB 170		No association between PCB 170 and risk of breast cancer in women (OR=1.28, 95%CI: 0.89, 1.86; 6 studies, 1,334 participants)	Subgroup based on PCB levels PCB 170 ≥ 12.5 ng/g lipid No association OR 1.05, 95%CI: 0.84 to 1.32; 5 studies, 1,274 participants	
			Type polychlorinated biphenyls (PCB) - PCB 99		Exposure to PCB 99 was associated with an increased odds in developing breast cancer in women (OR=1.36, 95%CI: 1.02, 1.80; 4 studies, 970 participants)	No subgroup analysis conducted	
			Type polychlorinated biphenyls (PCB) - PCB 153		No association between PCB 153 and risk of breast cancer in women (OR=1.04, 95%CI: 0.81, 1.34; 11 studies, 2,881 participants)	Subgroup based on quality appraisal score NOS ≥5 No association OR 0.95, 95%CI: 0.78 to 1.15; 10 studies, 2,821 participants	
			Type polychlorinated biphenyls (PCB) - PCB 180		No association between PCB 180 and risk of breast cancer in women (OR=1.02, 95%CI: 0.81, 1.29; 11 studies, 2,881 participants)	Subgroup based on country Others No association OR 1.10, 0.93 to1.32; 10 studies, 2,476 participants	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type polychlorinated biphenyls (PCB) - PCB 183		Exposure to PCB 183 was associated with an increased odds in developing breast cancer in women (OR=1.56, 95%CI: 1.25, 1.95; 6 studies, 1506 participants)	No subgroup analysis conducted	
						Subgroup of congeners reported by only two studies PCB 28 OR 2.39, 95%CI: 0.16 to -35.60; 2 studies, 135 participants PCB 52 OR 0.98, 95%CI: 0.78 to 1.23; 2 studies, 130 participants PCB 74 OR 0.94, 95%CI: 0.84 to 1.04; 2 studies, 334 participants unspecified PCB 77 OR 1.20, 95%CI: 0.39 to 3.73; 2 studies, 113 participants PCB 101 OR 1.02, 95%CI: 0.80 to 1.31; 2 studies, 130 participants unspecified PCB 105	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						OR 2.22, 95%CI: 1.18 to 4.17; 2 studies, 287 participants unspecified PCB 126 OR 1.40, 95%CI: 0.78 to 2.50; 2 studies, 113 participants unspecified PCB 167 OR 0.87, 95%CI: 0.07 to 10.71; 2 studies, 142 participants unspecified	
Li 2015 - Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: A meta-analysis of two highly exposed cohorts - No COIs reported							
Last search No search **Study types** Cohort **Included studies in the review =** 2 **Included studies in the meta-analysis =** 2	None	Adult men and women occupationally exposed to PCBs - workers from "Yusho" incident, Japan (1968) and "Yu-Cheng" incident, Taiwan (1979) N = 3,467	**Type** polychlorinated biphenyls (PCB) **Route** Yusho (1968) and Yu-cheng (1979) food contamination events **Measure** ICD-9 codes (cause of death)	All-cause mortality SMR (only reported where I^2 <50%)	Exposure to PCBs was associated with an increased **all-cause** standardised mortality rate (SMR=1.1, 95%CI: 1.1, 1.2; 2 studies, 3467 participants)	Exposure to PCBs was associated with an increased **all-cause** standardised mortality rate in **males** (SMR=1.2, 95%CI: 1.1, 1.3; 2 studies, 1690 participants)	4
				All cancer mortality		No association between PCB and **all-cause** standardised mortality in **females** (SMR=1.1, 95%CI: 0.9, 1.2; 2 studies, 1777 participants)	
						Exposure to PCBs was associated with an increased **all cancer** standardised mortality rate in **males** (SMR=1.3, 95%CI: 1.1, 1.6; 2 studies, 1690 participants)	
						No association between PCB and **all cancer** standardised mortality in **females** (SMR=0.8, 95%CI: 0.5, 1.3; 2 studies, 1777 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Exposure time Unspecified	Stomach cancer mortality	No association between PCB and **stomach cancer** standardised mortality in **females** (SMR=0.3, 95%CI: 0.1, 1.1; 2 studies, 1777 participants)	No subgroup analysis conducted	
				Rectum cancer mortality	No association between PCB and **stomach cancer** standardised mortality in **females** (SMR=1.0, 95%CI: 0.2, 5.8; 2 studies, 1777 participants)	No subgroup analysis conducted	
				Liver cancer mortality	Exposure to PCBs was associated with an increased **liver cancer** standardised mortality rate in **females** (SMR=2.0, 95%CI: 1.1, 3.6; 2 studies, 1777 participants)	No subgroup analysis conducted	
				Pancreas cancer mortality	No association between PCB and **pancreas cancer** standardised mortality in **females** (SMR=1.1, 95%CI: 0.4, 3.75.8; 2 studies, 1777 participants)	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Lung cancer mortality	Exposure to PCBs was associated with an increased **lung cancer** standardised mortality rate (SMR=1.5, 95%CI: 1.1, 2.1; 2 studies, 3467 participants)	Exposure to PCBs was associated with an increased **lung cancer** standardised mortality rate in **males** (SMR=1.2, 95%CI: 1.2, 2.3; 2 studies, 1690 participants)	
						No association between PCB and **lung cancer** standardised mortality in **females** (SMR=0.7, 95%CI: 0.3, 1.9; 2 studies, 1777 participants)	
				Breast (female) cancer mortality	No association between PCB and **breast cancer** standardised mortality in **females** (SMR=1.1, 95%CI: 0.4, 2.9; 2 studies, 1777 participants)	No subgroup analysis conducted	
				Uterus cancer mortality	No association between PCB and **uterus cancer** standardised mortality in **females** (SMR=1.1, 95%CI: 0.4, 3.4; 2 studies, 1777 participants)	No subgroup analysis conducted	
				Leukaemia mortality	No association between PCB and leukaemia standardised mortality in **males** (SMR=2.0, 95%CI: 0.6, 6.0; 2	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					studies, 1690 participants)		
				Hypertension mortality	No association between PCB and hypertension standardised mortality (SMR=1.6, 95%CI: 0.9, 2.9; 2 studies, 3467 participants)	No association between PCB and hypertension standardised mortality in **males** (SMR=1.5, 95%CI: 0.7, 3.4; 2 studies, 1690 participants)	
						No association between PCB and **hypertension** standardised mortality in **females** (SMR=1.4, 95%CI: 0.3, 5.6; 2 studies, 1777 participants)	
				Heart disease mortality	Exposure to PCBs was associated with an increased **heart disease** standardised mortality rate (SMR=1.3, 95%CI: 1.0, 1.7; 2 studies, 3467 participants)	No subgroup analysis conducted	
				Cerebrovascular disease mortality	No association between PCB and cerebrovascular disease standardised mortality (SMR=1.0, 95%CI: 0.8, 1.29; 2 studies, 3467 participants)	No association between PCB and cerebrovascular disease standardised mortality in **males** (SMR=0.9, 95%CI: 0.6, 1.2; 2 studies, 1690 participants)	
						No association between PCB and **cerebrovascular disease** standardised mortality in **females** (SMR=1.1, 95%CI: 0.8, 1.5; 2 studies, 1777 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Hepatic disease mortality	Exposure to PCBs was associated with an increased **hepatic disease** standardised mortality rate (SMR=1.5, 95%CI: 1.0, 2.4; 2 studies, 3467 participants)	Exposure to PCBs was associated with an increased hepatic disease standardised mortality rate in **males** (SMR=1.9, 95%CI: 1.3, 2.8; 2 studies, 1690 participants) No association between PCB and **hepatic disease** standardised mortality in **females** (SMR=1.0, 95%CI: 0.5, 1.9; 2 studies, 1777 participants)	
Nieminen 2013- Polychlorinated biphenyls (PCBs) in relation to secondary sex ratio –A systematic review of published studies- No COIs declared							
Last search end of 2011 (no specific on date) **Study types** No discussion on study type or design **Included studies in the review =** 15 **Included studies in the meta-analysis =** 15	Methodology quality was assessed by the authors. They did not use a formalised validated scale	No sample size was presented of the individual studies. The review included articles from pregnant women (Indigenous people of the Russian Artic; Lake Michigan mothers who had eaten Lake Michigan fish); Mothers who came to the hospital for delivery; female anglers; individuals who	**Type** Polychlorinated biphenyls (PCBs) **Route** Direct or indirect exposure of PCBs through maternal or paternal **Measure** Blood serum: µg/L or ng/g; Cord serum: ng/mL; Breast milk: mg/kg	secondary sex ratio (proportion of males) (Maternal exposure) The main outcome measure was the proportion of boys among the newborns Effect size with 95% CI	Direct high maternal exposure to PCBs and secondary sex ratio: 0.5 (95%ci: 0.45,0.551, 9 studies, participants unspecified) Indirect high maternal exposure to PCBs did not reveal any extremely low proportion of boys: 0.503 (95% CI: 0.487-0.519, 6 studies) Internal comparisons between high and low exposures groups: Please note that these are narrative figures alone- unable to	No subgroup analysis conducted	3

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
		purchased from contaminated farms, fish-eaters, residents of xop codes that contain PCB waste sites families in polluted JingHai country, individuals who ingested contaminated waste, women who had worked in three electrical capacitor plants.	High exposure group was taken as defined in the original papers: as the upper half (values above median), the highest quartile, quintile or 10th percentile group of the measured PCB distribution. A total sum of PCBs or a sum of more than six congeners measured in the studies was used as an exposure measure. Indirect assessment of PCB exposure includes studies were PCB levels		identify these in a table which reports differently to these. Unable to also verify the studies included in the narrative analysis. Difference in proportion of boys between direct high and low maternal exposure was -0.048 (95%CI: 0.121,0.026) Difference in proportion of boys between indirect high and low maternal exposure was -0.033 (95%CI:-0.017,0.011) Data extracted from table (4) No association between the difference of proportions of newborn males between groups with high and low indirect maternal exposure of PCBs: -0.003 (95% CI: -0.017;0.011, 4 studies)		

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			were not measured directly from each participant but other information existed showing that the parents were exposed to PCBs. **Exposure time** unspecified		Exposure to difference of proportions of newborn males between groups with high and low direct maternal exposure is associated with PCBs: -0.069 (95% CI: 0.174;0.022, 9 studies)		
Park 2016- Body burden of persistent organic pollutants on hypertension: a meta-analysis. No COI declared.							
Last search Jun-15 **Study types** Cross sectional (n=10) cohort (n=1) **Included studies in the review =** 11	Newcastle-Ottawa Scale. We decided to include all 11 studies, since the Newcastle-Ottawa scale scores of selected studies were equal to or greater than 6 (moderate-high quality).	General population N = 14,742	**Type** Polychlorinated biphenyls (PCB) **Route** Unspecified **Measure** Serum (n=10) adipose tissue (n=1) (ng/g lipid or pg/g	Hypertension OR and 95%CI Test unspecified, logistic regression unspecified	No association between PCB 118 and hypertension (OR=1.26, 95%CI: 1.00, 1.58; 5 studies, 9134 participants)	No subgroup analysis conducted	7
				Hypertension OR and 95%CI Test unspecified, logistic regression unspecified	No association between PCB 153 and hypertension (OR=1.09, 95%CI: 0.97, 1.23; 6 studies, 9431 participants)	No subgroup analysis conducted	
				Hypertension	No association between Dioxin-like PCBs and hypertension	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the meta-analysis = 11			lipid or µg/L or µg/kg lipid) **Exposure time** Unspecified	OR and 95%CI Test unspecified, logistic regression unspecified	(OR=1.45, 95%CI: 1.00, 2.12; 5 studies, 8793 participants)		
				Hypertension OR and 95%CI Test unspecified, logistic regression unspecified	No association between Non-Dioxin-like PCBs and hypertension (OR=1.00, 95%CI: 0.89, 1.12; 3 studies, 2048 participants)	No subgroup analysis conducted	
Roy 2015- Integrated Bioinformatics, Environmental Epidemiologic and Genomic Approaches to Identify Environmental and Molecular Links between Endometriosis and Breast Cancer. No COI declared							
Last search Unspecified **Study types** Case control (n=20), cohort (n=2), cross sectional (n=1) **Included studies in the review =** 23 **Included studies in the meta-analysis =** 12	No critical appraisal	Breast cancer patients and matched healthy controls N = 9,781	**Type** Polychlorinated biphenyl (PCB) **Route** NR **Measure** Serum or plasma (ng/g) **Exposure time** NR	Breast cancer OR and 95% Cis; unadjusted and/or adjusted logistic regression models.	No association between PCB exposure and risk of developing breast cancer in women (OR= 1.33, 95%CI: 0.72, 2.65; 6 studies, 2458 participants).	No subgroup analysis conducted	3

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Study types Case control **Included studies in the review =** 6	No critical appraisal	Women with endometriosis and matched healthy controls N = 1380 (case=542; control=838)	**Type** Polychlorinated biphenyl (PCB) **Route** NR **Measure** Serum (ng/g) **Exposure time** NR	Endometriosis OR and 95%CI No logistic regression	Exposure to PCB was associated with increased odds of developing endometriosis in women (OR= 1.91, 95%CI: 1.05, 5.54; 6 studies, 1380).	No subgroup analysis conducted	
Song 2016- Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. No COI declared.							
Last search Feb-14 **Study types** cross sectional (n=13) cohort (n=8)	unspecified	Unspecified N = 55,774	**Type** Polychlorinated biphenyls (PCB) **Route** Unspecified **Measure**	Type 2 diabetes RR and 95%CI; Highest versus Lowest exposure categories; highest (PCB153 concentrations of >104 to >1348 ng/g lipid) and lowest (corresponding to PCB153 concentrations of ≤60 to ≤455 ng/g lipid)	There was a positive association between PCB and type 2 diabetes (RR=2.39, 95%CI: 1.86, 3.08; 21 studies, 21530 participants)	There was a positive association between PCB and type 2 diabetes in cross-sectional studies (RR=2.90, 95%CI: 2.14, 3.92; 13 studies, 13419 participants). There was a positive association between PCB and type 2 diabetes in prospective cohort studies (RR=1.63, 95%CI: 1.15, 2.33; 8 studies, 4681 participants).	6

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the review = 49 **Included studies in the meta-analysis =** 20			serum (ng/g lipid) **Exposure time** Unspecified			The RR was greater in women (RR=2.65, 95%CI: 1.57, 4.48; No. studies and participants NR) than men (RR=1.73, 95%CI:0.80, 3.75; No. studies and participants NR). The RR was significantly lower white people (RR=1.94, 95%CI: 1.43, 2.62; No. studies and participants NR) than in non-white people (RR=2.91, 95%CI: 1.60, 5.30; No. studies and participants NR)	
				Fasting glucose MD and 95%CI; Highest versus Lowest exposure categories; highest (PCB153 concentrations of >104 to >1348 ng/g lipid) and lowest (corresponding to PCB153 concentrations of ≤60 to ≤455 ng/g lipid)	There was a positive association between PCB and fasting glucose (MD=3.27, 95%CI: 1.87 –4.67; 3 studies, 2882 participants)		
				2-h glucose MD and 95%CI; Highest versus Lowest exposure categories; highest (PCB153 concentrations of >104 to >1348 ng/g lipid) and lowest (corresponding to	No association (MD= 0.72, 95%CI: −7.44 – 8.87; 2 studies, 836 participants)		

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				PCB153 concentrations of ≤60 to ≤455 ng/g lipid)			
				Fasting insulin MD and 95%CI; Highest versus Lowest exposure categories; highest (PCB153 concentrations of >104 to >1348 ng/g lipid) and lowest (corresponding to PCB153 concentrations of ≤60 to ≤455 ng/g lipid)	No association (MD −0.48, 95%CI: −2.06 – 1.09; 3 studies, 2882 participants)		
				2-h insulin MD and 95%CI; Highest versus Lowest exposure categories; highest (PCB153 concentrations of >104 to >1348 ng/g lipid) and lowest (corresponding to PCB153 concentrations of ≤60 to ≤455 ng/g lipid)	No association (MD=−17.56, 95%CI; −59.06 –23.93; 2 studies; 836 participants)		
				HOMA- IR MD and 95%CI; Highest versus Lowest exposure categories; highest (PCB153 concentrations of >104 to >1348 ng/g lipid) and lowest (corresponding to	No association (MD=−2.05, 95%CI: −4.65–0.56; 3 studies, 933 participants)		

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				PCB153 concentrations of ≤60 to ≤455 ng/g lipid)			
Wu 2013 - Persistent Organic Pollutants and Type 2 Diabetes: A Prospective Analysis in the Nurses' Health Study and Meta-analysis - No COIs declared							
Last search Dec-11 **Study types** Cohort study with additional meta-analysis Case control (n=2) Prospective cohort (n=4) NOTE* authors also include their own data in the meta-analysis (2 nested case control included). **Included studies in the review =** 7 **Included studies in the meta-analysis =** 7	No critical appraisal was performed.	Adult men and women from the general population N = 3,474	**Type** Polychlorinated biphenyls (PCBs) **Route** Unspecified **Measure** Serum concentrations (lipid standardised (ng/g) **Exposure time** Unspecified	Incident diabetes OR and 95%CI All fixed effect analyses presented, authors indicated similar results with random effects	Positive association between exposure to total PCB and incidence of diabetes (OR=1.7, 95%CI:1.28, 2.27; 6 studies, 2413 participants). One study excluded (due to PCB and PCDF poisoning) OR 2.05,95% CI: 1.41 to 2.98; 5 studies, 2,035 participants Estimate OR 1.06 (95%CI 1.02 to 1.09) ng/g serum increase in total PCBs	No subgroup analysis conducted	4
			Type PCB – 118 **Route** Unspecified	Incident diabetes OR and 95%CI	No association between exposure to PCB 118 and incidence of diabetes (OR=1.20, 95%CI:0.73, 1.96; 4 studies, 2,471 participants).	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Measure Serum concentrations (lipid standardised (ng/g) **Exposure time** Unspecified				
			Type PCB – 138 **Route** Unspecified **Measure** Serum concentrations (lipid standardised (ng/g) **Exposure time** Unspecified	Incident diabetes OR and 95%CI	No association between exposure to PCB 138 and incidence of diabetes (OR=1.36, 95%CI:0.69,2.68; 2 studies, 1,820 participants)	No subgroup analysis conducted	
			Type PCB – 153	Incident diabetes OR and 95%CI	No association between exposure to PCB 153 and incidence of diabetes (OR=1.06,	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Route Unspecified **Measure** Serum concentrations (lipid standardised (ng/g) **Exposure time** Unspecified		95%CI: 0.79, 1.42; 4 studies, 2,742 participants)		
			Type PCB -180 **Route** Unspecified **Measure** Serum concentrations (lipid standardised (ng/g) **Exposure time** Unspecified	Incident diabetes OR and 95%CI	No association between exposure to PCB 180 and incidence of diabetes (OR=1.46, 95%CI:0.77,2.77; 3 studies, 2,000 participants)	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Zani 2013 - Polychlorinated Biphenyls and Cancer: An Epidemiological Assessment; no COI reported.							
Last Search Dec-12 **Study types** Case control and cohort **Included studies in the review =** 29 **Included studies in the meta-analysis =** 29	No critical appraisal was performed	General population and men/women occupationally exposed to PCBs (including workers from "Yusho" incident, Japan [1968] and "Yu-Cheng" incident, Taiwan [1979]) N = 16,067	**Type** polychlorinated biphenyl (PCB) **Route** rice oil accidentally contaminated by PCBs and polychlorinated **Measure** dibenzofurans (PCDFs) (ng/g Lipid) **Exposure time** single incident	Non-Hodgkin lymphoma OR and 95%CIs; quantiles	Exposure to PCBs was associated with an increased OR of non-Hodgkin lymphoma for the highest compared to the lowest PCB serum levels (OR=1.40, 95%CI: 1.14–1.71; 11 studies, 4422 participants)	No association found for individual measures of exposure and non-Hodgkin's lymphoma in subgroup of cohort studies (OR= 1.34, 95%CI: 0.97, 1.86; 7 studies, participants unspecified) Exposure to PCBs in subgroup of case-control studies were associated with a risk of Non-Hodgkin's lymphoma (OR= 1.51, 95%CI: 1.17, 1.96; 4 studies, participants unspecified)	2
				Breast Cancer OR and 95%CIs; quantiles	No association between PCB serum levels and risk of breast cancer (OR=1.15, 95%CI: 0.92–1.43; 18 studies, 11,645 participants)	No association found for PCBs and breast cancer for subgroups of cohort studies (OR=1.01, 95%CI: 0.78, 1.31; 6 studies, participants unspecified) and case-control studies (OR=1.19, 95%CI: 0.92, 1.43; 12 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Zhang 2015 - Environmental Polychlorinated Biphenyl Exposure and Breast Cancer Risk: A MetaAnalysis of Observational Studies; no COI reported.							
Last search Nov-2014 **Study types** prospective cohort (n=9) retrospective cohort (n=16) **Included studies in the review =** 25 **Included studies in the meta-analysis =** 25	Newcastle-Ottawa Scale: moderate to high (5 to 9 stars) - prospective studies higher (7 to 9 stars) than retrospective studies (5 to 8 stars).	Female (age: 18 years and over) N = 12,866	**Type** polychlorinated biphenyl (PCB) **Route** unspecified **Measure** adipose tissue, serum or plasma ng/g lipid **Exposure time** unspecified	Risk of Breast Cancer OR and 95%CI median and/or interquartile range; geometric mean and/or standard deviation	No association between PCB and risk of breast cancer in adult women (OR=1.09, 95%CI: 0.97, 1.22; 25 studies, 12,866 participants); Sensitivity analysis excluding 3 retrospective studies with divergent ORs OR 1.06, 95% CI 0.98 to 1.15; 22 studies, 11,729 participants	No association in subgroup of prospective studies (OR=1.02, 95%CI: 0.85, 1,23; 9 studies, participants unspecified) No association in subgroup of retrospective studies (OR=1.12, 95%CI: 0.96, 1.30; 16 studies, participants unspecified) No association in subgroups of retrospective studies by specimen type: Serum/plasma (OR 1.12, 95%CI 0.95 to 1.32; 14 studies, 7,556 participants), Adipose tissue (OR 1.06. 95%CI 0.70 to 1.60; 2 studies, 985 participants). No association in subgroups of retrospective studies in Asia (OR 1.91, 95%CI 0.34 to 10.68; 3 reviews, participants unspecified) but not in North America (OR 1.08, 95%CI 1.01 to 1.16; 12 reviews, participants unspecified Asia).	8
Zhao 2017 - Correlation between Prenatal Exposure to Polybrominated Diphenyl Ethers (PBDEs) and Infant Birth Outcomes: A Meta-Analysis and an Experimental Study; no COI declared.							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Jun-16 **Study types** cross sectional **Included studies in the review =** 7 **Included studies in the meta-analysis =** 7	A cross-sectional assessment tool - not named (studies of high quality)	infants (at birth) N = 1,332	**Type** polybrominated diphenyl ethers (PBDEs) **Route** via mother **Measure** ng/g lipid **Exposure time** prenatal	infant birth outcomes (IBO) - birth weight (g) beta coefficient (b)	Exposure to prenatal PBDE was negatively associated with birthweight in infants (b=-50.56, 95%CI: -95.91,-5.28; 7 studies, 1332 participants)	No association between prenatal PBDE and low birthweight in infant **females** (b=-50.598, 95%CI: -95.914,-5.252; 2 studies, 265 participants)	9
						Exposure to prenatal PBDE was negatively associated with birthweight in infant **males** (b= -121.456, 95%CI: -230.139,-12.773; 2 studies, 296 participants)	
						No association between prenatal PBDE and birthweight in the remaining studies that grouped infant **females and males** (b=-54.388, 95%CI: -115.982,7.206; 3 studies, 771 participants)	
			Type 2,20,4,40 - Tetrabromodiphenyl ether (BDE 47)	infant birth outcomes (IBO) - birth weight (g) beta coefficient (b)	No association between prenatal PBDE 47 and birthweight in infants (b=-41.54, 95%CI: -90.35,7.28; 3 studies, 601 participants)	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Type 2,20,4,40,5-Pentabromodiphenyl ether (BDE 99)	infant birth outcomes (IBO) - birth weight (g) beta coefficient (b)	No association between prenatal PBDE 99 and birthweight in infants (b=-29.78, 95%CI: -95.09,35.53; 3 studies, 601 participants)	No subgroup analysis conducted	
			Type 2,20,4,40,6-Pentabromodiphenyl ether (BDE 100)	infant birth outcomes (IBO) - birth weight (g) beta coefficient (b)	No association between prenatal PBDE 100 and birthweight in infants (b=-28.55, 95%CI: -91.19,34.10; 3 studies, 768 participants)	No subgroup analysis conducted	
			Type 2,20,4,40, 5,50 - Hexabromodiphenyl ether (BDE 153)	infant birth outcomes (IBO) - birth weight (g) beta coefficient (b)	No association between prenatal PBDE 153 and birthweight in infants (b=-41.22, 95%CI: -102.73,20.29; 3 studies, 768 participants)	No subgroup analysis conducted	
			Type polybrominated diphenyl ethers (PBDEs)	infant birth outcomes (IBO) - birth length (cm) beta coefficient (b)	No association between prenatal PBDE and birth length in infants (b=-0.33, 95%CI: -0.74,0.07; 2 studies, 320 participants)	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			polybrominated diphenyl ethers (PBDEs)	infant birth outcomes (IBO) - head circumference (cm) beta coefficient (b)	No association between prenatal PBDE and head circumference in infants (b=-0.175, 95%CI: -0.418,0.069; 3 studies, 632 participants)	No subgroup analysis conducted	
Zhao 2015 - The Correlation between Polybrominated Diphenyl Ethers (PBDEs) and Thyroid Hormones in the General Population: A Meta-Analysis; no COI reported.							
Last search Sep-14 **Study types** Cross sectional **Included studies in the review =** 19 **Included studies in the meta-analysis =** 17	Agency for Healthcare Research and Quality (Rostom A,Dube C,Cranney A,Saloojee N,Sy R, Garritty C, et al. Celiac Disease. Rockville (MD): Agency for Healthcare Research and Quality (US); 2004 Sep.(Evidence Reports/Technology Assessments, No. 104.) Appendix D. Quality Assessment Forms. http://www.ncbi.nlm.nih.gov/book	general population (children and adults) N = 2,922	**Type** Polybrominated diphenyl ethers (PBDEs) **Route** Unspecified **Measure** serum (ng/g lipid) **Exposure time** unspecified	Thyroid function - thyroid stimulating hormone (TSH) Transformation of Pearson correlation coefficients (r) to Fisher's z		No association between median PBDEs levels < 30 ng/g lipid and TSH levels; The pooled z value of subgroup one was random effects z -0.07 (95%CI -0.14, 0.00; 10 studies, 1064 participants); Fixed effects z -0.07, 95%CI -0.13, -0.01; 10 studies, 1,064 participants	9
				Thyroid function - total thyroxine (TT4) Transformation of Pearson correlation coefficients (r) to Fisher's z		Exposure to PBDEs levels between 35 ng/g and 100 ng/g lipid was positively associated with TT4 levels random and fixed effects z 0.15, 95%CI: 0.06, 0.24; 3 studies, 466 participants	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
	s/NBK35156.). Score 18 to 22 (n=4), 13 to 17 (n=7), 11 to 13 (n=5), 9 (n=1)						
Zou 2019 - Neonatal Weight and Prenatal Exposure to Polychlorinated Biphenyls: A Meta-Analysis; no COI declared.							
Last search Jun-18 **Study types** Not reported **Included studies in the review =** 7 **Included studies in the meta-analysis =** 7	not reported	infants (at birth) N = 8,054	**Type** Polychlorinated biphenyls (PCBs) **Route** Via mother **Measure** Maternal serum/cord blood **Exposure time** Unspecified	neonatal birth weight (g) beta coefficient (b) and 95%CI	Exposure to PCB throughout pregnancy was negatively associated with infant birth weight (b= -0.59, 95%CI: -0.85,-0.34; 7 studies, 8054 participants)	Each trimester was negatively associated with infant birthweight First trimester exposure (β -0.386, 95% CI: -0.559, -0.213; 3 studies, participants unspecified) Second trimester exposure (β -0.494, 95% CI: -0.660, -0.328,2 studies, participants unspecified) Third trimester exposure (β -0.657, 95%CI: -0.905, -0.410, 6 studies, participants unspecified)	4
						Exposure to PCB in a subgroup of Asian studies was negatively associated with infant birth weight β= -0.396g, 95%CI: -0.519 to -0.272; 2 studies, 680 participants	
						Exposure to PCB in subgroup of European studies was negatively associated with infant birth weight β= -0.601, 95%CI; -0.650, -0.551; 3 studies; 5618 participants	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						Exposure to PCB in subgroup of American studies was negatively associated with infant birth weight β= -0.876, 95%CI: -1.644 to -0.108; 2 studies; 1756 participants	
						Exposure to PCB in subgroup of cord serum measurement was negatively associated with infant birthweight β= -0.833, 95%CI: -1.695, -0.029; 2 studies, 1004 participants	
						Exposure to PCB in subgroup of maternal serum measurement was negatively associated with infant birthweight β= -0.504, 95%CI: -0.785 to -0.223; 5 studies, 7050 participants	
						Exposure to PCB in subgroup of prospective studies was negatively associated with infant birthweight β= -0.631, 95%CI: -0.910, -0.351; 6 studies; participants unspecified	
Zani et al. 2017 - Do polychlorinated biphenyls cause cancer? A systematic review and meta-analysis of epidemiological studies on risk of cutaneous melanoma and non-Hodgkin lymphoma - No COIs Reported							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search Dec-16 **Study types** case control (n=1) cohort (n=10) **Included studies in the review =** 11 **Included studies in the meta-analysis =** 10	No critical appraisal was performed	Workers (both men and women) in capacitor and transformer producing factories, in electrical power and in transformer manufacture and telecommunications industry N = 217,048	**Type** polychlorinated biphenyl (PCB) **Route** Unspecified (but occupational exposure) **Measure** ng/g lipid **Exposure time** occupational exposure	Mortality due to melanoma standardised mortality ratios (SMR) and 95%CI	Positive association between occupational exposure to PCBs and mortality due to melanoma (SMR=1.32, 9%CI: 1.05, 1.64; 8 studies, 214241 participants).	No subgroup analysis conducted	5
				Mortality for non-Hodgkin's lymphoma standardised mortality ratios (SMR) and 95%CI	There is a risk of exposure to PCBs and non-Hodgkin's lymphoma (OR 1.5, 95%CI: 1.1 to 1.7; 6 studies, 2,540 participants). Dose response OR 1.42, 95%CI: 1.10 to 1.83; 5 studies, 2,668 participants, for PCB serum levels around 1000 ng/g lipid, compared to values lower than, or next to, 500 ng/g lipid. No association between occupational exposure to PCBs and mortality due to non-Hodgkin's lymphoma (SMR=0.94, 95%CI:	No subgroup analysis conducted	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					0.73, 1.23; 7 studies, 174207 participants).		

APPENDIX 9 – TABLE OF CHARACTERISTICS OF INCLUDED REVIEWS AND POOLED ANALYSES ON PER- AND POLYFLUORINATED ALKYL SUBSTANCES (PFAS)

Table 9.1: Characteristics of included reviews and pooled analyses on per- and polyfluorinated alkyl substances (PFAS)

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Johnson 2014 - The Navigation Guide - Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Foetal Growth -- No COIs declared							
Last search 2017 (actual date NR) **Study types** Unspecified **Included studies in the review =** 47 **Included studies in the meta-analysis =** 5	GRADE - individual studies not critically appraised.	Children (<18 years old) N = 3,484	**Type** PFOA **Route** Postnatal (aged 6-18 years) **Measure** Urine (units unspecified) **Exposure time** Unspecified	Birth Weight Beta-coefficient effect size (natural units)	Prenatal PFOA exposure was associated with a reduced birth weight (b = -18.9 grams, 95% CI: -29.8, -7.9 grams, (p-value not specified); 9 studies; 4149 participants).	No subgroups were identified however, a sensitivity analysis was conducted that included one additional study deemed to be at a high risk of bias. Prenatal PFOA exposure was associated with reduced birth weight (b= -15.4 grams, 95% CI: -26.5, -4.3 grams, (p-value not specified); 10 studies; 8501 participants)	10
				Birth Length Beta-coefficient effect size (natural units)	Prenatal PFOA exposure was associated with a reduced birth length (b = -0.06 cm, 95% CI: -0.09, -0.02 cm, (p-value not specified); 5 studies; 2853 participants).	No subgroups (or sensitivity analysis) performed on this outcome	
				Ponderal Index Beta-coefficient effect size (natural units)	No association between prenatal PFOA exposure and ponderal index (b = -0.01, 95% CI: - 0.03, 0.01, (p-value not specified); 4 studies, 1510 participants).	No subgroups (or sensitivity analysis) performed on this outcome	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Head circumference Beta-coefficient effect size (natural units)	No association between prenatal PFOA exposure and head circumference (b=-0.03 cm, 95% CI: -0.08, 0.01, (p-value not specified); 4 studies, 2497 participants).	No subgroups (or sensitivity analysis) performed on this outcome	
Kim 2018 - Association between perfluoroalkyl substances exposure and thyroid function in adults :A meta-analysis- - No COIs declared							
Last search Apr-17 **Study types** cross sectional	A modified cross-sectional assessment provided by the Agency for Healthcare Research. All articles scored in 6-8 range. Authors	Adults >18years; mean age (39-63.6) Sportfish anglers(n=31) General population (n=556) General Population	**Type** PFOS **Route** Unspecified **Measure**	Thyroid Function: free T4 Pearson correlation coefficient transformed by the Fisher z-transformation. T4 was measured differently: chemiluminescent immunoassay (n = 5 studies), radioimmunoassay (n = 3	Exposure to PFOS and free T4 was associated with increased free t4 levels in the total adult population. Pooled Z values 0.05 (0.03; 0.08, 9 studies, 4741 participants). Sensitivity analysis between models (fixed	Subanalysis of different levels of free t4 occurred: No correlation between mean PFOS (<8ng/mL) and free t4. The pooled Z value was 0.05 (95% ci):-0.03; 0.13), 2 studies, 548 participants). Sensitivity analysis between fixed-effects models and random effects model 0.04 (-	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the review = 12 **Included studies in the meta-analysis =** 12	concluded that the quality of the cross-sectional studies did not affect the quality of the meta-analysis	(Inuit) (n=506) General Population (NHANES) (n=2863) General Population (Riverside)(n=87) Pregnant women (24-41 weeks) (n=392) Pregnant women (17-18 weeks) (n=903) Pregnant women (unspecified on gestation) (n=440) IVF clinic (n=246) Women attempting to conceive (n=99) N = 6,123	blood ng/mL < 8 ng/mL, (low), 8±16 ng/mL (intermediate), and > 16 ng/mL (high). **Exposure time** unspecified	studies), or enzyme-linked immunosorbent assay (n = 1 studies). However, no measurement ranges of T4 were notes.	vs random) showed no difference.	0.9; 0.16) showed no difference Exposure to mean PFOS (8-16ng/mL) was +ve correlated with increased free t4. The pooled Z value was 0.07 (95% CI): 0.02; 0.11, 3 studies, 1852 participants). Sensitivity analysis between fixed-effects models and random effects model 0.07 (95% CI): 0.02; 0.11) showed no difference Mean PFOS (>16ng/mL) was +ve correlated with increased free t4. The pooled Z value was 0.05 (95% CI):1.01;0.09), 4 studies, 2341 participants). Sensitivity analysis between fixed-effects models and random effects model occurred. Random effects model indicated no correlation between mean PFOS (>16ng/mL) and free t4 0.03 (-0.01;0.13). <u>Subanalysis between pregnant</u> and general population occurred: No association between PFOS and free T4 in pregnant women. Pooled Z values 0.05 (95% CI: -0.02;0.11, 3 studies). Exposure to PFOS was associated with increased free t4 levels in the general population. Pooled z	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						values 0.06 (95% CI) 0.02;0.09, 6 studies).	
				Thyroid Function: Total T4 Pearson correlation coefficient transformed by the Fisher z-transformation. T4 was measured differently: chemiluminescent immunoassay (n = 5 studies), radioimmunoassay (n = 3 studies), or enzyme-linked immunosorbent assay (n = 1 studies). However, no measurement ranges of T4 were notes.	Using Random effects model no association between PFOS and total T4 in total population. Pooled Z values 0.01 (95% CI):-0.05;0.07, 8 studies, 4489 participants) Sensitivity analysis between models (fixed vs random) showed no difference. Fixed-effects model: -0.03 (95%CI):-0.06;0.00, 8 studies, 4489 participants)	Subanalysis of different levels of total t4 occurred: no correlation between mean PFOS (<8ng/mL) and total t4 in total population. The pooled Z value was 0.02 (95% ci):-0.10; 0.05), 2 studies, 713 participants) Sensitivity analysis between fixed-effects models and random effects model 0.02 (95% ci):-0.10; 0.06) showed no difference no correlation between mean PFOS (8-16ng/mL) and total t4 in total population. The pooled Z value was -0.04 (95% CI): -0.09: 0.00 3 studies, 1839 participants) Sensitivity analysis between fixed-effects models and random effects model -0.01 (95% CI): -.11; 0.09) showed no difference no correlation between mean PFOS (>16ng/mL) and total t4 in total population. The pooled Z value was 0.02 (95% CI): -0.06;0.02), 3 studies, 1937 participants). Sensitivity analysis between fixed-effects models and random effects model 0.09 (95% CI): -	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						0.11; 0.28) Subanalysis between pregnant women/ general population and Total T4 occurred: No correlation between PFOS and total T4 in pregnant women. The pooled Z value was 0.06 (-0.03;0.15, 2 studies). No association between PFOS and total t4 in general population. Pooled Z value: 0.00 (-0.07;0.07, 6 studies)	
			Route unspecified **Measure** ng/mL **Exposure time** unspecified	Thyroid Function: T3 Pearson correlation coefficient transformed by the Fisher z-transformation.	Using Random effects model no association between PFOS and total T3 in total population-0.02 (95% CI):-0.07;0.04, 8 studies, 4555 participants). Sensitivity analysis between models (fixed vs random) showed the fixed-effects model was -ve associated pooled Z values (-0.05 (95%CI):-0.08; 0.02, 8 studies, 4555 participants).	Subanalysis of different levels of total t3 conducted no correlation between mean PFOS (<8ng/mL) and total t3 in total population. The pooled Z value was 0.02 (95% ci):-0.18; 0.14), 1 study, 155 participants) Sensitivity analysis between fixed-effects models and random effects model 0.02 (95% ci):-0.18; 0.14), 1 study, 155 participants) showed no difference exposure to mean PFOS (8-16ng/mL) was associated with total t3 in total population. The pooled Z value was -0.05 (95% CI): -0.10: -0.01 3 studies, 1843 participants) Sensitivity analysis between	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						(fixed vs random) models. Random effects model showed no association -0.03 (95% CI): -.11; 0.06). Exposure to mean PFOS (>16ng/mL) was associated with total t3 in total population. The pooled Z value was -0.05 (95% CI): -0.09;0.02), 4 studies, 2557 participants). Sensitivity analysis between (fixed vs random) models. Random effects model showed no association 0.01 (95% CI): -0.10:0.11) Subanalysis between pregnant women/ general population and Total t3 occurred: No correlation between PFOS and total T3 in pregnant women. The pooled Z value was -0.01 (-0.10;0.09, 2 studies). No association between PFOS and total t3 in general population. Pooled Z value: -0.01 (-0.08;0.06, 6 studies).	
			Route unspecified **Measure**	Thyroid Function: TSH Pearson correlation coefficient transformed by the Fisher z-transformation.	"Using Random effects model no correlation between PFOS and total TSH in total population -0.02 (95% CI):-0.07; 0.03, 12	Subanalysis of different levels of total TSH conducted: Exposure to mean PFOS (<8ng/mL) was correlated with total TSH in total population. The	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			ng/mL **Exposure time** unspecified		studies, 6445 participants). Sensitivity analysis between models (fixed vs random) showed no difference. Fixed effects pooled Z values -0.01 (95%CI):-0.04; 0.01, 12 studies, 6445 participants)."	pooled Z value was -.10(95% ci):-0.16; -0.65), 3 studies, 1105 participants) Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association -0.14 (95% CI) -0.28; 0.01). No correlation between mean PFOS (8-16ng/mL) andtotal TSH in total population. The pooled Z value was 0.03 (95% CI): 0.00; 0.07, 4 studies, 2753 participants) Sensitivity analysis between (fixed vs random) models showed no difference 0.03 (95% CI): 0.00: 0.07, 4 studies, 2753 participants). No correlation between mean PFOS (>16ng/mL) and total TSH in total population. The pooled Z value was -0.02 (95% CI): -0.06;0.02), 5 studies, 2587 participants). Sensitivity analysis between (fixed vs random) models. Random effects model showed no association -0.01 (95% CI): -0.08;0.07) Subanalysis between pregnant	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						women/ general population and total TSH conducted: No correlation between PFOS and total TSH in pregnant women. The pooled Z value was -0.08 (-0.12; 0.08, 4 studies). No association between PFOS and total TSH in general population. Pooled Z value: -0.01 (-0.04; 0.02, 8 studies).	
			Type PFHxS **Route** Unspecified **Measure** ng/mL < 0.8 ng/mL (low), and 0.8 ng/mL (high). **Exposure time** unspecified	Thyroid Function: free t4 Pearson correlation coefficient transformed by the Fisher z-transformation. T4 was measured differently: chemiluminescent immunoassay (n = 5 studies), radioimmunoassay (n = 3 studies), or enzyme-linked immunosorbent assay (n = 1 studies). However, no measurement ranges of T4 were notes.	Using Random effects model no correlation between PFHxS and free T4 in total population 0.02 (95% CI):-0.01; 0.05, 6 studies, 3641 participants). Sensitivity analysis between models (fixed vs random) showed no difference. Fixed effects pooled Z values 0.02 (95% CI):-0.01; 0.05, 6 studies, 3641 participants).	Subanalysis of different levels of total PFHxS conducted: No correlation between mean PFHxS (<8ng/mL) and free T4 in total population. The pooled Z value was - 0.00(95% ci):-0.10; 0.09), 3 studies, 415 participants) Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association - 0.00(95% ci):-0.10; 0.09), 3 studies, 415 participants) No correlation between mean PFHxS (>8ng/mL) and free T4 in total population. The pooled Z value was 0.02 (95% CI): -0.01; 0.06, 3 studies, 3226 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						effects model: 0.02 (95% CI): -0.01; 0.06, 3 studies, 3226 participants) Subanalysis between pregnant women/ general population and total TSH conducted: No correlation between PFHxS and free T4 in pregnant women. The pooled Z value was 0.01 (-0.01; 0.05, 2 studies). No association between PFHxS and free T4 in general population. Pooled Z value: 0.02 (-0.01; 0.05, 4 studies).	
			Route Unspecified **Measure** ng/mL **Exposure time** unspecified	Thyroid Function: : Total T4 Pearson correlation coefficient transformed by the Fisher z-transformation.	Using Random effects model no correlation between PFHxS and total T4 in total population 0.04 (95% CI):-0.04; 0.01, 6 studies, 4154 participants). Sensitivity analysis between models (fixed vs random). Fixed-effects model found exposure to PFHxS was correlated with total T4: Pooled Z values -0.04 (95% CI):-0.07; -0.01, 6	Subanalysis of different levels of total PFHxS occurred (fixed-effects model reported when < 5 studies) with sensitivity analysis on model (Fixed vs random effects model) type conducted: No correlation between mean PFHxS (<8ng/mL) and total T4 in total population. The pooled Z value was - 0.04(95% ci):-0.11; 0.02), 3 studies, 929 participants) Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association - 0.04(95% CI):-0.11; 0.02), 3 studies, 415 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					studies, 4154 participants).	No correlation between mean PFHxS (>8ng/mL) and total T4 in total population. The pooled z value was -0.04 (95% CI): -0.07; 0.00, 3 studies, 3225 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random effects model: -0.02 (95% CI): -0.09; 0.04, 3 studies, 3225 participants) Subanalysis between pregnant women/ general population and Total T4 conducted: No correlation between PFHxS and total T4 in pregnant women. The pooled Z value was 0.01 (-0.18; 0.20, 2 studies). Exposure to PFHxS correlated with total T4 in general population. Pooled Z value: -0.04 (-0.07; -0.01, 4 studies).	
				Thyroid Function: Total T3 Pearson correlation coefficient transformed by the Fisher z-transformation.	Using fixed-effects model no correlation between PFHxS and total T3 in total population 0.00 (95% CI):-0.03; 0.04, 5 studies, 3600 participants).	Subanalysis of different levels of total PFHxS conducted: No correlation between mean PFHxS (<8ng/mL) and total T3 in total population. The pooled Z value was - 0.03(95% ci):-0.13; 0.07), 2 studies, 375 participants)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					Sensitivity analysis between models (fixed vs random) found no difference. random effects model: 0.00 (95% CI):-0.03; 0.04, 5 studies, 3600 participants)	Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association 0.00(95% CI):-0.19; 0.19), 2 studies, 375 participants) No correlation between mean PFHxS (>8ng/mL) and total T3 in total population. The pooled Z value was 0.01 (95% CI): -0.03; 0.04, 3 studies, 3225 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random effects model: 0.01 (95% CI): -0.03; 0.04, 3 studies, 3225 participants) Subanalysis between pregnant women/ general population and Total T3 conducted: No correlation between PFHxS and total T3 in pregnant women. The pooled Z value was 0.01 (-0.16; 0.14, 2 studies). No correlation between PFHxS and total T3 in general population. Pooled Z value: -0.04 (-0.03; 0.04, 4 studies).	
			Route	Thyroid Function: TSH	Using random effects model no correlation	Subanalysis of different levels of total PFHxS conducted:	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			unspecified **Measure** ng/mL **Exposure time** unspecified	Pearson correlation coefficient transformed by the Fisher z-transformation.	between PFHxS and total TSH in total population 0.00 (95% CI):-0.03; 0.04, 8 studies, 5099 participants). Sensitivity analysis between models (fixed vs random) found no difference. Fixed-effects model: 0.00 (95% CI):-0.03; 0.03, 8 studies, 5099 participants)	No correlation between mean PFHxS (<8ng/mL) and total TSH in total population. The pooled Z value was 0.01(95% ci):-0.03; 0.06), 5 studies, 1872 participants) Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association 0.02(95% CI):-0.04; 0.07), 5 studies, 1872 participants) No correlation between mean PFHxS (>8ng/mL) and total TSH in total population. The pooled Z value was -0.00 (95% CI): -0.04; 0.03, 3 studies, 3227 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random effects model: -0.01 (95% CI): -0.07; 0.04, 3 studies, 3227 participants) Subanalysis between pregnant women/ general population and total TSH conducted: No correlation between PFHxS and total TSH in pregnant women. The pooled Z value was	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						0.00 (-0.12; 0.13, 3 studies). No correlation between PFHxS and total TSH in general population. Pooled Z value: 0.00 (-0.04; 0.03, 5 studies).	
			Type PFOA **Route** Unspecified **Measure** ng/mL < 2 ng/mL (low), 2±3 ng/mL (intermediate), and > 3 ng/mL (high) **Exposure time** unspecified	Thyroid Function: FREE T4 Pearson correlation coefficient transformed by the Fisher z-transformation. T4 was measured differently: chemiluminescent immunoassay (n = 5 studies), radioimmunoassay (n = 3 studies), or enzyme-linked immunosorbent assay (n = 1 studies). However, no measurement ranges of T4 were notes.	Using random effects model no correlation between PFOA and FREE T4 in total population 0.01 (95% CI):-0.02; 0.04, 8 studies, 4120 participants). Sensitivity analysis between models (fixed vs random) found no difference. Fixed-effects model:0.01 (95% CI):-0.02; 0.04, 8 studies, 4120 participants).	Subanalysis of different levels of total PFOA occurred (fixed-effects model reported when < 5 studies) with sensitivity analysis on model (Fixed vs random effects model) type conducted: No correlation between mean PFOA (<2ng/mL) and free T4 in total population. The pooled Z value was 0.02(95% ci):-0.08; 0.12), 2 studies, 423 participants) Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association:0.02(95% ci):-0.08; 0.12), 2 studies, 423 participants) No correlation between mean PFOA(2-3 ng/mL) and free T4 in total population. The pooled Z value was 0.02 (95% CI): -0.03; 0.06, 4 studies, 2008 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						effects model: 0.02 (95% CI): -0.03; 0.06, 4 studies, 2008 participants) No correlation between mean PFOA (>3ng/mL) and free T4 in total population. The pooled Z value was -0.00 (95% CI): -0.05; 0.05, 2 studies, 1689 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random effects model: 0.05 (95% CI): -0.12; 0.21, 2 studies, 1689 participants) Subanalysis between pregnant women/ general population and PFOA AND FREE T4 conducted: No correlation between PFOA and free T4 in pregnant women. The pooled Z value was 0.00 (-0.07; 0.06, 3 studies). No correlation between PFOA and free T4 in general population. Pooled Z value: 0.01 (-0.02; 0.05, 5 studies).	
			Route Unspecified **Measure**	Thyroid function: Total T4 Pearson correlation coefficient transformed by the Fisher z-	Using random effects model no correlation between PFOA and TOTAL T4 in total population 0.01 (95%	Subanalysis of different levels of total PFOA conducted: No correlation between mean PFOA (2-3 ng/mL) and TOTAL T4	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			ng/mL **Exposure time** unspecified	transformation. T4 was measured differently: chemiluminescent immunoassay (n = 5 studies), radioimmunoassay (n = 3 studies), or enzyme-linked immunosorbent assay (n = 1 studies). However, no measurement ranges of T4 were notes.	CI):-0.07; 0.05, 8 studies, 4487 participants). Sensitivity analysis between models (fixed vs random). Fixed-effects model found -ve correlation:-0.05 (95% CI):-0.08; -0.02, 8 studies, 4487 participants).	in total population. The pooled Z value was -0.04 (95% CI): -0.08; 0.00, 5 studies, 2552 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random effects model: -0.00 (95% CI): -0.08; 0.07, 5 studies, 2552 participants) Exposure between mean PFOA (>3ng/mL) was -ve correlated with TOTAL T4 in total population. The pooled Z value was -0.06 (95% CI): -0.10; -0.01, 3 studies, 1935 participants) Sensitivity analysis between (fixed vs random) model. Random effects model found no association: -0.00 (95% CI): -0.16; 0.16, 3 studies, 1689 participants) Subanalysis between pregnant women/ general population and PFOA AND TOTAL T4 conducted: No correlation between PFOA and TOTAL in pregnant women. The pooled Z value was 0.04 (-0.06; 0.13, 2 studies). No correlation between PFOA and TOTAL in general population.	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						Pooled Z value: -0.03 (-0.09; 0.04, 6 studies).	
			Route Unspecified **Measure** ng/mL **Exposure time** unspecified	Thyroid Function: T3 Pearson correlation coefficient transformed by the Fisher z-transformation.	Using random effects model no correlation between PFOA and TOTAL T3 in total population 0.05 (95% CI):0.00; 0.10, 7 studies, 3933 participants). Sensitivity analysis between models (fixed vs random). Fixed-effects model found no correlation: 0.03 (95% CI):0.00; 0.10, studies, 3933 participants).	Subanalysis of different levels of total T3 conducted: No correlation between mean PFOA (2-3 ng/mL) and TOTAL T3 in total population. The pooled Z value was 0.02 (95% CI): -0.02; 0.06, 4 studies, 1998 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Random effects model: 0.05 (95% CI): -0.03; 0.14, 4 studies, 1998 participants) No correlation between mean PFOA (>3ng/mL) and TOTAL T3 in total population. The pooled Z value was 0.04 (95% CI): 0.00; 0.08, 3 studies, 1935 participants) Sensitivity analysis between (fixed vs random) model. Random effects model found no association: 0.06 (95% CI): -0.02; 0.14, 3 studies, 1935 participants) Subanalysis between pregnant women/ general population and	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						PFOA AND TOTAL T3 occurred: No correlation between PFOA and TOTAL T3 in pregnant women. The pooled Z value was 0.04 (-0.05; 0.14, 2 studies). No correlation between PFOA and TOTAL T3 in general population. Pooled Z value: 0.05 (-0.01; 0.11, 5 studies).	
			Route Unspecified **Measure** ng/mL **Exposure time** unspecified	Thyroid Function: TSH Pearson correlation coefficient transformed by the Fisher z-transformation.	Using random effects model no correlation between PFOA and TSH in total population 0.00 (95% CI):-0.03; 0.04, 11 studies, 5823 participants). Sensitivity analysis between models (fixed vs random). Fixed-effects model found no correlation: 0.00 (95% CI):0.02; 0.03, 11 studies, 5823 participants).	Subanalysis of different levels of total TSH conducted: No correlation between mean PFOA (<2ng/mL) and TSH in total population. The pooled Z value was 0.04(95% ci):-0.06; 0.13), 2 studies, 423 participants) Sensitivity analysis between fixed-effects models and random effects model. Random effects model showed no association: 0.04(95% ci):-0.06; 0.13), 2 studies, 423 participants) No correlation between mean PFOA (2-3 ng/mL) and TSH in total population. The pooled Z value was -0.01 (95% CI): -0.06; 0.04, 6 studies, 3466 participants) Sensitivity analysis between (fixed vs random) models showed no difference. Fixed-effects model: -0.00 (95% CI): -	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						0.04; 0.03, 6 studies, 3466 participants) No correlation between mean PFOA (>3ng/mL) and TSH in total population. The pooled Z value was 0.00 (95% CI): -0.04; 0.05, 3 studies, 1934 participants) Sensitivity analysis between (fixed vs random) model. Random effects model found no association: 0.03 (95% CI): -0.06; 0.12, 3 studies, 1934 participants) Subanalysis between pregnant women/ general population and PFOA AND TSH occurred: No correlation between PFOA and TSH in pregnant women. The pooled Z value was 0.04 (-0.05; 0.14, 2 studies). No correlation between PFOA and TSH in general population. Pooled Z value: 0.05 (-0.01; 0.11, 5 studies).	
Liu 2018 - Perfluorooctanoic Acid (PFOA) Exposure in Early Life Increases Risk of Childhood Adiposity: A Meta-Analysis of Prospective Cohort Studies- No COIs declared							

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Last search May-18 **Study types** Prospective Cohort **Included studies in the review =** 10 **Included studies in the meta-analysis =** 10	Newcastle-Ottawa Scale. All studies scored between 7-8 and were therefore deemed as high quality.	Unclear in the characteristics of the included participants. Combined males and females, but age not noted. N = 6,077	PFOA Unspecified maternal serum/ plasma or cord blood Measured through pregnancy and up to 3 weeks postpartum. However, unspecified on when the PFOA entered blood stream of mother	Childhood Obesity Effect size (RR and OR) 95% CI. There was no clear definition in the research about what was considered obesity	PFOA in early life had a statistically significant association with childhood overweight risk (1.25, 95% CI: 1.04, 1.50, 8 studies, participants unspecified).*** Authors reported an effect size that was RR and OR combined.	When the studies stratified analysis by the effect size (relative risk vs. odds ratio), a significant correlation between early-life exposure to PFOA and childhood overweight risk was observed in group of relative risk (RR) (RR = 1.26, 95% CI: 1.01, 1.56; 6 studies, 4224 participants) while the odds ratio (OR) group had a slightly higher assessment but no significant risk for childhood overweight (OR = 1.39, 95% CI: 0.85, 2.28; 2 studies, 1223 participants).	7
				Childhood increased BMI Beta coefficients; 95% CI. There was no clear definition in the research about what was considered high BMI	Exposure to PFOA in early life could slightly increase the z-score of childhood BMI (β = 0.10, 95% CI: 0.03,.17, 9 studies, 5,411 participants); Sensitivity analysis β 0.07, 95% CI: 0.01 to 0.14; 5 studies, 3,825 participants	Studies were stratified by measurement timing: Prenatal exposure β= 95%CI: 0.09 0.02, 0.17, studies unspecified, 5505participants and Postnatal exposure β=0.16 95%CI: 0.01, 0.30, studies unspecified, 571 participants to PFOA indicated a small increase in the z-score of childhood BMI. Early-life exposure to PFOA and childhood BMI z-score a significant association was observed among the studies performed in Europe β=0.10 95%CI: 0.02, 0.17, 7 studies, 3545 participants	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						No association between early-life exposure to PFOA and childhood BMI z-score among the studies performed in Northern America β=0.19 95%CI: −0.05, 0.42, 3 studies, 2102 participants Early-life exposure to PFOA and childhood BMI z-score a significant association was observed in the group adjusted by adjusted by maternal parity β= 0.13 95%CI: 0.02, 0.24, 7studies, 3949 participants. However, no association between PFOA and when maternal parity was not adjusted β= 0.07 95%CI: −0.01, 0.15, 4 studies, 2127 participants. The subgroup of birth weight was evaluated, and PFOA exposure could statistically significantly increase the z-score of childhood BMI in the group that was not adjusted by birth weight β= 0.10 95%CI: 0.03, 0.17, 10 studies, 5705 participants. There was no association between PFOA and BMI z-score in girls β=0.0695%CI: −0.01, 0.13, studies unspecified, 1549	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						participants and in boys β=−0.01 95%CI:−0.10, 0.08, studies unspecified, 1628 participants.	
Luo 2020 - Exposure to perfluoroalkyl substances and allergic outcomes in children: A systematic review and meta-analysis- No COIs declared							
Last search Oct-19 **Study types** cohort (n=10), cross sectional (n=2), case control (n=1) **Included studies in the review =** 13 **Included studies in the meta-analysis =** 13	The 9-star Newcastle-Ottawa Scale (NOS). Two studies were classified as medium quality and 11 as high quality.	Children (birth to 18 years of age) N = 11,255	**Type** Perfluoroalkyl substances (PFAS) **Route** Prenatal exposure, except three studies. Details of exposure not reported in postnatal exposure studies. **Measure** Cord blood or plasma, serum, maternal serum or plasma (units NR)	Childhood asthma Odds ratio 95%CI. Analysis type NR.	No association between childhood asthma and PFOS (OR=1.11, 95%CI: 0.88, 1.40; 8 studies, 7050 participants), PFOA (OR=1.11, 95% CI: 0.85, 1.24; 8 studies, 7050 participants) or PFNA (OR=0.99, 95%CI: 0.81-1.21; 8 studies, 7050 participants) or PFHxS (OR=1.02, 95%CI: 0.85-1.24; 8 studies, 7050 participants)	When studies were stratified by region a significant positive association was found in Asia for PFOS (OR=2.47, 95%CI: 1.43, 4.25; 2 studies, participants unspecified), PFHxS (OR=3.66, 95%CI: 2.06, 6.49; 2 studies, participants unspecified) and PFNA (OR=2.37, 95%CI: 1.34, 4.20; 2 studies participants unspecified), but not for PFOA (OR=2.37, 95%CI: 0.62, 9.13; 2 studies, participants unspecified) There was no association found in Europe for PFOS (OR=0.98, 95%CI: 0.78, 1.23; 5 studies, participants unspecified), PFOA (OR=0.92, 95%CI: 0.78, 1.07; 5 studies, participants unspecified), PFHxS (OR=0.94, 95%CI: 0.84, 1.04; 5 studies, participants unspecified), or PFNA (OR=0.90, 95%CI: 0.73, 1.09; 5 studies, participants unspecified). When studies were grouped by exposure, there was no association found for PFOA and prenatal (OR 0.92, 95%CI: 0.79 to	7

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Exposure time NR			1.07; 6 studies, participants unspecified) and postnatal (OR 2.05, 95%CI: 0.58 to 7.27; 2 studies, participants unspecified) exposure; PFOS and prenatal exposure (OR 0.99, 95%CI: 0.80 to 1.22; 6 studies, participants unspecified) and postnatal exposure (OR 1.57, 95%CI: 0.62 to 4.00; 2 studies, participants unspecified); PFHxS and prenatal exposure (OR 0.94, 95%CI: 0.84 to 1.05; 6 studies, participants unspecified) and postnatal exposure (OR 1.83, 95%CI: 0.45 to 7.38; 2 studies, participants unspecified), and PFNA and prenatal (OR 0.90, 95%CI: 0.74 to 1.06; 6 studies, participants unspecified) and postnatal (OR 1.52, 95%CI: 0.60 to 3.85; 2 studies, participants unspecified) exposure.	
				Childhood wheeze Odds ratio 95%CI. Analysis type NR.	No association between childhood wheeze and PFOS (OR=0.90, 95%CI: 0.78, 1.04; 6 studies, 6672 participants), PFOA (OR=1.03, 95%CI: 0.93, 1.15; 6 studies, 6672 participants), PFHxS (OR=0.97, 95%CI: 0.87,	When stratified by region, there was no association found in Asia between childhood wheeze and PFOS (OR=0.79, 95%CI: 0.55, 1.13; 2 studies, participants unspecified), PFOA (OR=0.98, 95%CI: 0.60, 1.60; 2 studies, participants unspecified), PFHxS (OR=0.73, 95%CI: 0.50, 1.05; 2 studies, participants unspecified),	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					1.08; 6 studies, 6672 participants), or PFNA (OR=0.98, 95%CI: 0.88, 1.08; 6 studies, 6672 participants).	or PFNA (OR=0.96, 95%CI: 0.49, 1.87; 2 studies, participants unspecified). There was no association found in Europe between childhood wheeze and PFOS (OR=0.95, 95%CI: 0.74, 1.22; 3 studies participants unspecified), PFOA (OR=1.04, 95%CI: 0.88, 1.23; 3 studies, participants unspecified), PFHxS (OR=1.04, 95%CI: 0.93, 1.16; 3 studies, participants unspecified), or PFNA (OR=0.98, 95%CI: 0.84, 1.15; 3 studies, participants unspecified). When studies were grouped by exposure, there was no association found for PFOA and prenatal exposure (OR 1.03, 95%CI: 0.90 to 1.17; 5 studies, participants unspecified); PFOS and prenatal exposure (OR 0.91, 95%CI: 0.76 to 1.09; 5 studies, participants unspecified); PFHXs and prenatal exposure (OR 1.00, 95%CI: 0.89 to 1.13; 5 studies, participants unspecified); and PFNA and prenatal exposure (OR 0.99, 95%CI: 0.86 to 1.13; 5 studies, participants unspecified)	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
				Childhood eczema Odds ratio 95%CI. Analysis type NR.	PFNA exposure was found to be inversely associated with childhood eczema (OR=0.89, 95%CI: 0.80, 0.99; 5 studies, 5276 participants). No association between childhood eczema and exposure to PFOS (OR=0.91, 95%CI: 0.81, 1.02; 5 studies, 5276 participants), PFOA (OR=0.99, 95%CI: 0.88, 1.10; 5 studies, 5276 participants), PFHxS (OR=1.07, 95%CI: 0.96, 1.20; 5 studies, 5276 participants) was found.	When stratified by region, there was no association found in Europe between childhood eczema and PFOS (OR=0.92, 95%CI: 0.81, 1.04; 4 studies, participants unspecified), PFOA (OR=1.00, 95%CI: 0.89, 1.12; 4 studies, participants unspecified), PFHxS (OR=1.09, 95%CI: 0.97, 1.23; 4 studies participants unspecified), or PFNA (OR=0.90, 95%CI: 0.81, 1.00; 4 studies, participants unspecified).	
				Atopic dermatitis	PFOS exposure was found to be significantly associated with atopic dermatitis (OR=1.26, 95%CI: 1.01, 1.58; 4 studies, 2650 participants). There was no association between atopic dermatitis and PFOA (OR=1.39, 95%CI: 0.89, 2.18; 4 studies, 2650 participants), PFHxS	When stratified by region, there was an association found in Asia between atopic dermatitis and PFOS (OR=1.54, 95%CI: 1.03, 2.31; 3 studies, participants unspecified), but not PFOA (OR=1.49, 95%CI: 0.73, 3.06; 3 studies, participants unspecified), PFHxS (OR=1.20, 95%CI: 0.77, 1.88; 2 studies, participants unspecified), or PFNA (OR=1.00, 95%CI: 0.66, 1.53; 3 studies, participants unspecified).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
					(OR=1.08, 95%CI: 0.92, 1.27; 4 studies, 2650 participants), or PFNA (OR=0.96, 95%CI: 0.65, 1.43; 4 studies, 2650 participants).		
				Allergic rhinitis Odds ratio 95%CI. Analysis type NR.	Exposure to PFOA was significantly associated with risk of allergic rhinitis in children (OR=1.32, 95%CI: 1.13, 1.55; 4 studies, 3396 participants). There was no association between risk of allergic rhinitis and PFOS (OR=1.07, 95%CI: 0.89, 1.29; 4 studies, 3396 participants), PFHxS (OR=0.94, 95%CI: 0.79, 1.13; 4 studies, 3396 participants), or PFNA (OR=0.99, 95%CI: 0.71, 1.37; 4 studies, 3396 participants).	When stratified by region, there was no association found in Europe between allergic rhinitis and PFOS (OR=1.0p3, 95%CI: 0.75, 1.41; 2 studies, no. participants NR), PFOA (OR=1.29, 95%CI: 0.98, 1.69; 2 studies, no. participants NR), PFHxS (OR=1.01, 95%CI: 0.86, 1.20; 2 studies, no. participants NR), or PFNA (OR=1.11, 95%CI: 0.79, 1.54; 2 studies, no. participants NR). When studies were grouped by exposure, there was no association found in PFOA and prenatal exposure (OR 1.29, 95%CI: 1.00 to 1.66; 3 studies, participants unspecified); PFOS and prenatal exposure (OR 0.97, 95%CI: 0.74 to 1.29; 3 studies, participants unspecified); PFHxS and prenatal exposure (OR 0.99, 95%CI: 0.84 to 1.16; 3 studies, participants unspecified); and PFNA and prenatal exposure (OR	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						0.83, 95%CI: 0.47 to 1.46; 3 studies, participants unspecified)	
Negri 2017 - Exposure to PFOA and PFOS and foetal growth: a critical merging of toxicological and epidemiological data - No COIs declared							
Last search Nov-15 **Study types** Cross sectional (n=4) Prospective Cohort (n=9) Case Control (n=3) **Included studies in the review =** 16 **Included studies in the meta-analysis =** 9	Two researchers independently assessed the methodological aspects of each study using a modification of the "Newcastle-Ottawa Quality Assessment Scale". For the four cross-sectional studies, the evaluation ranged between 4 and 5 out of a total of 6 points. Potential bias could emerge from incomplete control of confounding and lack of representativeness of the study. Population. Among the 12 cohort studies	Children born to pregnant mothers studied during the reproductive / developmental time period (before and / or during pregnancy. Mothers and children exposed to PFFA as assessed using a biological sample N = 8,335	**Type** Perfluoralkyl acids (PFAA) Which include: Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS) **Route** Unspecified, but detection limited to maternal or umbilical cord serum, plasma or whole blood or maternal milk **Measure** Authors have presented both natural units as mean PFAA (ng/mL)	Birth Weight ONLY CONSIDERING PFOA Beta-coefficient effect size (natural units; untransformed)	Prenatal exposure to PFOA was associated with a decrease in birthweight (b = -12.8 grams, 95% CI: -23.21, -2.38grams, (p-value not provided); 12 studies; 6501 participants); untransformed data; estimated linear regression coefficient range -213 to 154g for an increase of 1 loge ng/mL PFOA	No association between PFOA and birthweight via location using untransformed data: America (b - 11.8, 95%CI: -32.1 to 8.6; 4 studies) and Europe (b -15.5, 95%CI: -35.4 to 4.4; 5 studies, participants unspecified); however, in Asia, exposure to PFOA was associated with decreased birthweight (b -12.2, 95%CI: -27.3 to 3.0; 3 studies, participants unspecified) No association between PFOA and birthweight via maternal blood samples collected in the first to second trimester using untransformed data (b -10.5, 95%CI: -23.6 to 2.6; 6 studies, participants unspecified) and third trimester (b -20; 95%CI: -52.1 to 12.1; 2 studies, participants unspecified), and in via cord samples using untransformed data (b -35.3, 95%CI: -101.0 to 30.7; 4 studies, participants unspecified)	8

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
	(authors included case control as a 'cohort' study), the evaluation ranged from 3/7 to 7/7. Again, potential risk of bias could mostly derive from lack of control of confounding and unclear adequacy of follow-up of women from recruitment to delivery.		and then the natural log **Exposure time** Unspecified But exposure was prenatal				
			Type Perfluoralkyl acids (PFAA) Which include: Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS) **Route** Unspecified, but detection limited to maternal or umbilical cord serum, plasma or whole blood or maternal milk **Measure**	Birth Weight ONLY CONSIDERING PFOA Beta-coefficient effect size (natural log; transformed)	Prenatal exposure to PFOA was associated with a decrease in birthweight per 1 log(ng/ml) PFOA (-27.12grams, 95% CI: -50.64, -3.60grams, (p-value not provided); 9 studies; 3844 participants); transformed data; estimated LRC ranged from 142 to 5 g for an increase of 1 loge ng/mL PFOA,	No association between prenatal PFOA exposure and birthweight in subgroups of location using transformed data: America (b -28.2, 95%CI: -64.5 to 8.1; 6 studies, participants unspecified), however, prenatal exposure to PFOA was associated with a decrease in birthweight in Asia (b -31.9, 95%CI: -63.6 to -0.2; 4 studies, participants unspecified) No association between prenatal PFOA exposure and birthweight via maternal blood samples collected in the first to second trimester using transformed data (b-10.6, 95%CI: -43.2 to22.0; 4 studies, participants unspecified). However, PFOA exposure was associated with decreased birthweight in maternal blood samples collected in the third trimester (b -51.0, 95%CI: -86.6 to -15.5; 3 studies, participants unspecified). No association between prenatal	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			Authors have presented both natural units as mean PFAA (ng/mL) and then the natural log **Exposure time** Unspecified But exposure was prenatal			PFOA exposure and birthweight via cord samples using transformed data (b -24.4, 95%CI: -66.3 to 18.2; 3 studies)	
			Type Perfluoralkyl acids (PFAA) Which include: Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS) **Route** Unspecified, but detection limited to maternal or umbilical cord serum, plasma or whole blood	Birth Weight ONLY CONSIDERING PFOS Beta-coefficient effect size (natural units; untransformed)	No association was found between PFOS and birthweight (b = -0.92grams, 95% CI: -3.43, 1.60grams), (p-value not provided); 8 studies; 5465 participants); untransformed data; estimated linear regression coefficient range - 11.3 to 5.8g a change of 1 ng/mL in PFOS level	No association between prenatal exposure to PFOS and birthweight in subgroups of location using untransformed data: America (b -1.6, 95%CI: -4.9 to 8.1; 2 studies, participants unspecified) and Europe (b -0.5, 95%CI: -1.6 to 2.7; 4 studies, participants unspecified), however, prenatal exposure to PFOS was associated with decreased birthweight in Asia (-11.2, 95%CI: -16.7 to -5.8: 2 studies, participants unspecified) No association between prenatal PFOS exposure and birthweight via maternal blood samples collected in the first to second trimester using untransformed data (b 0.6, 95%CI: -1.4 to 2.5; 5	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			or maternal milk **Measure** Authors have presented both natural units as mean PFAA (ng/mL) and then the natural log **Exposure time** Unspecified But exposure was prenatal			studies) and third trimester (b -4.0, 95%CI: -16.3 to 8.2; 2 studies, participants unspecified). Only 1 study for umbilical cord subgroup	
			Type Perfluoralkyl acids (PFAA) Which include: Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS) **Route** Unspecified, but detection limited to	Birth Weight ONLY CONSIDERING PFOS Beta-coefficient effect size (natural log; transformed)	Prenatal exposure to PFOS was associated with a decrease in birthweight per 1 log(ng/ml) PFOS (b = -46.09, 95% CI: -80.33, -11.85grams, (p-value not provided); 8 studies; 3677 participants); transformed; estimated linear regression coefficient range -140 to 66.1g for an increase of 1 loge ng/mL PFOS	Prenatal exposure to PFOS was associated with a decrease in birthweight in subgroups of location using transformed data: America (b -25.4, 95%CI: -66.0 to -15.2; 6 studies, participants unspecified) and Asia (b -85.7, 95%CI: -135 to -36.3; 3 studies, participants unspecified) No association between prenatal PFOS exposure and birthweight via maternal blood samples collected in the first to second trimester using transformed data (b -4.0, 95%CI: -62.3 to 54.3; 4 studies, participants unspecified).	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			maternal or umbilical cord serum, plasma or whole blood or maternal milk **Measure** Authors have presented both natural units as mean PFAA (ng/mL) and then the natural log **Exposure time** Unspecified But exposure was prenatal			However, PFOS exposure was associated with decreased birthweight in maternal blood samples collected in the third trimester (b -65.1, 95%CI: -127.0 to -3.2; 2 studies, participants unspecified) and umbilical cord samples collected (b -93.2, 95%CI: -149.0 to -37.8; 3 studies, participants unspecified)	
Steenland 2018- Serum Perfluorooctanoic Acid and Birthweight: An Updated Meta-analysis With Bias Analysis- No COIs declared							
Last search Dec-17 **Study types** Unspecified	No critical appraisal appears to have been conducted	No further characteristics given N = 19,173	**Type** PFOA **Route** unspecified **Measure**	birthweight Assumed birthweight mean of about 3500grams. Summary coefficient (95% CI)	Exposure to PFOA there was an association between a change of birthweight of -10.5 g (-16.7, -4.4) for every ng/ml of maternal or cord blood (24studies, 19,173 participants); approximately a drop	No association between PFOA and when blood sampling was early (First trimester a mixture of first and second, or mostly/all preconception) was found s -3.3 [-9.6, 3.0, 7 studies, 5,393 births) compared with studies in which the blood sampling was late (either second or third trimester,	4

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
Included studies in the review = 24 **Included studies in the meta-analysis =** 24			ng/ml of maternal or cord blood log-untransformed PFOA. For studies that gave results only for log-transformed PFOA (nine studies; 11 results), we approximated the results for an untransformed analysis by iteratively minimising the squared deviation of a new linear curve from the original logarithmic one, over a scale of 0 to 10 ng/ml PFOA, **Exposure time** In utero but unspecified about how		of 0.3% in weight per unit of serum PFOA, assuming a mean birthweight of about 3,500 g	or a mixture of second/third trimester) and measurement of PFOA in blood sampling. -17.8 [-25.0, -10.6, 17 studies, 7,563 births). subanalysis of maternal blood studies to cord blood studies, found exposure to PFOA to be associated with blood studies, a change in birthweight -9.2 (-15.6, -2.8) g per ng/ml serum PFOA, 15 studies, no participant data). Cord blood studies found an association between change in birthweight of -13.3 (-24.7, -1.8) g per ng/ml serum PFOA, 9 studies	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
			mothers were exposed.				
Forns 2020- Early Life Exposure to Perfluoroalkyl Substances (PFAS) and ADHD: A Meta-Analysis of Nine European Population-Based Studies. No COI declared.							
Last search Unspecified **Study types** European cohort **Included studies in the review =** 9 **Included studies in the meta-analysis =** 9	unspecified	Children (≤18 years old) and mothers (maternal exposure) N = 4826 mother-child pairs	**Type** Perfluoroalkyl substances (PFAS)-perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) **Route** Prenatal exposure, unless exposure measured in breast milk **Measure** Maternal serum/plasma or breast milk (ng/mL) **Exposure time** First 24 months of life	Attention deficit and hyperactivity disorder (ADHD) children 4-11 years old OR and 95%CIs; logistic regression models		No associations between PFOA and ADHD in various time periods based on the model used: at birth (OR, 1.01, 95%CI: 0.93 to 1.11; 9 cohorts, 4,826 participants), 3 months (OR 1.02, 95%CI: 0.93 to 1.11; 9 cohorts, 4,826 participants), 6 months (OR 1.01, 95%CI: 0.91 to 1.12; 9 cohorts, 4,826 participants), 12 months (OR 1.00, 95%CI: 0.89 to 1.12;9 cohorts, 4,826 participants) and 24 months (OR 0.99, 95%CI: 0.88 to 1.12;9 cohorts, 4,826 participants) No associations between PFOS and ADHD in various time periods based on the model used: at birth (OR 0.99, 95%CI: 0.92 to 1.07; 9 cohorts; 4,826 participants), 3 months (OR 0.99, 95%CI:0.92 to 1.06; 9 cohorts; 4,826 participants), 6 months (OR 0.98, 95%CI:0.90 to 1.06; 9 cohorts; 4,826 participants), 12 months (OR 0.96, 95%CI: 0.87 to 1.06; 9 cohorts; 4,826 participants) and 24 months (OR 0.97, 95%CI: 0.88 to 1.07; 9 cohorts; 4,826 participants)	3

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						An association between PFOA and ADHD in girls was found at birth (OR 1.28, 95%CI: 1.03 to 1.59; 9 cohorts, 82 participants) and at 3 months (OR, 1.28, 95%CI: 1.01 to 1.62; 9 cohorts, 82 participants). No association was found at 6 months (OR 1.29, 95%CI: 1.00 to 1.66; 9 cohorts, 82 participants), 12 months (OR 1.24, 95%CI: 0.96 to 1.61; 9 cohorts, 82 participants), 24 months (OR 1.30, 95%CI: 0.98 to 1.73; 9 cohorts, 82 participants). No association between PFOA and ADHD in boys in various time periods: at birth (OR 0.98, 95%CI:0.87 to 1.09; 9 cohorts, 306 participants), 3 months (OR, 1.00, 95%CI:0.89 to 1.11; 9 cohorts, 306 participants), 6 months (OR, 1.02, 95%CI: 0.86 to 1.22; 9 cohorts, 306 participants), 12 months (OR 1.03, 95%CI: 0.85 to 1.25; 9 cohorts, 306 participants) and 24 months (OR 0.97, 95%CI: 0.83 to 1.14;9 cohorts, 306 participants)	
						No associations between PFOS and ADHD in various time periods based on the model used in subgroup of girls: at birth (OR 1.14, 95%CI: 0.91 to 1.34; 9	

Study details	Appraisal details	Participants	Plastic exposure	Health outcomes	Findings	Subgroup findings	AMSTAR score
						cohorts, 82 participants), 3 months (OR 1.12, 95%CI :0.94 to 1.34; 9 cohorts, 82 participants), 6 months (OR 1.13 95%CI: 0.93 to 1.36; 9 cohorts, 82 participants), 12 months (OR 1.19, 95%CI: 0.92 to 1.53; 9 cohorts, 82 participants), 24 months (OR 1.26, 95%CI: 0.93 to 1.72; 9 cohorts, 82 participants) No associations between PFOS and ADHD in various time periods based on the model used in subgroup of boys: at birth (OR 0.96, 95%CI: 0.88 to 1.05; 9 cohorts, 306 participants), 3 months (OR 0.96, 95%CI: 0.89 to 1.05; 9 cohorts, 306 participants), 6 months (OR 0.95, 95%CI: 0.86 to 1.05; 9 cohorts, 306 participants), 12 months (OR 0.93, 95%CI: 0.83 to 1.04; 9 cohorts, 306 participants), 24 months (OR 0.92, 95%CI: 0.81 to 1.03; 9 cohorts, 306 participants)	

APPENDIX 10 – SUMMARY OF PARENT PHTHALATE COMPOUNDS AND THEIR PRIMARY METABOLITES

Parent phthalate compounds and their primary metabolites included in this Umbrella Review and *for completeness, other parent phthate compounds and their respective metabololites (i.e. in italics).*

Phthalates are diesters of 1,2-benzenedicarboxylic acids (phthalic acid) and are broadly classified into short-branched low molecular weight phthalates and long-branched high molecular phthalates (Frederiksen et al., 2007; Zhang et al., 2021). Parent phthalate diesters are metabolised into specific monoesters, the characteristics of which are dependent on the length of the side chains. More branched phthalates form a greater number of isomers which are hydrophobic (Frederiksen et al., 2007). Phthalate metabolism involves at least two steps namely hydrolysis to the monoester and conjugation. Short-branched phthalates are primarily excreted in urine as monoester phthalates and long-branch phthalates undergo further biotransformation steps to be excreted as conjugated compounds in urine and faeces. Examples of short-branched phthalates include DMP and DEP which are excreted in urine as the monoesters MMP and MEP. By contrast, an example of a long-branched phthalate is DEHP which undergoes a more complex metabolism with a number of metabolites including MEHP, MEHHP, MEOHP, MECPP and MCMHP (Frederiksen et al., 2007; Zhang et al., 2021).

Table A10.1: Parent phthalate compounds, their primary metabolites, and abbreviations

PARENT PHTHALATES		**SPECIFIC METABOLITES**	
Parent Diester Name	**Parent Diester Abbreviation**	**Metabolite**	**Metabolite abbreviation**
Dimethyl phthalate	DMP	monomethyl phthalate	MMP
Diethyl phthalate	DEP	monoethyl phthalate	MEP
Di-n-propyl phthalate	*no consistent abbreviation*	*mono-n-propyl phthalate*	-
Di-n-butyl phthalate	DnBP (also DBP, used interchangeably; DnBP used in Umbrella Review)	mono-n-butyl phthalate	MnBP (also MBP, (used interchangeably; MnBP used in Umbrella Review)
Diisobutyl phthalate	DiBP	monoisobutyl phthalate	MiBP
Di-n-pentyl phthalate	*no consistent abbreviation*	*mono-n-pentyl phthalate*	
Butyl benzyl phthalate (syn. Benzyl butyl phthalate)	BBzP (also BBP, BzBP)	monobenzyl phthalate	MBzP
Dicyclohexyl phthalate	*DCHP*	*monocyclohexyl phthalate*	*MCHP*
Di-n-hexyl phthalate	*no consistent abbreviation*	*mono-n-hexyl phthalate*	-
Diisohexyl phthalate	*no consistent abbreviation*	*monoisohexyl phthalate*	-

Diisoheptyl phthalate	*no consistent abbreviation*	*monoisoheptyl phthalate*	-
Di(2-ethylhexyl) phthalate	DEHP	mono(2-ethylhexyl) phthalate	MEHP
Di(2-ethylhexyl) phthalate	DEHP	mono(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
Di(2-ethylhexyl) phthalate	DEHP	mono(2-ethyl-5-oxohexyl) phthalate	MEOHP
Di(2-ethylhexyl) phthalate	DEHP	mono(2-ethyl-5-carboxypentyl) phthalate	MECPP
Di(2-ethylhexyl) phthalate	DEHP	mono(2-carboxymethyl-5-hexyl) phthalate	MCMHP
Di(n-octyl) phthalate	DNOP	mono-n-octyl phthalate	MnOP
Di(n-octyl) phthalate	*DNOP*	*Mono (3-carboxypropyl) phthalate*	*MCPP*
Diisooctyl phthalate	*DIOP*	*monoisooctyl phthalate*	-
Diisononyl phthalate	*DINP (also DNP)*	*monoisononyl phthalate*	*MNP/MiNP*
Diisononyl phthalate	*DINP (also DNP)*	*mono(hydroxyisononyl) phthalate*	*MHiNP*
Diisononyl phthalate	*DINP (also DNP)*	*mono(oxoisononyl) phthalate*	*MONP/MOiNP*
Diisononyl phthalate	*DINP (also DNP)*	*mono(carboxyisooctyl) phthalate*	*MCOP/MCiOP*
Di(2-propylheptyl) phthalate	*DPHP*	*mono(2-propylheptyl) phthalate*	-
Diisodecyl phthalate	*DIDP (also DDP)*	*monoisodecyl phthalate*	*MDP/MiDP*
Diisodecyl phthalate	*DIDP (also DDP)*	*monohydroxyisodecyl phthalate*	*MHiDP*
Diisodecyl phthalate	*DIDP (also DDP)*	*Mono (carboxynonyl) phthalate*	*MCNP*
Diisodecyl phthalate	*DIDP (also DDP)*	*monocarboxyisononyl phthalate*	*MCiNP*

APPENDIX REFERENCES

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Independent Planning Commission
Level 15, 135 King Street
Sydney NSW 2000

20 January 2025

Moss Vale Plastics Recycling Facility
SSD-9409987

Dear Commissioners

We refer to your meeting with NSW Health and others on 3 December 2024.

During that meeting, representatives from NSW Health outlined the current science as to the health impacts of microplastics, as well as the position of numerous authorities including the World Health Organization (WHO), Food Standards Australia New Zealand (FSANZ) and European Food Safety Authority (EFSA) in relation to microplastics.

With respect, as detailed below, it would appear that NSW Health has relied on outdated science and, furthermore, grossly misrepresented the position of WHO.

Rapidly evolving science

At the outset, it is important to note that the science regarding human health impacts of microplastics is rapidly evolving and that most of the critical studies in this area are less than 12 months old.

For example, the key study that discovered that microplastics accumulate in the human brain was published in May 2024.

The umbrella review of meta-analyses conducted by the Minderoo Foundation in collaboration with JBI at the University of Adelaide, which is arguably the most critical piece of research that has been done to date exploring the links between plastics exposure and human health, was published in August 2024.

Another key study that was the first globally to find possible links between microplastics and cancer (colon and lung) was published in December 2024.

Accordingly, any position as to the health effects of microplastics that has not been updated in the past year simply cannot be relied upon as current science.

FSANZ position

During the 3 December meeting, [redacted] of NSW Health stated in respect of the European and FSANZ position that:

> "the European Agency as well as Food Standards Australia they say it's for the current levels of exposure through food and water, the humans, we're unlikely to have a harmful effect on humans".

The current position of FSANZ in respect of microplastics can be found here: https://www.foodstandards.gov.au/consumer/our-safe-food-supply/microplastics It states

that “our current view is that plastic contamination of the food chain is unlikely to result in immediate health risks to consumers”.

Notably, this position statement was last updated in December 2023 and thus does not take into account the latest science outlined above.

Furthermore, it states that its view is supported by the EFSA but links to a position statement that has now been removed from the EFSA website.

Crucially, the EFSA position on microplastics is subject to review in light of the 2023 European microplastics ban.

European microplastics ban

In 2023, the European Commission announced a ban on synthetic polymer particles under five millimeters in size that are organic, insoluble and resist degradation. The ban involves a rolling implementation with deadlines for the phaseout of microplastics in specified products, with some already in effect (such as loose glitter).

Due to concerns about microplastics entering food supplies, the ban includes products for agricultural and horticultural uses, fertilisers, plant protection products, seed treated with such products and biocidal products.

Furthermore, in May 2024 the European Environment Agency noted that “… research has linked microplastic exposure to adverse health impacts in humans. The scientific evidence therefore indicates a need for policies to mitigate current and future risks to ecosystems and human health.”

Respectfully, [redacted] assertion in respect of the European position does not take into account these recent developments.

2022 WHO position

During the 3 December meeting, [redacted] stated in respect of the WHO position that:

> “they say it’s for the current levels of exposure through food and water, the humans, we’re unlikely to have a harmful effect on humans. That’s the stance that the World Health Organization … have taken”.

In 2022, WHO published this paper on microplastics. Although the paper concluded that the evidence at the time of publication (more than two years ago) was insufficient to conclusively determine risks to human health it emphasised that:

> “The findings cited in this report do not, however, imply that exposure to [microplastics] is “safe”, as concluded by some stakeholders.”

In its Executive Summary, the WHO publication outlined some known health harms, for example:

> “The adverse effects of inhalation of microplastics include oxidative stress, inflammation, lipid peroxidation, DNA damage and aggravation of underlying effects such as asthma and chronic obstructive pulmonary disease.”

Although [redacted] has suggested that the WHO position is that microplastics are “unlikely” to have harmful effects on humans, it is clear that even two years ago the WHO rejected such a conclusion.

Latest WHO position

In November 2024, the WHO updated its position on microplastics, launching a plastics and health initiative in recognition of new scientific findings as to the serious human health harms linked to microplastics, stating:

> "Health risks exist at all stages of the plastic lifecycle, from production and use to recycling and disposal, as well as from legacy plastics in the environment. Increasing evidence about the consumption and inhalation of micro- and nano-plastics, concerns over exposure to hazardous chemicals used to give plastics specific properties, and the need for better waste management practices are becoming central to public health discussions.
>
> As a result, the Seventy-sixth World Health Assembly called upon Member States to support the WHO in scaling up its work on plastics and health. …
>
> Throughout the negotiations WHO's view has been guided by … the need
>
> 1. to pursue the highest attainable standard of human and environmental health;
> 2. to address the known and predicted health risks and exposures associated with plastic polymers, chemicals and additives, microplastics and nanoplastics at all stages of the plastics lifecycle …"

Below is an extract from a November 2024 WHO paper published as part of this plastics and health initiative (emphasis added):

> **PLASTIC CRISIS IS ALSO A HEALTH CRISIS**
>
> Plastic pollution contributes negatively to the triple planetary crisis of climate change, biodiversity loss, and pollution, all of which pose serious concerns to human health. Moreover, **scientific research has documented a wide range of risks and potential adverse impacts on human health** at every stage of the plastics lifecycle. … The body of scientific evidence on these health implications continues to grow. Examples of the health aspects of plastics are given below:
>
> - **Numerous recent studies confirm that many of the thousands of chemicals used in plastics (including monomers, polymers and additives) are hazardous to health**. These studies highlight that some of the chemicals and additives contained in plastics, and used in their production, are endocrine disruptors and can cause **hormonal imbalance, reproductive disorders, infertility and increase the risks of renal disease and cancer**.
> - There is also growing evidence that exposure to chemicals in plastics can be linked to **dyslipidemia, insulin resistance, obesity, and diabetes**, all of which are risk factors for cardiovascular diseases. Many of the chemicals used in plastics can be released during use of the plastic or following its disposal. Human biomonitoring studies frequently identify chemicals associated with plastics in both adults and children. Systematic evidence reviews have linked exposures to many of these chemicals to a range of adverse health effects, including effects on **reproduction, child neurodevelopment, circulatory and respiratory disorders and certain cancers**.
> - There is growing scientific evidence that the release of nano- and microplastics across the life cycle of plastics presents **adverse health risk**. … Microplastics that are found in the environment include … secondary microplastics originating from degradation and weathering of larger pieces of plastic waste after deposit in landfills or when lost in the environment, **including from recycling facilities**.
> - Several recent reports, including by the European Commission (2023), UNEP (2023) and the World Health Organization (WHO) highlight that nano and **micro-plastics accumulate in the human body, potentially causing inflammation, organ damage, and immune system disruption**.

Respectfully, [redacted] does not seem to be aware of this update in the WHO's position on the human health harms of microplastics. It is clear that the WHO has serious concerns as

detailed above and is now seeking an international legally binding instrument to help tackle the serious harms posed by plastic pollution.

Microplastics in human organs

During the 3 December meeting, [redacted] stated: "... there is a biological possibility of certain small microplastics can pass from the gut into the tissues. But the amount that is absorbed is very, very minimal..."

With respect, it can only be assumed that [redacted] is not aware of the mounting evidence in respect of the bioaccumulation of microplastics in human organs. For example, this 2024 study found that the human brain is on average 0.5 per cent microplastics, which amounts to **one heaped teaspoon of plastic per brain**. It is difficult to fathom how such an amount could be described as “very, very minimal”.

Microplastics have been found in virtually every human organ including the lungs, liver, bone marrow, reproductive systems and brain. They have even been found in breastmilk and placenta. The latest science leaves no doubt that the bioaccumulation of microplastics in human organs is certainly more than a “biological possibility”.

Yours faithfully

Dr Jacqueline Jones

Palliative Care Specialist Physician
MBBCh (Wales), FRACP, FAChPM, DipBus (FrtMgmt)

Dr Jacqueline Duc

Paediatrician, Palliative Care Specialist
MBBS, BA (Hons I), MPH

Dr Helen Maloof

General Practitioner
MBBS, GradDipSpMed

Louise Keats

BA (Hons I), LLB (Hons I), GradDipNut
(currently: Masters Human Nutrition)