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Human health impacts of exposure to phthalate plasticizers: An overview of reviews

J. Eales [a,*], A. Bethel [b], T. Galloway [c], P. Hopkinson [d], K. Morrissey [a], R.E. Short [e], R. Garside [a]

[a] European Centre for Environment and Human Health, University of Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, Cornwall, UK
[b] PenARC, University of Exeter Medical School, St. Luke's Campus, Exeter EX1 2LU, UK
[c] College of Life and Environmental Sciences, Streatham Campus, Exeter EX4 4QD, UK
[d] Exeter Centre for Circular Economy, University of Exeter Business School, Streatham Campus, Exeter, UK
[e] Stockholm University, Frescativägen, 114 19 Stockholm, Sweden

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ABSTRACT

In this review of reviews, we overview the current global body of available evidence from structured reviews of epidemiological studies that explore human health outcomes associated with exposure to phthalates (chemical plasticisers commonly found in plastics). We found robust evidence for an association with lower semen quality, neurodevelopment and risk of childhood asthma, and moderate to robust evidence for impact on anogenital distance in boys. We identified moderate evidence for an association between phthalates/metabolites and low birthweight, endometriosis, decreased testosterone, ADHD, Type 2 diabetes and breast/uterine cancer. There was some evidence for other outcomes including anofourchette distance, fetal sex hormones, pre-term birth, lower antral follicle count, reduced oestrodiol, autism, obesity, thyroid function and hearing disorders. We found no reviews of epidemiological human studies on the impact of phthalates from recycled plastics on human health. We recommend that future research should use urine samples as exposure measures, consider confounders in analyses and measure impacts on female reproductive systems. Our findings align with emerging research indicating that health risks can occur at exposure levels below the "safe dose" levels set out by regulators, and are of particular concern given potential additive or synergistic "cocktail effects" of chemicals. This raises important policy and regulatory issues for identifying and controlling plastics and health related impacts and highlights a need for more research into substances of concern entering plastics waste streams via recycling.

1. Background

Many chemical additives used in plastic production are hazardous to humans (Lithner et al., 2011) who may be exposed occupationally (Montano, 2014), through subsequent use of the product or due to transfer into products from plastic packaging (Hahladakis et al., 2018) (Fig. 1).

As recognized by the Lancet Commission on Pollution and Health, new chemicals have proliferated since 1950 (alongside the advent of plastics) with regulations and testing unable to keep pace. Since then, only half of an estimated 140,000 newly invented chemicals (which include plastic additives) have been tested for safe toxicity levels prior to broad use (Landrigan et al., 2018).

Phthalates have been identified by a number of studies and reviews as some of the most hazardous chemical additives in plastics for health, in terms of likelihood of impact by recycling processes (Geueke et al., 2018), frequency of use in primary plastic products (Groh et al., 2019), and human health hazard score (Hahladakis et al., 2018). This group of chemicals have received significant media attention due to their identification as endocrine and metabolic disruptors and the extent of their use within plastics. These issues also being brought to the fore by global scientific consortia. The Endocrine Society and the International Pollutants Elimination Network (IPEN), recently summarised the widespread health impacts of various endocrine disrupting chemicals in plastics including phthalates, and acknowledged the growing concern around such chemicals in the circular economy (Flaws et al., 2020). People can be exposed to phthalates via ingestion, inhalation and dermal contact (Lyche, 2011).

* Corresponding author.
E-mail address: j.f.eales@exeter.ac.uk (J. Eales).

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2. Objective of this overview

We address the question of how exposure to phthalates (which often originate from plastics) may be linked to human health outcomes. Whilst recognizing that exposure to phthalates may come from non-plastic sources (e.g. perfumes and cosmetics), plastic widely considered to be a predominant exposure source, particularly via the diet (Serrano et al., 2014; Wang et al., 2018; Gkrillas et al., 2021). Exposure to high molecular weight phthalate compounds may come predominantly from the diet, whilst low molecular weight phthalate metabolites within the body are likely to arise from other sources, such as personal care products, dust and indoor air exposure (Koch et al., 2013). There is currently a high rate of production of primary and secondary research on the health impacts of phthalate exposure, although this mounting evidence has led to little action in broad-scale regulation. As such there is a critical need for a digestible and policy-relevant synthesis of the current evidence.

Our objective is to provide a systematic overview of the current, global body of synthesized evidence regarding explicit links between exposure to phthalates and subsequent health outcomes which may be directly attributable to this exposure. Our research question is "What is the evidence for the effect of exposure to phthalates on human health?" The key elements of this question (the population, exposure and outcome) correspond to humans, phthalates, and health effects, respectively.

We aim to draw inferences as to the amount and quality of evidence pertaining to specific health outcomes arising from phthalate exposure; identify key evidence gaps and provide a basis of evidence for future policy and regulation concerning plastics and phthalates and research questions regarding the potential health impacts from phthalates and recycling of plastics via circular economy. We have undertaken an overview of reviews, rather than a review of primary research, due to the heterogeneity of health outcomes and phthalate exposures, and the sufficient number of reviews across this broad but rapidly developing topic. Planning for the methodology of this review has drawn on methods and discussions outlined in Lunny et al. (2017) and Lunny et al. (2018).

3. Methods

We produced an a priori protocol to guide this overview, available online at Zenodo (https://doi.org/10.5281/zenodo.3900088; www.zenodo.org).

3.1. Search strategy

We searched five bibliographic databases: Medline (OvidSP), Web of Science Core Collection (Clarivate Analytics), Scopus (Elsevier), Epistemonikos (Epistemonikos Foundation) and ProQuest Dissertations & Theses Global), in February 2020 for relevant evidence reviews. These databases cover a broad range of health and environment topics and were deemed to represent good coverage of the relevant literature sources by the review team. All searches were limited to studies from 2000 onwards, to capture relevant evidence in the past 20 years, except the thesis database, PQDT Global which we searched from 2010 onwards because research contained within thesis after 2010 is likely to have been published in journals. Where possible, we restricted the searches to evidence reviews only by using search filters.

We searched databases with slightly different search strings that reflected the functions of each database, details are provided in Additional File 1. In general, the search strings included sets of terms for "plastic", "phthalate" and "review" joined by the Boolean operator "AND". We used synonyms for these terms, derived from subject experts and the project team (MeSH terms were consulted but proved unhelpful). We removed studies with a focus on plastic surgery or reconstructive surgery, using synonyms for these topics with the "NOT" Boolean operator within the search strings. To determine the comprehensiveness of the search strategy, we used 40 "test articles" that were identified during an initial scoping stage as potentially relevant articles, Additional File 2. We did not complete grey literature searches and hand searching of relevant journals and institutions because of the low likelihood of relevant systematic reviews retrieved from grey literature searching, following discussions with the project team, and also due to resource constraints.

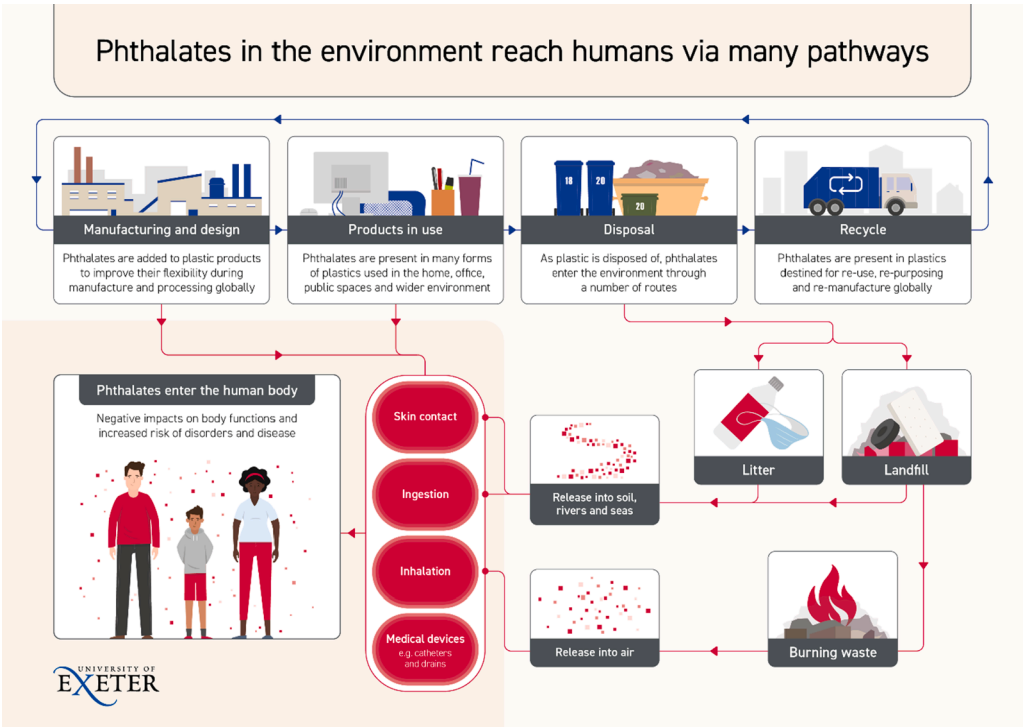

Fig. 1. Migration, release and fate of chemical additives in plastic throughout the life cycle. The environmental pathways, indicated by red arrows, are: manufacture (e.g. via inhaling factory smoke); product use (e.g. skin contact with plastic toys); soil, rivers and sea (e.g. ingestion from drinking water) and release into the air (e.g. inhalation of fumes from burning). We include "Medical devices" as a route into the body, not because they represent a functionally different pathway to enter the body, but because they have been flagged as a concern by regulatory agencies, particularly when used in neonates or the chronically ill (Latini et al., 2010; Chou and Wright, 2006; Tickner et al., 2001). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Screening for relevance

Records retrieved through the searches of the five databases were collated in Endnote X9 (www.endnote.com). We used filters to remove studies that were not English language publications. We also removed reviews that included the word "plasticity", due to the retrieval of reviews that were on the topic of "phenotypic plasticity", a non-relevant topic in the field of evolutionary biology. The remaining records were de-duplicated using Endnote, which resulted in 900 reviews remaining. We used the screening software Rayyan (Ouzzani et al., 2016), an open-source software designed for systematic reviews. This software identified additional duplicates not picked up by Endnote, and after manual checking, these were removed from the list of reviews, leaving 875 reviews to be screened for eligibility to our overview. We structured our eligibility criteria according to the key elements of our research question, Table 1.

Table 1
Eligibility criteria for this overview of reviews of the health effects of phthalates.

	Inclusion criteria	Exclusion criteria
Population	Humans, anywhere globally. No age or sex limit.	Animals
Exposure	Phthalates, measurable as the amount of phthalate (or phthalate metabolite, see Box 1) detected in urine, blood, serum or tissue, or amount of environmental exposure. Exposure routes are typically environmental (e.g. inhalation), direct (e.g. skin contact, ingestion), or prenatal, i.e. via intrauterine pathways. Any environmental exposure to phthalates was eligible, unless the source was specifically stated as non-plastic. Studies which addressed exposure to multiple chemical groups were eligible as long as these chemical groups were fully disaggregated in analyses and that the resulting included studies would still constitute a review, with associated synthesis, of phthalates as a disaggregated group.	Lab-based tissue exposure
Outcome	Any human health outcome. Based on scoping, these were likely to include (but not limited to): endocrine disruption, congenital disorders, neurodevelopment disorders, birth outcomes and diabetes.	Reviews that only reported body burdens of phthalates/ metabolites
Review design	All structured reviews of quantitative and empirical evidence, that met the following criteria – Report an explicit search methodology. – Report a screening process in the methodology. – Synthesised, summarized or described included studies	Reviews that do not meet the criteria for search, screen and synthesis (see left). Reviews including modeling studies
Timeframe	Published from 2000 onwards. Research into impacts of phthalates from environmental exposures began around 1985, however scoping searches in Medline suggested little to no review activity for human health impacts prior to 2000. This also aligns with generally increased uptake of structured and systematic review methods in environmental toxicity fields.	Published prior to 2000
Language	English	Non-English

The titles and abstracts of each of the 875 reviews were screened according to the inclusion and exclusion criteria listed above, by two reviewers (RS and KM) independently. In the 44/875 (5%) instances where there were disagreements in the reviewers' decisions for a particular review, the conflict was resolved by discussion. 753 reviews were excluded at this stage, and the remaining 122 reviews were screened by at least two reviewers independently (RS, KM and JE). Where there were conflicts in reviewer's decisions or reason for exclusion (32 of 122 reviews; 26%), the reasoning for the decision was revisited by the two reviewers and the conflict resolved, involving a third reviewer where necessary. 42 reviews were included after assessment at full text.

3.3. Data extraction

We extracted data from each review including; review question, number of included studies, phthalates, exposure route and measurement method, health outcomes, population characteristics and the summary of health outcomes from the review authors. We noted the type of synthesis undertaken by the review, categorized as meta-analysis, narrative synthesis, sequential narrative only, sequential narrative with a summary statement and summary statement only. Meta-analysis results were extracted where appropriate. The extracted data are presented in Additional File 3. Where reviews focused on multiple chemicals, we extracted information relating only to phthalates. Data for each review was extracted by a member of the team (JE, KM or RS). 19/42 (45%) were double checked by a second reviewer to ensure quality. As planned in the protocol for this overview, we did not pursue any missing data, due to resource limitations. We also extracted information for each of the phthalate focused studies within included reviews. This information was captured to facilitate the assessment of inter-review overlaps (described in methods below).

3.4. Reliability assessment

Though we had planned to use the AMSTAR tool (Shea et al., 2017) to score the quality of included reviews, on encountering the range of review types in this overview, many of which did not follow all stages of a full systematic review, we opted to use a tool which was designed for a range of review types. The CEESAT tool (O'Leary et al., 2016; Konno et al., 2020) has been designed to assess the reliability of reviews published in a broad field of environmental sciences (though not specific to reviews only in that field), and able to capture the breadth of quality represented in the structured reviews contained in this overview.

Each review was assessed using the CEESAT criteria by a member of the review team (JE, KM or RS). 23/42 (55%) reviews were assessed by an experienced user of the CEESAT tool, and the remaining 19 (45%) were assessed by KM or RS, and double-checked by a second reviewer. We used the CEESAT criterion scores, alongside a summary reliability statement from the reviewer, to categorise reviews as Good, Medium or Low reliability. Where reviews were particularly low reliability for one or more key criteria, the review team discussed the review and used this to inform a final inclusion decision (along with information about the overlap of reviews). The reliability assessment is reported in Additional File 3.

3.5. Synthesis

3.5.1. Considerations for overviews of reviews

The synthesis of outcomes from multiple reviews requires the consideration of a set of scenarios, unique to overviews, each of which, if unaddressed, may cause bias in the overview synthesis (Lunny et al., 2017). We detail the approaches we used to deal with these potentials for bias in our overview synthesis in Table 2.

One of the most recognized challenges in overviews of reviews is the issue of inter-review overlap (Pieper et al., 2014), i.e. where reviews

Box 1
Some common phthalates and their metabolites detected in urine, blood, serum or tissue.

Phthalate	Metabolite
Butyl benzyl phthalate (BBP/BBzP)	Mono benzyl phthalate (MBzP)
Benzyl butyl phthalate (BzBP)	
Diisononyl phthalate (DINP)	Mono isononyl phthalate (MINP) Mono(carboxyisooctyl) phthalate (MCIOP) Mono(oxoisononyl) phthalate (MOINP) Mono (hydroxyisononyl) phthalate (MHINP)
Di-n-octyl phthalate (DOP)	Mono (3-carboxypropyl) phthalate (MCPP)
Di-n-butyl phthalate (DBP/DnBP)	Mono-n-butyl phthalate (MBP/MnBP)
Di-methyl phthalate(DMP)	Mono-methyl phthalate (MMP)
Di-ethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)
Di-isobutyl phthalate (DiBP)	Mono-isobutyl phthalate (MiBP)
Di(2-ethylhexyl) phthalate (DEHP)	Mono(2-ethylhexyl) phthalate (MEHP) Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)

Table 2
Scenarios encountered during overview synthesis and approaches used to address them in this overview.

Scenario causing potential bias or concern	Approaches used to deal with the scenario
Reviews include overlapping information and data (e.g. from the same primary studies)	Assess the overlap across reviews using corrected covered area (CCA), publication date, methodological quality, and review design and exclude reviews that do not contain any unique primary studies
Reviews report discrepant information and data	Extract information from one/several reviews that meet minimum quality criteria, contain the most complete information, and/or the meta-analysis with the greatest number of primary studies
Reviews are not up-to-date	Exclude non-up to date reviews
Review methods raise concerns about bias, quality or reliability	Use CEESAT tool summaries to determine which reviews to prioritise

reported a summary of the same outcome including partially or wholly the same set of studies. It is imperative that overviews report the degree of overlap, how reviewers minimized the impact of overlap, and what effect any remaining overlap may have on the overview's summary. Overlaps were identified systematically and addressed on a case-by-case basis. For each health outcome, we used the Corrected Covered Area (CCA) approach, as described in (Pieper et al., 2014), Box 2. Calculations are provided in Additional File 4. This method plots the primary studies against reviews in a matrix and divides the frequency of repeated occurrences of an index primary study by the product of index studies and reviews.

We used the categories of overlap from the approach in Box 2, along with direct numerical comparisons of overlap (particularly when there were less than three reviews to compare). Where high or very high overlap occurred, we considered selecting the most recent review provided that the quality appraisal was the same or of higher reliability. We also considered whether a review's synthesis was appropriate and comprehensive, when determining whether to, and which reviews to prioritise when synthesizing across reviews.

Box 2
Corrected Covered Area approach to review overlap.

$$CCA = \left(\frac{N - r}{(r^{*}c) - r}\right)^{*}100$$

N = total number of occurrence of primary studies.
r = number of index primary studies (rows in matrix)
c = number of reviews (columns in matrix)

Categories of overlap:
Slight 0–5%
Moderate 6–10%
High 11–15%
Very high >15%

From: (Pieper et al., 2014)

3.5.2. Summarising evidence from each review

For each health outcome, we first summarise the evidence from each key review, referring to tabulated results of studies, and using the descriptive categories in Box 3. Descriptions were informed by the CEESAT reliability assessment and the type of synthesis and the number and consistency of effect estimates. The type of review synthesis was also considered, for example, a meta-analysis with sub-groups and weighting was considered higher strength of evidence than a description of each studies' results (a "sequential narrative").

3.5.3. Summarising evidence across reviews and across outcomes

For each health outcome we then undertook a strength of evidence assessment, reporting our confidence that the body of evidence, across reviews, represents the true effect. Again, we used the evidence descriptors detailed in Box 3. With the whole body of evidence, we highlight key research and review gaps and make recommendations for future research. We use our findings to suggest implications for the public, for regulations and the use of phthalates in plastics within circular economy methods.

4. Results

We present our results in four sections. First, we summarise the results of our search, screening and the characteristics of the reviews we identified as relevant to this overview. Second, we narratively synthesise the review results, grouped by health outcome, discussing the body of evidence for each health outcome, whilst considering overlap between reviews, publication date and review reliability. Third, we provide an assessment of the strength of evidence for each health outcome identified. Finally, we report on the comprehensiveness of the reviews found and identify current research gaps.

4.1. Reviews found by this overview

4.1.1. Search and screening

The records retrieved by the bibliographic searches and the records remaining after screening is presented in a PRISMA flow diagram (Moher et al., 2009) (Additional File 5). All 40 of the test articles were returned by the search, indicating that the searches were comprehensive. A list of all reviews excluded at full text due to non-relevance is given in Additional File 6, with the reason for exclusion of each. After de-duplication and removal of non-relevant reviews using filters and manual checking, 875 reviews were assessed at title and abstract, 122 at full text and 42 structured reviews were included in the overview after screening against the eligibility criteria. We found 17 reviews looking at interventions for exposure to phthalates (e.g. remediation of phthalates in the environment). Though not relevant for inclusion in this overview, we have collated them in Additional File 7 as an additional resource.

4.1.2. Data extraction

Data extracted from each of the 42 reviews are presented in Additional File 3 and summary table of key information is given in Table 3. The 42 reviews covered 334 unique studies. As Table 3 shows, some reviews presented only sequential narrative descriptions of individual studies, rather than synthesized result, for the health outcomes of interest. Though these reviews do not fall into the definition of true "synthesis" reviews, we did not exclude them from this overview on this criterion, because they either provide information on health outcomes that are poorly covered by other reviews, or they were unable to synthesise due to having only identified a single primary study relating to a health outcome. Details of individual studies reported within reviews are in Additional File 3.

4.1.3. Reliability assessment

We assigned a summary reliability rating of Good to eight reviews: (Blakeway et al., 2020; Dorman et al., 2018, Hipwell et al., 2019; Hipwell et al., 2019; Radke et al., 2018, 2019a, 2019b), and a summary rating of Low reliability to three reviews: (Bowman and Choudhury, 2016; Poursafa et al., 2015; Zarean et al., 2016). The remaining 31 reviews were given a summary reliability rating of Medium. The rationale for each review's summary rating is given in the narrative synthesis tables in the section below, and the full CEESAT assessment with ratings for all individual criteria, is provided in Additional File 4.

4.2. Narrative synthesis of review results

Additional File 8, Tables A1–A13 present the meta-data for reviews, separated into tables for each outcome. Shortened versions of these tables are provided within the text here for the reader (Tables 4–23).

4.2.1. Congenital reproductive disorders

We found 10 reviews of congenital disorders, published across 8 articles, reporting outcomes including anogenital distance (AGD), hypospadias (malpositioning of the urethra in males), undescended testes, genital measurements and fetal sex hormone changes. Five of the nine reviews on genital malformations focused only on males. There were no reviews that focused solely on female genital malformations. This indicates an evidence gap for female reviews (and primary studies) in this area.

4.2.2. Fetal sex hormone changes

One medium reliability review (Marie et al., 2015) reported a narrative synthesis of three studies on this topic, and found some evidence of the involvement of prenatal phthalate exposure in changing the fetal production of sex hormones (including testosterone, estradiol and progesterone) and insulin-like-factor 3 during pregnancy (Table 4).

Box 3
Glossary of descriptors used for the strength of evidence (within reviews) and confidence in evidence base (across reviews). Use of descriptions are informed by the CEESAT reliability criteria and synthesis type.

Robust evidence	Multiple reviews/studies, each reporting an effect in the same direction, to varying degrees
Moderate evidence	Majority of reviews/studies reporting a similar effect
Some evidence	Evidence of effect across some but not all reviews/studies
Slight evidence	Evidence of effect across a small number of the total reviews/studies
Inconsistent evidence	Majority of reviews reported conflicting study results OR the results of reviews/studies conflicted each other
Null evidence of effect/ association	Only null results were reported by reviews/studies
Lack of evidence	Limited number of studies

Table 3
Summary of data extraction for each of 42 reviews.

Citation	Exposure measure	Health outcome	Sex	Age category	No. of studies	Synthesis	Reliability summary
Blakeway et al., 2020	Bodily (urine)	Atopic dermatitis	All	All	2	Sequential narrative only	Good
Bonde et al. 2016	Bodily (serum)	Hypospadias and/or Cryptorchidism	M	Infant	1	Sequential narrative only	Medium
	Bodily (multiple)	Sperm count	M	Adult	1	Sequential narrative only	Medium
Cai et al. 2015	Bodily (multiple)	Sperm quality	M	Adult	20	Meta-analysis	Medium
Cai et al. 2019	Bodily (urine)	Endometriosis	F	Adult	8	Meta-analysis	Medium
Dorman et al. 2018	Bodily (urine)	Anogenital distance	M	Infant	6	Meta-analysis	Good
Ejaredar et al. 2015	Bodily (urine)	Neurodevelopment outcomes	All	Children (<16)	11	Sequential narrative and summary statement	Medium
Fu et al., 2017	Bodily (urine)	Breast cancer	F	Adult	4	Meta-analysis	Medium
	Bodily (urine)	Uterine leiomyoma	F	Adult	5	Meta-analysis	Medium
Golestanzadeh et al. 2019	Bodily (multiple)	Cardiometabolic risk factors	All	Children (<19)	9	Meta-analysis and narrative synthesis	Medium
	Bodily (multiple)	Obesity	All	Children (<19)	26	Meta-analysis and narrative synthesis	Medium
	Bodily (multiple)	Birthweight	All	All	11	Meta-analysis and narrative synthesis	Medium
Goodman et al. 2014	Bodily (multiple)	Obesity	All	All	22	Narrative synthesis	Medium
	Bodily (multiple)	Diabetes risk	All	All		Narrative synthesis	Medium
	Bodily (multiple)	CVH/CVD risk	All	All	4	Narrative synthesis	Medium
Hipwell et al. 2019	Bodily (multiple)	Time to pregnancy	All	Adult	5	Narrative synthesis	Good
Høyer et al. 2018	Environmental/ multiple	Time to pregnancy	M	Adult	3	Narrative synthesis	Medium
	Bodily (multiple)	Semen quality and sperm DNA damage	M	Adult	21	Narrative synthesis	Medium
	Bodily (multiple)	Reproductive Hormones	M	Adult	18	Narrative synthesis	Medium
Jeddi et al. 2016	Bodily (multiple)	Autism	All	Children (<16)	5	Narrative synthesis	Medium
Kim et al. 2019a	Bodily (urine)	Thyroid function	All	All	13	Meta-analysis	Medium
Kim et al. 2019b	Environmental/ multiple	Time to pregnancy	All	Adult	10	Narrative synthesis	Medium
Kuo et al. 2013	Bodily (urine)	Diabetes	All	Adult	3	Narrative synthesis	Medium
Lee et al. 2018	Bodily (urine)	Neurodevelopment disorders	All	Children (<16)	5	Meta-analysis	Good
Li et al. 2017	Environmental/ multiple	Asthma	All	Children (<16)	9	Meta-analysis	Good
	Bodily (urine)	Asthma	All	Children (<16)	up to 3 per metabolite	Meta-analysis	Good
	Indoor environment	Asthma	All	Children (<16)	up to 3 per metabolite	Meta-analysis	Good
Marie et al. 2015	Bodily (blood)	Birthweight/body size	All	Infant	11	Narrative synthesis	Medium
	Bodily (blood)	Pre-term birth; gestational age	All	Infant	16	Narrative synthesis	Medium
	Bodily (blood)	Anogenital distance, hypospadias; cryptorchidism; other congenital malformations	All	Infant	14	Narrative synthesis	Medium
	Bodily (blood)	Fetal sex hormone changes	All	Infant	3	Narrative synthesis	Medium
Nilsen and Tulve 2020	Bodily (urine)	ADHD	All	Children (<16)	5	Meta-analysis	Medium
Patelarou and Kelly 2014	NR	Gestational age	F	Adult	1	Sequential narrative only	Medium
Poursafa et al. 2015	NR	Early onset puberty	All	Children (<16)	12	Sequential narrative and summary statement	Low
Radke et al. 2018	Bodily (urine)	Anogenital distance, hypospadias; cryptorchidism	M	Adult	10	Narrative synthesis	Good
	Bodily (urine)	Time to pregnancy	M	Adult	1	Sequential narrative only	Good
	Bodily (urine)	Semen parameters	M	Adult	15	Narrative synthesis	Good
	Bodily (urine)	Pubertal development (male)	M	Adult	3	Summary statement only	Good
	Bodily (urine)	Testosterone levels	M	Adult	13	Narrative synthesis	Good
Radke et al. 2019a	Bodily (urine)	Poor metabolic outcomes measured as Type 2 diabetes, insulin resistance, Gestational diabetes, obesity, renal effects	All	All	24	Narrative synthesis	Good
	Bodily (urine)	Obesity	All	All	8	Sequential narrative only	Good
	Bodily (urine)	Renal effects	All	All	2	Not synthesised	Good
Radke et al. 2019b	Bodily (urine)	Pubertal development (female)	F	All	7	Narrative synthesis	Good
	Bodily (urine)	Pre-term birth; Spontaneous abortion	F	All	7	Narrative synthesis	Good
	Bodily (urine)	Time to pregnancy	F	All	4	Narrative synthesis	Good
Ribeiro et al. 2019	NR	Adiposity	All	Adult	25	Meta-analysis	Medium
	NR	Adiposity in children	All		25	Meta-analysis	Medium

(*continued on next page*)

Table 3 (*continued*)

Citation	Exposure measure	Health outcome	Sex	Age category	No. of studies	Synthesis	Reliability summary
				Children (<16)			
Shoshtari-Yeganeh et al. 2019	NR	Insulin Resistance	All	All	8	Meta-analysis	Medium
Song et al. 2016	Bodily (urine)	Type 2 Diabetes and related metabolic traits	All	All	6	Meta-analysis	Medium
Sun et al. 2017	NR	Type 2 diabetes	All	All	13	Sequential narrative and summary statement	Medium
Sweeney et al. 2019	Bodily (urine)	Anogenital distance	NR	Infant	10	Narrative synthesis	Medium
	Bodily (urine)	Bone health	NR	NR	4	Narrative synthesis	Medium
	Bodily (urine)	Inflammation	NR	NR	5	Narrative synthesis	Medium
	Bodily (urine)	Oxidative stress	NR	NR	14	Narrative synthesis	Medium
Wen et al. 2019	Bodily (urine)	Endometriosis	F	Adult	6	Meta-analysis	Medium
Wen et al. 2015	Bodily (multiple)	Precocious puberty	F	Children (<16)	14	Meta-analysis	Medium
Zarean et al. 2019	Bodily (urine)	Anogenital distance	All	Infant	10	Meta-analysis	Medium
Zarean et al. 2018	NR	Childhood obesity	NR	Children (<16)	13	Narrative synthesis	Medium
Zhang et al. 2019	Bodily (urine)	Neurodevelopment and behaviour/Cognitive development	NR	Children (<16)	26	Narrative synthesis	Medium
Zheng et al. 2017	Bodily (urine)	Kidney function	NR	Children (<16)	2	Sequential narrative only	Medium
Bowman and Choudhury 2016	NR	Anogenital distance/; genital measurements	M	Infant	3	Sequential narrative only	Low
	NR	Adolescent reproductive outcomes	NR	Adolescent	2	Summary statement only	Low
Fabelova et al. 2019	Bodily (urine)	Hearing disorders	NR	Adults (50+)	1	Sequential narrative only	Medium
Zarean et al. 2016	NR	Gestational age; birthweight	All	Infant	17	Sequential narrative and summary statement	Low
	NR	Respiratory	All	All	4	Summary statement only	Low
	NR	Neurodevelopment	All	Children (<16)	4	Sequential narrative only	Low
Foster et al. 2017	Indoor environment	Congenital genital abnormalities	M	Infant	4	Narrative synthesis	Medium
	NR	Anogenital distance/undescended or Cryptorchid testes	All	Infant	8	Narrative synthesis	Medium
Gaston et al. 2020	Bodily (multiple)	Birthweight	NR	Infant	2	Narrative synthesis	Medium
	Bodily (urine)	Cardiometabolic health	NR	Adult	1	Sequential narrative only	Medium
Vabre et al. 2017	Bodily (urine)	Fertility	F	Adult	1	Sequential narrative only	Medium
Yaghjyan et al.	Bodily (multiple)	Pre-term birth; gestational age	All	Infant	10	Narrative synthesis	Medium
	Bodily (multiple)	Birthweight	All	Infant	10	Narrative synthesis	Medium

Table 4
Summary of structured reviews investigating association between phthalates/metabolites and fetal sex hormone changes.

Review	Population details	Exposure route	Outcome measure	No. of studies	Synthesis	Reliability summary
Marie et al. 2015	M&F; Infant	Intrauterine	Fetal sex hormone changes	3	Narrative synthesis	Medium: Though described as a systematic review, no protocol, and lacking detail in methods for key stages.

4.2.3. *Hypospadias, undescended testes and cryptorchidism*

There was a very high degree of overlap of studies (CCA = 22%) across all 4 reviews reporting these outcomes (Foster et al., 2017; Marie et al., 2015; Radke et al., 2018; Bonde et al., 2016), Table 5. Slight or inconsistent evidence (depending on the phthalate measured) was reported in the good reliability narrative review, in which three of the four included studies were unique to that review (Radke et al., 2018). Two medium reliability narrative reviews, Foster et al. (2017) and Marie et al. (2015), contained 5 studies in common; the latter reported slight evidence for an association, and Foster et al. (2017) reported that the evidence is inconsistent. Inconsistent evidence was also reported in the remaining medium reliability sequential narrative review, which added one unique study (Bonde et al., 2016). Taken together the evidence is suggestive of a relationship between prenatal phthalate exposure and malformation of testes, but evidence was inconsistent.

4.2.4. *Anogenital distance (AGD)*

Table 6 summarises seven reviews reporting prenatal phthalate exposure and AGD. We exclude one review of low reliability (Bowman and Choudhury, 2016), whose studies were reported by other reviews. The overlap between the six reviews for this outcome was very high (CCA = 55%). One good reliability meta-analysis (Dorman et al., 2018) showed robust evidence that exposure of the male fetus to DEHP is associated with decreased AGD. The good reliability narrative review (Radke et al., 2018) reported moderate evidence of an inverse association between male AGD and exposure to DEHP and DBP, though evidence for DINP, BBP, DIBP, and MMP was slight (Radke et al., 2018). One medium reliability review, Marie et al. (2015) shared many of the

Table 5
Summary of structured reviews investigating association between phthalates/metabolites and hypospadias, undescended testes and cryptorchidism.

Review	Population details	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2018	M; Adult (16–65)	NR	Hypospadias/ cryptorchidism	4	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Marie et al. 2015	M&F; Infant	Intrauterine	Hypospadias/ cryptorchidism	7	Narrative synthesis	Medium: Though described as a systematic review, no protocol, and lacking detail in methods for key stages.
Foster et al. 2017	M; Infant	Parental environmental/ occupational	Hypospadias, undescended or cryptorchid testis	7	Narrative synthesis	Medium: Lacking cross-checking and critical appraisal. Provides lengthy descriptions of studies and consideration of confounders.
Bonde et al. 2016	M; Infant	Prenatal/postnatal	Hypospadias/ cryptorchidism	2	Sequential narrative only	Medium: Lacking critical appraisal and full data reporting, but well conducted synthesis and limitations section.

Table 6
Summary of structured reviews investigating association between phthalates/metabolites and anogenital distance.

Review	Population details	Exposure route	Outcome measure	No. of studies	Synthesis	Reliability summary
Dorman et al. 2018	M; Infant	Intrauterine	Anogenital distance; anogenital index; anoscrotal distance; anopenile distance	6	Meta-analysis	Good: Well-conducted systematic review with meta-analysis, including critical appraisal with consistency checking
Radke et al. 2018	M; Adult (16–65)	NR	Anogenital distance, hypospadias/ cryptorchidism	6	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Foster et al. 2017	M&F; Infant	Parental environmental	Anogenital distance; Anogenital index; anoscrotal distance; anopenile distance;	6	Narrative synthesis	Medium: Lacking cross-checking and critical appraisal. Provides lengthy descriptions of studies and consideration of confounders.
Marie et al. 2015	M&F; Infant	Intrauterine	Decreased anogenital distance, cryptorchidism, hypospadias and congenital malformation.	7	Narrative synthesis	Medium: Though described as a systematic review, no protocol, and lacking detail in methods for key stages.
Sweeney et al. 2019	NR	NR	Anogenital distance	10	Narrative synthesis	Medium: A well-conducted systematic review, though missing a protocol and some details.
Zarean et al. 2019	M&F; Infant	NR	Anogenital distance	10	Meta-analysis	Medium: A well-conducted systematic review, though missing a protocol and some details.
Bowman and Choudhury 2016	M; Infant	Intrauterine	Anthropometric and genital measurements; anogenital distance	3	Sequential narrative only	Low: Poor methodology, poorly reported. Only descriptive analysis of the studies and limited consideration of confounders.

Table 7
Summary of structured reviews investigating association between phthalates/metabolites and spontaneous abortion.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2019b	F; All	NR	Spontaneous abortion	7	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.

Table 8
Summary of structured reviews investigating association between phthalates/metabolites and preterm birth.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2019b	F; All	NR	Preterm birth	7	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Marie et al. 2015	M & F; Infant	Intrauterine	Preterm birth, gestational age < 37 weeks, change in gestational age	16	Narrative synthesis	Medium: Though described as a systematic review, no protocol, and lacking detail in methods for key stages.
Patelarou and Kelly 2014	F; Adult (16–65)	NR	Shorter gestational age	1	Sequential narrative only	Medium: Acceptable review, though missing critical appraisal and some cross checking/ details.
Yaghjyan et al. 2016	M & F; Infant	NR	Preterm birth, gestational age at delivery	10	Narrative synthesis	Medium: Acceptable review, recognition of confounders, but lacking critical appraisal, cross checking and some detail.
Zarean et al. 2016	M & F; Infant	NR	Gestational age	17	Sequential narrative and summary statement	Low: Lacking narrative description, recognition of limitations, note all studies included in narrative synthesis.

Table 9
Summary of structured reviews investigating association between phthalates/metabolites and birthweight.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Gaston et al. 2020	NR; Infant	Environmental (unspecified)	Birthweight	2	Narrative synthesis	Medium: Acceptable review, recognised limitations, though lacking critical appraisal, cross checking and some detail.
Golestanzadeh et al. 2019	M & F; All	NR	Birthweight	11	Meta-analysis and narrative synthesis	Medium: Acceptable review, though missing critical appraisal and some details.
Marie et al. 2015	M & F; Infant	Intrauterine	Birthweight/ body size	11	Narrative synthesis	Medium: Though described as a SR, no protocol, and lacking detail in methods for key stages.
Yaghjyan et al. 2016	M & F; Infant	NR	Birthweight	10	Narrative synthesis	Medium: Acceptable review, recognition of confounders, but lacking critical appraisal, cross checking and some detail.
Zarean et al. 2016	M & F; Infant	NR	Birthweight	17	Sequential narrative and summary statement	Low: Lacking narrative description, recognition of limitations, note all studies included in narrative synthesis.

Table 10
Summary of structured reviews investigating association between phthalates/metabolites and time to pregnancy.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Hipwell et al. 2019	M&F; (16–65)	NR	Time to pregnancy	5	Narrative synthesis	Good: A good review, well conducted, including critical appraisal
Radke et al. 2018	M; (16–65)	NR	Time to pregnancy	1	Sequential narrative only	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Radke et al. 2019b	F; All	NR	Time to pregnancy	4	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Høyer et al. 2018	M; (16–65)	NR	Time to pregnancy	3	Narrative synthesis	Medium: Acceptable review, though missing some methodological details
Kim et al. 2019b	M&F; (16–65)	Environmental (unspecified)	Time to pregnancy	10	Narrative synthesis	Medium: Generally well-reported and conducted review, though missing a few methodological details, and insufficient protocol

Table 11
Summary of structured reviews investigating association between phthalates/metabolites and female fecundity outcomes.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Cai et al. 2019	F; Adult (16–65)	Environmental (unspecified)	Endometriosis Incidence	8	Meta-analysis	Medium: Authors report acceptable methodology but methods are brief
Vabre et al. 2017	F; Adult (16–65)	NR	Antral Follicle Count	1	Sequential narrative only	Medium: Acceptable review but methodological details lacking for key stages
Wen et al. 2019	F; Adult (16–65)	NR	Cases of endometriosis	6	Meta-analysis	Medium: Review methods are generally acceptable, limitations recognised, but pooling of phthalate metabolites in one of the meta-analyses

Table 12
Summary of structured reviews investigating association between phthalates/metabolites and hormone levels in men.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2018	M; Adult (16–65)	NR	Testosterone	13	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Høyer et al. 2018	M; Adult (16–65)	NR	Total and free testosterone, and a range of other hormone levels	18	Narrative synthesis	Medium: Acceptable review, though missing some methodological details

same studies and found robust evidence for a relationship between in-utero exposure to phthalates and decreased AGD of boys.

Two reviews of medium reliability (Sweeney et al., 2019; Zarean et al., 2019) contained similar studies to those contained in Radke et al. (2018) and Marie et al. (2015). The meta-analysis (Zarean et al., 2019) found that exposure to phthalates in general was not associated with short AGD, though in subgroup analyses, short anopenile distance was associated with MBP, MEP, MiBP, and the sum of DEHP metabolites, the latter was also associated with shortened anoscrotal distance. In girls, the only association was between anofourchette distance and MBzP (Zarean et al., 2019). The narrative synthesis found null or inconsistent evidence of an association between AGD and concentrations of either MEP or MiBP (Sweeney et al., 2019). These reviews differ in their summaries, which may be explained by the ability of the meta-analysis to detect significant effect sizes from combining studies, and/or the difference in study composition of the two reviews. A medium reliability narrative review (all six included studies were covered by other reviews) reported significant associations with AGD though there was limited consistency in terms of the metabolites measured (Foster et al., 2017).

Prioritising evidence from the good reliability reviews (Radke et al.,

Table 13
Summary of structured reviews investigating association between phthalates/metabolites and semen quality parameters.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2018	M; Adult (16–65)	NR	Semen parameters	15	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Bonde et al. 2016	M; Adult (16–65)	Prenatal/postnatal	Sperm count incidence	1	Sequential narrative only	Medium: Lacking critical appraisal and full data reporting, but well conducted synthesis and limitations section.
Cai et al. 2015	M; Adult (16–65)	Environmental (unspecified)	Sperm concentration, motility, morphology, volume	20	Meta-analysis	Medium: Authors report acceptable methodology but methods are brief
Høyer et al. 2018	M; Adult (16–65)	NR	Sperm concentration, count, motility, DNA-damage and normal morphology, volume of ejaculate	21	Narrative synthesis	Medium: Acceptable review, though missing some methodological details

Table 14
Summary of structured reviews investigating association between phthalates/metabolites and pubertal outcomes.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2019b	F, All	Environmental (unspecified)	Pubertal development	7	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Radke et al. 2018	M, Adult (16–65)	Environmental (unspecified)	Timing of pubertal development	3	Summary statement only	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Wen et al. 2015	F, Children (<16)	Environmental (unspecified)	Cases of precocious puberty	14	Meta-analysis	Medium: Appears to be a well-conducted systematic review, despite some a few details missing
Bowman and Choudhury 2016	Adolescent	Environmental (unspecified)	Reproductive development; pubertal timing; hormone levels	2	Summary statement only	Low: Poor methodology, poorly reported. Only descriptive analysis of the studies and limited consideration of confounders.
Poursafa et al. 2015	M&F, Children (<16)	Environmental (unspecified)	Various indicators of early onset puberty for boys and girls, mostly early onset menarche	12	Sequential narrative and summary statement	Low: Lacking method description for key stages and lacking a true synthesis

Table 15
Summary of structured reviews investigating association between phthalates/metabolites and Autism/ADHD.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Jeddi et al. 2016	M&F; Children (<16)	Pre-and post-natal/ environmental	Autism in childhood	5	Narrative synthesis	Medium: Appears to include a thorough combining of studies but methods difficult to verify
Nilsen and Tulve 2020	M&F; Children (<16)	Environmental (unspecified)	ADHD	5	Meta-analysis	Medium: Protocol, critical appraisal and pooled results from meta-analysis presented, but lacking some cross-checking

Table 16
Summary of structured reviews investigating association between phthalates/metabolites and neurodevelopment.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Lee et al. 2018	M&F; Children (<16)	Pre-and post-natal/ environmental	Performance Intelligent quotient; Verbal Intelligent Quotient; Motor development index and others	5	Meta-analysis	Good: Generally well conducted review and meta-analysis though missing a protocol
Ejaredar et al. 2015	M&F; Children (<16)	Pre-and post-natal/ environmental	Measures of cognition, internalizing and externalising behaviours	11	Sequential narrative and summary statement	Medium: Acceptable review, though missing some methodological details
Zhang et al. 2019	NR; Children (<16)	NR	Multiple measures including cognitive and mental development indices, social behaviour and internalising and externalising behaviours	26	Narrative synthesis	Medium: Generally well conducted, missing some details and consideration of the limited confounders
Zarean et al. 2016	M&F; Children (<16)	Environmental (unspecified)	Mental development; motor development; behavioural development; internalising behaviours	4	Sequential narrative only	Low: Lacking narrative description, recognition of limitations, note all studies included in narrative synthesis.

Table 17
Summary of structured reviews investigating association between phthalates/metabolites and obesity.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2019a	M&F; All, (including prenatal exposure)	NR	Obesity	8	Sequential narrative only	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly
Ribeiro et al. 2019	M&F; Adult (16–65)	NR	BMI, Waist Circumstance, Obesity, Weight to Height Ratio	25	Meta-analysis	Medium: Adequate review, though missing a few methodological details, and no protocol
Ribeiro et al. 2019	M&F; Children (<16)	NR	BMI, Waist Circumstance, Obesity, Weight to Height Ratio	25	Meta-analysis	Medium: Adequate review, though missing a few methodological details, and no protocol
Zarean et al. 2018	NR; Children (<16)	NR	BMI z score; Waist circumference, Weight to Height Ratio, other body metrics including at birth	13	Narrative synthesis	Medium: Acceptable but limited reporting on methods and limited comparing and contrasting between studies
Golestanzadeh et al. 2019	M&F; Children (<19)	NR	Childhood obesity; eBMI; BMI z-score; waist circumference	26	Meta-analysis and narrative synthesis	Medium: Acceptable review, though missing critical appraisal and some details.
Goodman et al. 2014	M&F; All	NR	BMI, WC, obesity, fat distribution	22	Narrative synthesis	Medium: Generally acceptable methodology but lacking some methods e.g. critical appraisal

Table 18
Summary of structured reviews investigating association between phthalates/metabolites and type 2 diabetes.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2019a	M&F; Children, Adolescents, Adults	NR	Type 2 diabetes, insulin resistance, Gestational diabetes	24	Narrative synthesis	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Kuo et al. 2013	M&F; Adult	Ingestion	Risk of diabetes	3	Narrative synthesis	Medium: Acceptable review, but lacking detail in methods for key stages and no critical appraisal
Shoshtari-Yeganeh et al. 2019	M&F; 12–74	NR	Homeostatic Model Assessment of Insulin Resistance	8	Meta-analysis	Medium: Adequate review, though missing a few methodological details, and no protocol
Song et al. 2016	M&F; Adult	NR	Homeostatic Model Assessment of Insulin Resistance; fasting glucose	6	Meta-analysis	Medium: Generally well conducted with a protocol but missing details on methods and a clearly separated critical appraisal
Sun et al. 2017	M&F; Adult	NR	Increased blood glucose levels, insulin resistance, or gestational diabetes	13	Sequential narrative and summary statement	Medium: Acceptable review but lacking any detail in methods
Goodman et al. 2014	M&F; All	NR	Glucose metabolism, diabetes	4	Narrative synthesis	Medium: A good review, but lacking critical appraisal

Table 19
Summary of structured reviews investigating association between phthalates/metabolites and cardiovascular health.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Golestanzadeh et al. 2019	M&F; Children (<19)	NR	Elevated blood pressure; hyperglycaemia; dyslipidemia; blood pressure; lipids	9	Meta-analysis and narrative synthesis	Medium: Acceptable review, though missing critical appraisal and some details.
Goodman et al. 2014	M&F; All	NR	Markers of cardiovascular health, cardiovascular disease	4	Narrative synthesis	Medium: A good review, but lacking critical appraisal
Gaston et al. 2020	Adult (16–65); focusing on minority populations	Environmental (unspecified)	At least 3 symptoms of possible metabolic syndrome	1	Sequential narrative only	Medium: Acceptable review, recognised limitations, though lacking critical appraisal, cross checking and some detail.

2018; Dorman et al., 2018), and considering the overlap of studies, we found moderate to robust evidence of an inverse association between AGD distance in boys and prenatal exposure to DEHP and DBP, (MBP, MEP, MiBP with anoscrotal distance) with slight or lack of evidence for other phthalates/metabolites. Few reviews reported a synthesis of the evidence for girls, however, there was some evidence for prenatal exposure to MBzP and shorter anofourchette distance.

4.2.5. Gestation and birthweight

We found seven reviews reporting on the measures of birthweight, gestational age/pre-term birth and spontaneous abortion.

4.2.6. Spontaneous abortion

We found one good reliability narrative review, reporting that spontaneous abortion (Radke et al., 2019b) had slight evidence of an association for prenatal exposure to some phthalates, Table 7. The authors of this review recommend further primary research with repeated exposure measures, high study sensitivity (e.g., varied exposure levels, large sample size), and prospective outcome ascertainment.

Table 20
Summary of structured reviews investigating association between phthalates/metabolites and respiratory health.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Li et al. 2017	M&F; Children (<16)	Environmental (unspecified);	Asthma	9	Meta-analysis	Good: A well conducted review with protocol, critical appraisal and pooled results from meta-analysis presented
	As above	Pre-and post-natal/ environmental	As above	up to 3 per metabolite	As above	As above
	As above	Environmental (dust)	As above	up to 3 per metabolite	As above	As above
Zarean et al. 2016	M&F; All	NR	Asthma symptoms; Persistant allergic symptoms	4	Summary statement only	Low: Lacking narrative description, recognition of limitations, note all studies included in narrative synthesis.

Table 21
Summary of structured reviews investigating association between phthalates/metabolites and reproductive cancers.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Fu et al., 2017	F; Adult (16–65)	Bodily (urine)	Risk of breast cancer	4	Meta-analysis	Medium: A good review, but lacking full reporting for eligibility screening and critical appraisal
	As above	As above	Risk of uterine leiomyoma	5	As above	As above

Table 22
Summary of structured reviews investigating association between phthalates/metabolites and renal function.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Radke et al. 2019a	M&F; All	NR	Renal effects	2	Not synthesised	Good: Protocol, critical appraisal and pooled results from meta-analysis presented clearly.
Zheng et al. 2017	NR; Children (<16)	Pre-and post-natal/ environmental	Urine albumin/creatinine ratio; prevalence of microalbuminuria (urine β2MG levels); urine NAG	2	Sequential narrative only	Medium: Well conducted, but missing a few methodological details and explanation of limitations

Table 23
Summary of structured reviews investigating association between phthalates/metabolites and other health outcomes.

Review	Population details (Sex; Age)	Exposure route	Outcome	No. of studies	Synthesis	Reliability summary
Blakeway et al., 2020	M&F; All	Environmental (unspecified)	Atopic dermatitis	2	Sequential narrative only	Good: A well conducted review of two studies
Kim et al. 2019a	M&F; All	NR	Thyroid function markers	13	Meta-analysis	Medium: Acceptable review, though a few discrepancies between text and figures and lacking critical appraisal
Sweeney et al. 2019	NR; NR	NR	Circulating vitamin D; Bone mineral density	4	Narrative synthesis	Medium: A well-conducted SR, though missing a protocol and some details.
Sweeney et al. 2019	NR; NR	NR	Inflammation biomarkers	5	Narrative synthesis	Medium: A well-conducted SR, though missing a protocol and some details.
Sweeney et al. 2019	NR; NR	NR	Oxidative stress biomarkers	14	Narrative synthesis	Medium: A well-conducted SR, though missing a protocol and some details.
Fabelova et al. 2019	NE; Adults (50+)	NR	Hearing disorders	1	Sequential narrative only	Medium: Acceptable review but lacking in methodological detail

4.2.7. Preterm birth

Table 8 presents five reviews reporting on preterm birth or gestational age. We excluded Zarean et al. (2016) from our narrative synthesis due to a low reliability rating and lack of true synthesis, and one review (Patelarou and Kelly, 2014) of only one study which was included in two other reviews. The overlap between the remaining three reviews was very high (CCA = 24%).

The good reliability review (Radke et al., 2019b) reported that three of the six phthalates investigated (DEHP, DBP, and DEP) had moderate evidence of a positive association with preterm delivery, and the remaining three phthalates had slight evidence. The medium reliability review (Yaghjyan et al., 2016) reported inconsistent evidence of an association for either pre-term delivery or gestational age. Both these reviews identify that study heterogeneity and methodological issues may have resulted in the lack of positive associations. The remaining, medium quality review (Marie et al., 2015) contained mainly studies reported by the other two reviews and reported moderate evidence for an increased risk of preterm birth and inconclusive evidence for an effect on the overall duration of pregnancy. Taken together, there was some evidence for a positive association of prenatal phthalate exposure with preterm birth, with a need for more methodologically sound studies.

4.2.8. Birthweight

Table 9 summarises five reviews on prenatal phthalate exposure and

birthweight. We excluded one review due to low reliability and lack of true synthesis (Zarean et al., 2016). There was slight overlap (CCA = 4.4%) between the remaining four medium reliability reviews. The meta-analysis by Golestanzadeh et al., (2019) reported a significant association between prenatal phthalate exposure and low birth weight, providing moderate evidence. Subgroup analyses showed no association when low molecular weight phthalates and high molecular weight phthalates were considered separately. When assessing metabolites separately, there was a significant association for MEP and low birth weight.

Two narrative reviews found null evidence for an association of phthalates and body size at birth, probably because of limitations and methodological differences between studies (Marie et al., 2015; Yaghjyan et al., 2016). The last narrative review of two studies focused on minority populations and reported null evidence for an association (Gaston et al., 2020).

Across the reviews, taking into account the reliability summaries, there is moderate evidence of an association between prenatal phthalate exposure and low birthweight, though better quality studies are required.

4.2.9. Time to pregnancy

Of the five narrative reviews of time to pregnancy, Table 10, we excluded one (Radke et al., 2018) that only included one study, which was contained within all other reviews.

Overlap was very high for the remaining four reviews (CCA = 43%). The two good reliability reviews reported inconsistent evidence for association between phthalates and time to pregnancy. There was large overlap between these two reviews: three of the four studies in Radke et al. (2019b) were contained within Hipwell et al. (2019). The medium reliability review by Høyer et al. (2018) did not find an association for DEHP and delayed time to pregnancy, and the medium reliability review by Blakeway et al. (2020) found evidence of an association though the direction was inconsistent.

Taken together, there is inconsistent evidence for an association between patient exposure to phthalates/metabolites and time to pregnancy. Most of the reviews reported that inconsistencies may be due to the metabolite measured, exposure measurement, a lack of studies and/or problems with study design.

4.2.10. Female fecundity outcomes

Three medium reliability reviews were found that addressed two health outcomes related to female fecundity, Table 11. The study found by Vabre et al. (2017) reported a significant association between high urinary phthalates and lower antral follicle count in infertile patients, indicating some evidence. One of the meta-analyses on endometriosis (Wen et al., 2019) was superseded by the other (Cai et al., 2019), which included the same six studies and two additional studies. Moderate evidence for an association was reported by Cai et al. (2019); patient MEHHP levels were significantly associated with the risk of endometriosis, though in subgroup analyses, the association was significant for populations in Asia, but not in the USA.

4.2.11. Male fecundity outcomes

We found four reviews reporting on adult male fecundity outcomes (Bonde et al., 2016; Cai et al., 2015; Høyer et al., 2018; Radke et al., 2018), including semen parameters and hormone levels.

4.2.12. Hormone levels

Of the two reviews investigating hormone levels in men (Table 12), the good reliability review (Radke et al., 2018) found moderate evidence of an association between patient exposure to DEHP, DINP, and DIBP and decreased testosterone levels, slight evidence for exposure to DBP, and inconsistent evidence for BBP and DEP. There was very high overlap (12 shared studies) with the medium reliability narrative review (Høyer et al., 2018), which found moderate evidence for a negative association between patient DEHP metabolites and testosterone levels, sometimes with a concomitant reduction in oestradiol, across 16 studies. Across the two reviews, there was moderate evidence of decreased testosterone in adult males, and some evidence for a reduction in oestrodiol.

4.2.13. Semen quality parameters

Of the four reviews which reported on semen quality, Table 13, we excluded from our narrative synthesis one review (Bonde et al., 2016) because the study was included in the good reliability review. The overlap between the remaining three reviews was very high (CCA = 31%). Because each of the three reviews contained at least four unique articles, we consider the results of all three reviews below, whilst acknowledging the very high overlap. The good reliability review (Radke et al., 2018) reported moderate to robust evidence of an association between DBP, BBP, DEHP, and DINP exposure and sperm parameters, slight evidence for DIBP (perhaps due to fewer studies), and inconsistent evidence for DEP (perhaps due to lower relative potency or activity). The strongest evidence was observed for sperm concentration, while evidence for motility and morphology was more limited (with the exception of BBP and DINP, respectively). The medium reliability meta-analysis (Cai et al., 2015) found moderate evidence for alterations in multiple sperm quality measures: MBP and MBzP were associated with reduced sperm concentration, and MBP and MEHP were inversely associated with straight-line velocity of sperm). The other narrative synthesis (Høyer et al., 2018) reported some evidence of an association between DEHP exposure and reduced sperm concentration and motility, and the proportion of spermatozoa with damaged DNA.

Taken together the results show robust evidence for an association between some phthalate metabolites and a variety of semen quality parameters, primarily reduced sperm concentration and motility.

4.2.14. Pubertal outcomes

Excluding two low reliability reviews, slight overlap was indicated by the CCA (4.5%) for the five remaining reviews assessing pubertal outcomes, mainly via patient, rather than prenatal exposure, summarised in Table 14. Across two good reliability reviews (Radke et al., 2019b, 2018), and one medium reliability meta-analysis (Wen et al., 2015) there was slight or inconsistent evidence for an effect on early onset puberty for girls (in the meta-analysis, particularly DEHP and DBP) and boys (in one of the narrative syntheses). The addition of the two low reliability reviews indicated a slightly stronger case for an effect on girls. The reviews identified a need for well-designed epidemiological studies on this topic.

Autism and Attention Deficit Hyperactivity Disorder (ADHD)

Table 15 summarises two studies on autism or ADHD. For autism, a medium reliability review of five studies found some evidence of connection with exposure to phthalates, including prenatal exposure, but called for further research which included appropriate attention to exposure assessment and relevant prenatal and environmental confounders (Jeddi et al., 2016). A medium reliability review of two studies reported moderate evidence for an association between ADHD symptoms and post-natal phthalate exposure in both sexes (Nilsen and Tulve, 2020).

4.2.15. Neurodevelopment

Across the three good/medium reliability reviews assessing neurodevelopment, Table 16, the CCA was 17%, indicating very high overlap, the majority was between Ejaredar et al. (2015) and Zhang et al. (2019). Of these two reviews, we prioritise the more recent Zhang et al. (2019), which included more studies and outcomes. The good reliability meta-analysis (Lee et al., 2018) showed robust evidence for an effect on neurodevelopment (significant association between DEHP metabolites and decreased verbal intelligence or performance intelligence indices, and that increased DEHP metabolites in the urine of pregnant women was associated with significantly lower psychomotor development index). In the medium reliability narrative synthesis, Zhang et al.

(2019), authors found moderate evidence for an effect on neurodevelopment. prenatal DEHP, DBP, BBP and DEP exposure was associated with lower cognitive scores and worse behavior in offspring, though sex specific effects were more inconsistent. Ejaredar et al. (2015) also reported moderate evidence for an association between prenatal and childhood exposure to phthalates and adverse neurodevelopment measures. The low reliability review of four studies (Zarean et al., 2016) reported inconsistent evidence.

Taken together, and considering the reliability of reviews there is robust evidence for an association between some phthalates/metabolites, particularly DEHP and neurodevelopment outcomes, both for prenatal exposure and for post-natal environmental exposure.

4.2.16. Obesity

We found six studies assessing weight outcome, two of which were from the same article (Ribeiro et al., 2019), Table 17. The CCA was 9.5%, indicating a moderate overlap across the publications. Overlap was generally even across reviews and there were some differences in population (assessing babies, children, adults or a mixture) and exposure (Radke et al., 2019a included prenatal exposure).

For three of the six reviews, including the good reliability review, the evidence was generally null or inconsistent (Radke et al., 2019a; Goodman et al., 2014; Ribeiro et al., 2019, for under-16 s). In the remaining three medium reliability reviews, all reported a positive, significant effect for some phthalates, for some outcomes, but not others, and these differed with sex and age. MECPP was significantly associated with adult obesity in the meta-analysis by Ribeiro et al. (2019). Significant risk of obesity, high BMI and waist circumference was reported in children (Golestanzadeh et al., 2019; Zarean et al., 2018). In Zarean et al. (2018), weight and BMI were significantly associated, but with inconsistent directions in girls vs boys. Taken together, the reviews show some evidence that phthalate exposure may be an increased risk of obesity for children in particular.

4.2.17. Type 2 diabetes

CCA overlap for all six studies of diabetes outcomes (Table 18) was high (14%). Kuo et al. (2013) and Goodman et al. (2014) did not contain any unique studies, though they shared one study that was not reported by any other reviews. Six of the 12 studies in Sun et al. (2017) were not included in the largest review of good reliability, Radke et al. (2019a), which contained 24 studies. Based on this, we focus on the results of the two largest narrative reviews, Sun et al. (2017) and Radke et al. (2019a), and the two meta-analyses, Shoshtari-Yeganeh et al. (2019) and Song et al. (2016). Across the two largest narrative reviews, an association between exposure to phthalates and insulin resistance was detected, but evidence was considered slight due to small study size and some conflicting studies (Sun et al., 2017, medium reliability; Radke et al., 2019a, good reliability). Both medium reliability meta-analyses showed significant positive correlation between phthalate exposure and risk of type 2 diabetes (Shoshtari-Yeganeh et al., 2019; Song et al., 2016).

Taking into account review reliability and overlap, we found moderate evidence for an association between patient phthalate exposure and risk of type 2 diabetes.

4.2.18. Cardiovascular health

Across the reviews assessing aspects of cardiometabolic or cardiovascular health (Table 19), there was slight overlap (CCA = 3.8%). For lipids in children and adolescents, though individual studies reported significant associations for low-density lipoprotein cholesterol and triglyceride, in meta-analyses, the same was not observed, except for MEOHP and high-density lipoprotein cholesterol), and there was no association with blood pressure levels (Golestanzadeh et al., 2019). One review of four studies found inconsistent associations with cardiovascular disease (Goodman et al., 2014). In the review focusing on minority populations, authors found one study on urinary phthalate that found positive association with metabolic abnormalities (for MnBP and MiBP), that varied by sex (Gaston et al., 2020). Across the three studies, there was inconsistent evidence to support an association between patient phthalate exposure and cardiovascular health.

4.2.19. Respiratory health

Table 20 summarises two articles assessing respiratory outcomes. One good reliability meta-analysis (Li et al., 2017) reported data for general environmental exposure to phthalates, pre/postnatal exposure and indoor (dust) exposure separately, and focused on children and childhood risk of asthma. The review found that for general environmental exposure, BBzP exposure was significantly associated, whilst no significant results were observed for DEHP, DnBP, DiBP, and DEP. Prenatal exposure to BBzP had a stronger association with the risk of childhood asthma, compared to those with postnatal exposure. Finally, postnatal, indoor exposure to DEHP and BBzP from dust had strong positive associations with childhood asthma. There was no overlap in the studies between the two reviews. The low reliability review (Zarean et al., 2016) stated that "the present review showed that DEHP exposure associated with adverse effects on respiratory system". Focusing on the good reliability meta-analysis, there is robust evidence that phthalate exposure via a number of routes (including pre- and post-natal), may increase the risk of childhood asthma.

4.2.20. Reproductive cancers

One medium reliability meta-analysis (Fu et al., 2017, Table 21) reported significantly positive associations between multiple phthalate metabolites (DEHP and MECPP) and risk of breast cancer and uterine leiomyoma, indicating moderate evidence for an effect, though total phthalate metabolites were not significantly associated.

4.2.21. Renal function

Two reviews investigated kidney function, both included the same two studies, Table 22. The good reliability review reported low confidence for both studies due to selection bias, possible reverse causation (Radke et al., 2019a) and because of inconsistency between the studies' results.

4.2.22. Other health outcomes

We found single reviews reporting the effect of patient phthalate exposure on a range of other health outcomes, including atopic dermatitis, thyroid function, bone health, inflammation, oxidative stress and hearing loss, Table 23. All reviews were of medium reliability, except Blakeway et al. (2020), which was good reliability and reported slight evidence of association with atopic dermatitis. For bone health and inflammation, a medium reliability review reported null or inconsistent evidence, due to limited quality or consistency of evidence from included studies (Sweeney et al., 2019). One medium reliability meta-analysis reported a significant association between exposure to DEHP metabolites and thyroid functioning (Kim et al., 2019a). Slight evidence for an association with biomarkers of oxidative stress was found by Sweeney et al. (2019), who reported a significant association with both MiBP and MEP, though the overall effects of phthalates was inconclusive. Fabelova et al. (2019) found one study reporting significant association with hearing disorders, indicating some evidence for this outcome.

4.3. Summary of strength of evidence for association between phthalates and health outcomes

We assigned the evidence for health outcomes into categories that describe the strength of evidence, Table 24. The methodological reliability of reviews (Good or Medium or Low), the type of review (narrative or meta-analysis) and the size of the evidence base (number of reviews) were used to arrive at the strength of evidence assessment, see Methods.

Table 24
Summary table of strength of evidence for health outcomes included in this Overview of Reviews.

Health Outcome	Strength of evidence	Total No. reviews	Synthesis approach	Reliability
Infant reproductive system/congenital abnormalities				
Anogenital distance in boys	Moderate-robust	7	Narrative	1 Good 2 Medium 1 Low
			Meta-analysis	1 Good 2 Medium
Anofourchette distance	Some	1	Narrative	1 Medium
Fetal sex hormones	Some	1	Narrative	1 Medium
Pre-term birth	Some	5	Narrative	1 Good 3 Medium 1 Low
Low birthweight	Moderate	5	Narrative	3 Medium 1 Low
			Meta-analysis	1 Medium
Malformation of testes	Inconsistent	4	Narrative	1 Good 3 Medium
Spontaneous abortion	Slight	1	Narrative	1 Good
Adolescent or adult reproductive system				
Lower antral follicle count	Some	1	Narrative	1 Medium
Endometriosis risk	Moderate	1	Meta-analysis	1 Medium
Time to pregnancy	Inconsistent	5	Narrative	2 Good 3 Medium
Decreased testosterone	Moderate	2	Narrative	1 Good 1 Medium
Reduced oestrodiol	Some	1	Narrative	1 Medium
Lower semen quality	Robust	4	Narrative	1 Good 2 Medium
			Meta-analysis	1 Medium
Early onset puberty	Slight/ inconsistent	5	Narrative	2 Good 2 Low
			Meta-analysis	1 Medium
Behaviour and neurodevelopment				
Attention Deficit Hyperactivity Disorder (ADHD)	Moderate	1	Meta-analysis	1 Medium
Autism	Some	1	Narrative	1 Medium
Neurodevelopment	Robust	4	Narrative	2 Medium 1 Low
			Meta-analysis	1 Good
Cardiovascular health				
Obesity	Some	6	Narrative	1 Good 2 Medium
			Meta-analysis	3 Medium (2 from same publication)
Type 2 Diabetes	Moderate	6	Narrative	1 Good 3 Medium
			Meta-analysis	2 Medium
Indicators of cardiovascular health	Inconsistent	3	Narrative	3 Medium
Other				
Childhood Asthma	Robust	4	Meta-analysis	3 Good (all from one publication)
			Narrative	1 Low
Risk of breast and uterine cancer	Moderate	1	Meta-analysis	1 Medium
Kidney function	Inconsistent	1	Narrative	1 Good
Oxidative stress	Slight	1	Narrative	1 Medium
Thyroid function	Some	1	Meta-analysis	1 Medium
Atopic dermatitis	Slight	1	Narrative	1 Good
Bone health	Null	1	Narrative	1 Medium
Inflammation	Null	1	Narrative	1 Medium
Hearing disorders	Some	1	Narrative	1 Medium

4.4. Evidence gaps

We found no major evidence gaps in terms of the *range* of health outcomes covered by the reviews in this overview. In accordance with the known mechanisms of action of phthalates and their metabolites on human health (oestrogenic/anti-androgenic and via inflammatory/oxidative stress pathways), most of the outcomes found were either linked to the reproductive system and/or cardio/metabolic pathways. We found a disproportionate number of reviews (and studies) on male reproductive health outcomes compared to females. Five of the nine reviews on genital malformations focused only on males. There were no reviews that focused solely on female genital malformations. Four reviews on semen parameters and two reviews on hormone levels in men, compared to three reviews on female reproductive disorders, and none investigating hormone levels in women, Additional File 8, Table A4, A5. The number of studies within reviews was also fewer (8 or less for reviews focusing on women, and generally between 13 and 21 for reviews focusing on men). This discrepancy may be partly explained by the documented oestrogenic/anti- androgenic mechanism of action of phthalates which may be presumed to be more detectable in males. However, the effects of phthalates in female fetuses, girls and women, though less well documented, may have similarly undesirable impacts, and this represents a gap in the *amount* of evidence available on health outcomes.

One main evidence gap was the lack of reviews that focused on phthalates from recycled plastics, which may differ from virgin plastics in both concentration and possible 'cocktail effects'. The evidence gap stems from the current inability to separate exposure to recycled materials from non-recycled plastics in empirical studies. Yet concern is building over the circular economy route, with more studies focusing on the presence of potentially harmful chemicals in recycled plastics and/or food and drink contained within such plastics (Keresztes et al., 2013; Pivnenko et al., 2016). Significantly higher levels of DiBP, DBP and DEHP have been measured in waste plastic samples and recycled household plastics than in virgin and recycled industrial plastic, Pivnenko et al. (2016). A study by Lee et al. (2014), found that increased frequency of recycled board and PET bottles led to increased childhood exposure to DBP. These increased exposures would be expected to have increased negative effects on human health outcomes. More direct links may be made in laboratory studies that are able to investigate the impacts of phthalates (and other potentially harmful additives) in recycled plastics on health outcomes. Such in-vitro studies are, by their nature, unable to include the complex interactive effects that happen during metabolism in the human body, and the "cocktail effect" of other chemicals and external factors at an individual and a population scale that will influence the impact of any substance on the body.

5. Summary

5.1. Limitations of evidence base and recommendations for future primary research

The ability to accurately measure exposure to phthalates is a recognised challenge (CDC, 2020). Many primary studies report the amounts of metabolites in urine, which is the most accepted measure (Dirven et al., 1993; Blount et al., 2000), but still only provides a "snapshot" of exposure, due to fast rates of metabolism (Hauser and

Calafat, 2005). Other studies report amounts of metabolite in blood or serum, amounts in dust, and some reviews did not report the measures used by each study. The reliability of exposure measurement is crucial to determining the strength of effect on health (Needham et al., 2007). Urine concentrations, with samples across multiple timeframes are considered the most accurate estimation of human phthalate exposure (Papadopoulou et al., 2016).

As with any health outcome which is affected by multiple and external factors, many primary studies and reviews face challenges in controlling for those factors, and thus determining a causal relationship between phthalates and health outcomes (Needham et al., 2007). We acknowledge that cause-and-effect is difficult to determine for phthalates because of this. In addition, the "cocktail effect", in which chemical compounds that the human body is exposed to are metabolized together, may result in additive effects (EC, 2012). The impacts on the body will vary according to the mix of compounds, which can vary greatly between individuals, populations and over time within an individual. Though the cocktail effect is very difficult to control for, large scale studies that are able to control or adjust for other factors are recommended (EC, 2012).

We found the methodological quality of the reviews in our overview was generally adequate. A few reviews had methodological flaws (such as apparent selection of studies for synthesis, and a lack of consideration of the limitations of the evidence base, Additional File 3). Others simply did not fully report all methodological stages of reviewing and thus, quality was uncertain for some aspects of each review. A misunderstanding of the methodological rigour of a "systematic review" was evident: some reviews that were described by authors as "systematic" did not strictly adhere to methodological guidelines for systematic reviews. We recommend that review authors should report methods for all stages of review and describe the limitations of their work for full transparency.

5.2. Limitations of this overview and recommendations for future overviews

Though we made considerable effort to identify the available reviews on this topic with a well-informed and tested *a priori* search strategy, along with review screening that involved consistency checking, we acknowledge that there is always a risk that some reviews may have been missed.

We found that the CCA metric (Box 2) had limited application in our overview as a measure of overlap, because it does not reflect the nuanced differences between the reviews in terms of their focus of study- a high degree of overlap could be indicated with the metric, yet the real degree of overlap may be less, due to each review focusing on different populations, interventions or outcomes reported by each study. We dealt with the overlap between reviews for each health outcome by: identifying the degree (using the CCA across reviews and comparing directly between key reviews); determining where the most significant overlap lay; incorporating the date of publication, quality assessment and using this information to summarise across reviews. However, there remains a small potential for the influence of some studies that were included by the majority of reviews to have a disproportionate influence on the overview results. We recommend that a future synthesis could overcome this by undertaking a synthesis of primary studies (narratively or quantitatively) identified from reviews.

We used the CEESAT reliability assessment to arrive at a categorical, summary reliability rating for each review, along with an explanatory statement. The CEESAT assessment tool has been tested and undergone several refinements, yet there are some aspects where a review may appear to be downgraded despite making reasonable effort to avoid bias. Notably, a review will receive a "red" rating, if it does not contain a meta-analysis, even if it was inappropriate to undertake one (7.2), and will receive a "red" rating if the quality assessment was not standardized across all studies (5.1) or if quality assessment was not undertaken by more than one person (5.2). Recognising these limitations, we have taken such potential downgradings into account when determining the summary reliability score and presenting the explanatory statement for each review.

Our overview used descriptors of the strength of evidence and the confidence in the evidence base (Box 3), to provide readers with a concise, clear and comparable descriptive synthesis of the evidence. We recognize that nuances in the type of evidence presented by reviews cannot be fully represented in this way, and refer the user to Additional File 3 and Additional File 8 Tables A1 to A13. which present the individual review findings in more detail.

5.3. Current state of the evidence

Our overview found robust evidence for an association between phthalates/metabolites and lower semen quality, neurodevelopment and risk of childhood asthma, and moderate to robust evidence for impact on anogenital distance in boys. We identified moderate evidence for an association between phthalates/metabolites and low birthweight, endometriosis, decreased testosterone, ADHD, Type 2 diabetes and breast/uterine cancer. There was some evidence for other outcomes including anofourchette distance, fetal sex hormones, pre-term birth, lower antral follicle count, reduced oestrodiol, autism, obesity, thyroid function and hearing disorders. Other outcomes had slight, inconsistent or a lack of results: malformation of testes, spontaneous abortion, time to pregnancy, early onset puberty, indicators of cardiovascular health, kidney function, oxidative stress, atopic dermatitis, bone health, and inflammation. Based on this overview, we recommend future primary research in these latter areas, and further studies and reviews on female reproductive effects, which are generally under-represented.

5.4. Implications for the public and for regulation

Our overview of reviews focused on the range of human health outcomes associated with phthalates, and the nature of an overview meant that investigations of critical thresholds of dose were inappropriate. We refer to a recent review of 41 studies (reported in Maffini et al., 2019, 2021) which found impacts on human health associated with phthalate exposure levels below the regulatory "safe dose" as determined by the European Chemicals Agency in 2016 (ECHA, 2017, 2020). The graphic in Fig. 2 was produced using the data and with permission from the authors of the review, and also shows that human exposure to DEHP is nearing an order of magnitude higher than the regulatory safe dose (240 vs 35 μg/kg of body weight). Combined with the evidence presented in our overview, there is clear cause for concern and areas of human health risk. Rapid innovation in response to such public health concern as identified here, can lead to unforeseen or unintended consequences (WHO, 2019). This is particularly the case where new synthetic man-made products or alternative processes are used, and caution is clearly required where alternatives are substituted for phthalates (Chemsec, 2019).

The presence or accumulation of substances of concern has the potential to undermine public confidence and future positive uses for plastic. A key challenge is that the highly globalized nature of plastic production and recycled materials, combined with the often opaque knowledge on the additives even in primary-use products (Groh et al., 2019) means that ensuring safety in recycled products has become extremely problematic. European recycling standards hold the use of some additives to account, with a focus on food contact materials and toys which may be put in the mouth. This is achieved through restrictions on use of certain recycled inputs, limits on the levels of contaminants within recycled polymers, and/or controls on entire processes (Geueke et al., 2018). However it is argued that such regulations are inadequate and/or slow to react to new chemical additives, largely due to poor data on many impacts of chemicals on health (Muncke et al., 2017).

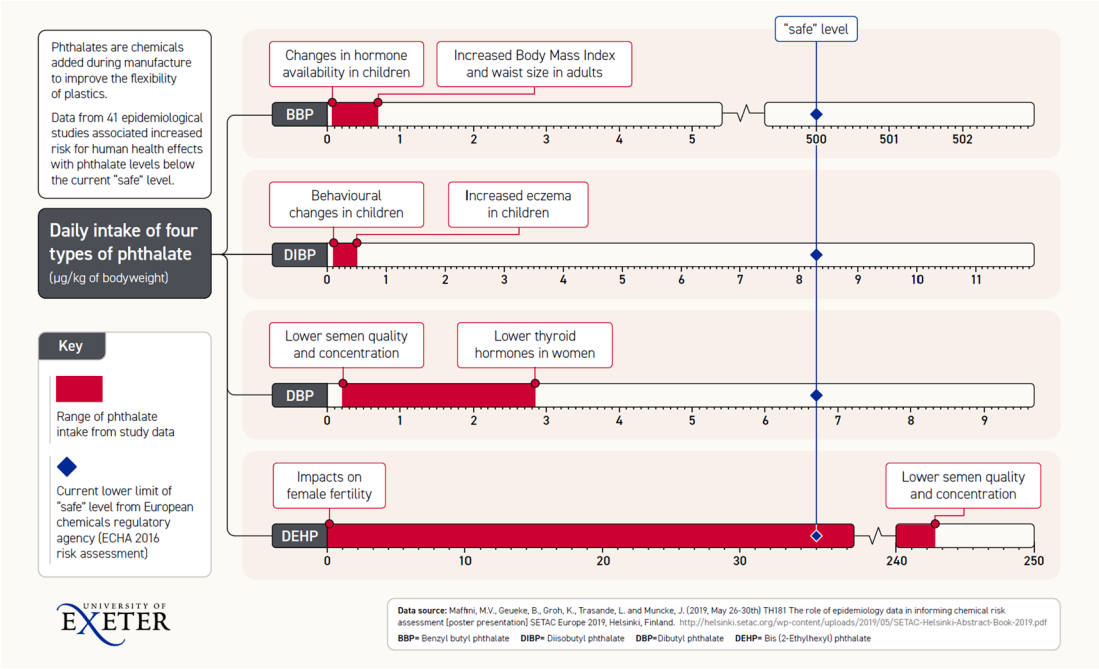

Fig. 2. Health impacts of phthalates associated with exposures below current European Regulatory Levels deemed safe (indicated by the blue vertical line). Graphic produced using data from Maffini et al. (2019, 2021), a review of 41 epidemiological studies which associated increased risk for human health effects with levels of phthalates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Accordingly, much more attention is needed on the chemical composition of all materials used in final products and services, including recycled materials. Systematic research and evidence synthesis on substances of concern is needed for a wider range of chemicals and their interactions across multiple life cycles to give confidence to all stakeholders involved in future plastic value chains. This includes greater understanding of the composition of virgin vs recycled plastics in products, the potential for more or less exposure to phthalates and their associated impacts whilst taking into account the "cocktail effect" of other compounds in the body. Future primary studies should consider confounding factors in analyses, and use accepted methods of exposure assessment (urine samples) across multiple time points. Future evidence overviews could overcome the impact of review overlap by using primary studies identified by the reviews to inform a novel narrative or quantitative synthesis.

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Declaration of Competing Interest

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

Appendix A. Supplementary material

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