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Phenols, Parabens, Phthalates and Puberty: a Systematic Review of Synthetic Chemicals Commonly Found in Personal Care Products and Girls' Pubertal Development

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Abstract

Purpose of Review—Exposure to endocrine disrupting chemicals through personal care products (PCPs) is widespread and may disrupt hormone-sensitive endpoints, such as timing of puberty. Given the well-documented (and ongoing) decline in age at menarche in many populations, we conducted a systematic review of the epidemiological literature on exposure to chemicals commonly found in PCPs (including certain phthalates, phenols, and parabens) in relation to girls' pubertal development.

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Recent Findings—The preponderance of research on this topic has examined phthalate exposures with the strongest evidence indicating that prenatal monoethyl phthalate (MEP) concentrations may be associated with slightly earlier timing of puberty, including age at menarche. Findings examining peri-pubertal phthalate exposures and pubertal outcomes were less consistent as were studies of prenatal and peri-pubertal phenol exposures. Very few studies had examined parabens in relation to girls' pubertal development. Common study limitations included potential exposure misclassification related to use of spot samples and/or mistimed biomarker assessment with respect to the outcomes. The role of body size as a mediator in these relationships remains unresolved.

Summary—Overall, evidence of associations between chemical exposures in PCPs and girls' pubertal development was conflicting. When associations were observed, effect sizes were small. Nevertheless, given the many environmental, social, and behavioral factors in the modern environment that may act synergistically to accelerate timing of puberty, even marginal changes may be cause for concern, with implications for cancer risk, mental health, and cardiometabolic disease in later life.

Keywords

Puberty; Menarche; Thelarche; Endocrine disrupting chemicals; Personal care products

Introduction

Worldwide, there has been a decades-long secular trend towards earlier age at puberty and the median age at menarche in the USA is now 11.9 years old, down from 16.5 years old in 1840 [1, 2]. The trend towards earlier maturation in girls, in particular, has caused concern due to links between early age at menarche (the first menstrual period) and reproductive cancers, metabolic dysregulation, and adverse mental and behavioral health [3–7]. The causes of this trend are widely debated but are surely multifactorial and include overnutrition and increased sedentism [8]. Most recently, endocrine-disrupting chemicals (EDCs), which interfere with typical hormone activity and act as metabolic disruptors, have been implicated [8, 9]. Among the EDCs of greatest concern are phthalates, phenols, and parabens, all of which are widely found in consumer products including personal care products (PCPs) such as soaps and body cleansers, lotions, and cosmetics, as well as hair and oral care products [10, 11]. Among industrialized populations, exposure to many such EDCs is virtually ubiquitous across the lifespan, with well-documented disparities in exposure by age, gender, race, and ethnicity [12–14].

Periods of reproductive development, including gestation, early childhood, and puberty, may be vulnerable windows of susceptibility during which EDC exposure exerts long-lasting impacts on health outcomes [15, 16•]. These are periods of intense and tightly regulated endocrine activity as the hypothalamic-pituitary–gonadal (HPG) axis and other hormone systems are established and activated [17–19]. Ultimately, the onset of puberty relies upon the interaction of multiple hormones including gonadotropinreleasing hormone (GnRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone (DHEA), and estrogens [20, 21]. This complex cascade of endocrine activity may be vulnerable to disruption by EDCs, with potential impacts on onset and tempo of adrenarche,

pubarche (development of pubic hair), thelarche (breast development), and menarche. Major dysregulation of these hormone-dependent processes can result in precocious puberty, the development of secondary sexual characteristics (including pubarche and thelarche), before 8 years of age [22].

Given that, a number of epidemiological studies have examined EDC exposures in relation to girls' pubertal development as well as precocious puberty. Here, we systematically review this literature focusing on EDCs commonly found in PCPs including: low molecular weight (LMW) phthalates (specifically diethyl phthalate (DEP) and di-n-butyl phthalate (DBP)), phenols (specifically the UV filter benzophenone-3 (BP-3), the anti-microbial triclosan (TCS), and its breakdown products, 2,4-dichlorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5-DCP)), and parabens (preservatives used to lengthen shelf life in cosmetics) (Fig. 1). We additionally consider papers evaluating PCP use as a proxy for EDC exposures.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and registered on PROSPERO (accessible at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020202399.2) [23].

Eligibility Criteria

Our aim was to assess current epidemiologic evidence linking phenols, parabens, and phthalates commonly found in PCPs to pubertal development in girls. Inclusion criteria were as follows: (1) primary research studies including randomized-controlled trials (RCTs), cohort studies, case–control studies, and cross-sectional studies; (2) human female participants; (3) publication dates from 2000 to June 2020 (when the initial searches were performed); (4) published in English; (5) study population of any race, ethnicity, or socioeconomic status from any geographical location. Studies not meeting these criteria were excluded. Whenever possible, in this review, we highlight literature published in the last 5 years.

Databases and Search Strategy

Databases searched were PubMed, Scopus, and Web of Science. Major concepts for searching were PCPs and girls' pubertal development. MeSH headings as well as synonyms and related keywords were identified for each concept. The search strategy was tested repeatedly in PubMed and validated by subject experts who reviewed the first one hundred references retrieved. Finalized search strategies are provided in Supplemental Table 1. Updated searches were run in PubMed in January and July 2021 to capture any newly published papers.

Study Selection

In total, 760 references were retrieved and exported into EndNote. After duplicate removal, 555 references were exported for title and abstract screening in Rayyan, a web-based screening tool for systematic reviews [24]. Each reference (title and abstract) was screened

by two independent reviewers, resulting in 509 references excluded and 46 references selected for full-text review. Full texts were reviewed by two independent reviewers, resulting in 18 additional references excluded. Conflicts were resolved through discussion among the reviewers. Ultimately, 28 articles were selected for qualitative synthesis (Fig. 2).

Data Extraction

Data were extracted using a structured form (Table 1). To evaluate the risk of bias for each of the included studies, we applied an established framework developed by the Office of Health Assessment and Translation (OHAT) at the National Toxicology Program (NTP)/ National Institute of Environmental Health Sciences (NIEHS), with customization for our research topic (OHAT Handbook 2019 [25]; Table 2). We classified each study as tier 1 to 3 (lowest to highest risk, with emphasis on "key elements") [25, 26], based on assessment of risk related to the following sources of bias: selection bias, confounding bias (key element), attrition/exclusion bias, detection bias (exposure – key element), detection bias (outcome – key element), selective reporting bias, and other threats to internal validity. For each paper, risk of bias was evaluated by two independent reviewers; conflicts were discussed and resolved by consensus.

Results

Of 28 articles reviewed, 24 considered relevant phthalates, 10 considered relevant phenols, and 7 considered parabens, with some studies considering more than one chemical class. In addition, two papers considered self-reported PCP use (specifically hair products) without directly quantifying chemical bioburden. Here, we summarize the results by chemical and timing of exposure.

Phthalates

Prenatal Exposures and Pubertal Development

The impact of prenatal exposure to phthalates on pubertal outcomes in girls has been studied in several cohorts. The Mexican ELEMENT cohort measured urinary phthalate metabolites in each trimester of pregnancy and daughters participated in a peri-pubertal study visit at age 8–13 years (average age of study visit 10.0 years, $n = 120$). Interquartile range (IQR) increases in first and third trimester MEP were associated with 3.9 and 2.4 times (respectively) the odds of menarche onset at the time of the visit [16•]. Associations were stronger when MEP was averaged across all visits ($OR = 4.33$, 95% CI: 1.25, 15.00); no associations with DBP metabolites were observed [16•, 27]. Serum hormone levels were also measured in daughters and third trimester IQR increases in maternal urinary MEP and MiBP were associated with higher serum testosterone in daughters (%Δ = 25.5, 95% CI: 2.10, 54.10) DHEA-S (%Δ = 19.5, 95% CI: 1.10, 41.30), respectively [27]. Associations were once again stronger when exposures were averaged across all trimesters [16•]. Few associations with pubertal or hormone outcomes were observed in relation to phthalate metabolites measured contemporaneously in daughters' urine, with the exception of a trend towards association between MiBP and E2 (IQR/%Δ14.2, 95% CI: − 1.3, 32.2) [27]. Later work in the cohort (including an additional visit at ages 9–18 (mean 13.3 years), when

78% of participants had reached menarche) observed no associations between prenatal MEP, MiBP, and MnBP concentrations (based on geometric mean levels across trimesters) and pubertal outcomes [28].

In the US CHAMACOS cohort, maternal urinary phthalate metabolites were measured in early and mid-pregnancy and Tanner staging was conducted in daughters every 9 months from ages 9–13 years [29•]. Overall, higher maternal phthalate metabolites (average of the two prenatal measurements) were associated with earlier timing of pubertal milestones; however, only the association between MEP and pubarche (Tanner stage PH2 +) was statistically significant ($\beta = -1.30$, 95% CI: − 2.50, − 0.10 months for a doubling of MEP concentrations). MEP was not statistically significantly associated with menarche onset and no associations were observed between DBP metabolites and pubertal outcomes.

Finally, the Australian Raine study measured phthalate metabolite concentrations in 121 pregnant women in pooled mid- and late-pregnancy blood samples [30]. Age at menarche among resulting daughters was retrospectively assessed by questionnaire [31]. In bivariate correlations, neither MEP nor the DBP metabolites were associated with age at menarche. Maternal MEP was inversely associated with daughters' serum sex hormone binding globulin (SHBG) levels ($r = -0.17$, $p < 0.05$) and positively correlated with free testosterone index (total testosterone/SHBG) ($r = 0.16$, $p < 0.05$) at age 14–16 years. A follow-up analysis with a larger sample from the cohort similarly found no associations between the phthalates of interest and age at menarche [32•]. Study design differences, the short half-life of phthalate metabolites in serum (a non-preferred matrix), and the potential for contamination make it difficult to compare these results to other studies.

Postnatal Exposures and Pubertal Development

Results of studies on postnatal exposures to LMW phthalate metabolites and pubertal milestones have been inconsistent. For example, in an early analysis of data from the Breast Cancer and Environment Research Program (BCERP) cohort ($n = 1151$), weak, positive associations were observed between ΣLMW metabolites at age 6–8 and prevalence of thelarche (quintile 5 vs. quintile 1: $PR = 1.06$, 95% CI: 0.99, 1.14; $P_{trend} = 0.09$) and pubarche (quintile 5 vs. quintile 1: $PR = 1.06$, 95% CI: 0.98, 1.13; $P_{trend} = 0.08$), assessed contemporaneously and 1 year later [33]. After up to 6 years of follow-up, no significant associations between ΣLMW metabolites at enrollment and age at thelarche or pubarche were observed; however, MBP was weakly, inversely associated with age at pubarche considered continuously ($HR = 0.92$, 95% CI: 0.85, 1.00) [34]. In subsequent analyses, ΣLMW phthalate metabolites ($HR = 1.15$, 1.07, 1.24) and MEP ($HR = 1.13$, 95% CI: 1.07, 1.20) were associated with earlier age at menarche, with associations attenuated after adjustment for race/ethnicity and education [34]. Pre- and peri-pubertal MiBP and MBP were not associated with age at menarche. In the Chilean Growth and Obesity Cohort Study (GOCS; $n = 200$), urinary phthalate metabolites were measured at age 6–9 and 9–13 [35]. Somewhat consistent with findings from BCERP, higher MEP before puberty was associated with earlier age at menarche among overweight or obese girls ($HR = 1.24$, 95% CI: 1.05, 1.47), but not among those of normal weight.

In the longitudinal Copenhagen Puberty Study, 84 girls aged 5–12 were examined every 6 months to assess pubertal development [36]. No associations between urinary phthalate metabolites and age at thelarche or pubarche were observed, but findings suggested that higher ΣMBP_{i+n} (sum of the monobutyl phthalate isoforms) was associated with increasing age at pubarche as well as lower DHEAS and androstenodione. DBP was additionally inversely associated with several hormones including FSH, LH, E2, and testosterone. In another analysis from this cohort, higher urinary phthalate metabolite concentrations were found in older girls at more advanced stages of development compared to younger girls at less advanced stages of development; however, phthalate metabolites were not associated with timing of thelarche, pubarche, or hormone levels (FSH, LH, estradiol and testosterone) [37].

In contrast to the several studies suggesting MEP exposure might be associated with accelerated pubertal development [35, 38], in 198 German girls, urinary MEP exposure at 8–10 years old was marginally associated with delayed pubertal development in follow-up visits (using a summary score calculated based on pubic hair growth and breast development) ($\beta = -0.12$, 95% CI: − 0.26, 0.02, $p \leq 0.10$) [39]. MEP concentrations were also inversely associated with odds of thelarche ($OR = 0.60$, 95% CI: 0.40, 0.88); no associations were observed with timing of menarche. Several additional cross-sectional studies have observed no associations between PCP-related phthalate exposures and pubertal milestones [40–42, 43•].

Precocious Puberty

Evidence from small case–control studies examining PCP-related phthalates and precocious puberty is mixed. Several studies comparing girls with central precocious puberty (CPP, GnRH-dependent) and/or peripheral precocious puberty (PPP, GnRH-independent) to age-matched controls reported no differences in phthalate metabolites between groups [44, 45], while others observed statistically non-significant higher MBP and MEP in girls with precocious puberty compared to healthy controls [46, 47]. A small number of studies have noted differences between groups. In a Turkish study, urinary MEP was significantly higher in premature thelarche (PT) cases compared to controls [48]. Among cases, moreover, MiBP was inversely correlated with free thyroxine, but not LH, FSH, TSH, or estradiol [48]. In Puerto Rican girls, Colon et al. (2000) described elevated serum DBP in girls with PT compared with controls; however, no additional statistical analyses were presented [49]. Finally, in a study of girls with CPP, MBP was correlated with higher kisspeptin (a measure of pubertal timing) ($r^2 = 0.25$, $p < 0.001$); however, the association was weaker after creatinine adjustment [50].

Phenols

Prenatal Exposures and Pubertal Development

Few studies have examined phenols commonly found in personal care products in relation to pubertal development. In the CHAMACOS cohort, TCS, BP-3, and 2,4- dichlorophenol were measured in maternal urine in early and mid-gestation, and in the resulting daughters at age 9 [29•]. Timing of thelarche, pubarche, and menarche was assessed as adjusted

mean shift (in months) based on a twofold increase in phenol concentrations. Earlier age at menarche in daughters was associated with maternal TCS (β = − 0.7 months; 95% *CI*: − 1.20, − 0.20) and with timing of thelarche or pubarche nor were any peri2,4-dichlorophenol (β = − 0.80 months, 95% CI: − 1.60, pubertal phenol concentrations associated with any out 0.00), but not BP-3. No prenatal phenols were associated come of interest.

Articles are presented by risk of bias tier (in ascending order), then by year of publication, and alphabetized by first author. [a] In this study, Tanner stage was used to assess thelarche every 6 months, but the primary outcome (menarche onset) was assessed using questionnaires that asked study participants to report the date of their first menstruation every 6 months before they reached Tanner stage 4 and every 3 months after they reach Tanner stage 4. Notably, the questionnaire attempted to distinguish between other causes of vaginal bleeding (e.g., vaginal infection, urinary tract infection, trauma). [b] In this study, prenatal urinary phthalate exposures were assessed in pregnant women (mothers of study participants) during pregnancy. [c] Although it was not clear that loss to follow-up existed in this study, not all eligible cohort members had available data on the exposures of interest. [d] This study assessed the proportion of study participants with the presence (vs. absence) of concentrations of phthalate esters in their serum, comparing girls diagnosed with premature thelarche to those who were not diagnosed with premature thelarche. As such, this study did not directly assess the impact of phthalate exposures on pubertal timing. [e] In this study, the authors stated that age at menarche was “prospectively recorded using a purpose-designed questionnaire at ages 8, 10, 14, and 17. If menarche had been reached since previous follow-up, caregivers were asked to contemporaneously report the exact date of onset”

Postnatal Exposures and Pubertal Development

A small number of studies have examined postnatal exposures to phenols in PCPs in relation to pubertal development, with some evidence that higher exposures correspond to earlier age at pubertal milestones. For instance, in a cross-sectional analysis using NHANES data from 440 girls ages 12–16 years, higher summed urinary phenols were associated with earlier age at menarche (Σ2,5-DCP and 2,4-DCP: *HR*=1.10, 95% CI: 1.01, 1.19), with no associations observed for TCS or BP-3 [41]. Similarly in the GOCS cohort, higher BP-3 at the first stage of thelarche (B1) was associated with earlier menarche (*HR*=1.17; 95% CI: 1.06, 1.29) [35]. Moreover, the median age at menarche was 4.1 months earlier in girls in the second versus the first tertile of BP-3; no differences were observed between the first and third tertiles. A log (ng/mL) increase in TCS was further associated with earlier menarche among overweight or obese girls (HR 1.16, 95% CI: 1.01, 1.34), but not among those of normal weight.

In the Copenhagen Puberty Study, pre-pubertal TCS was significantly associated with thelarche in adolescent girls compared to younger girls (β = 3.703, *P* = 0.009) [51]. In the BCERP cohort, BP-3 was positively associated delayed thelarche (based on up to 7 years of follow-up) (*HR* = 0.95, 95% CI: 0.92, 0.98), while TCS was associated premature thelarche (*HR* = 1.05, 95% CI: 1.01, 1.09) [52•]. Neither chemical was significantly associated with age at pubarche. With further follow-up (up to 11 years), BP-3 concentrations were associated with later age at menarche (*HR* = 0.95, 95% CI: 0.93, 0.98), but associations were

attenuated with adjustment for race/ethnicity and education [38]. TCS concentrations were not significantly associated with age at menarche; however, adjusted median age at thelarche was 6.5 months later (range 1st–5th 106–112.5 months) and 5 months earlier (range 1st to 5th 109.5–104.5) for girls in the 5th vs. 1st quintile of BP-3 and TCS concentrations, respectively [38]. Finally, in an NHANES analysis using a machine-learning approach to study multiple exposures, TCS and 2,4-dichlorophenol were both associated with earlier menarche among girls who also had lower levels of MEHP, a metabolite of DEHP found primarily in food [43•].

Parabens

Few studies have examined parabens in relation to pubertal development, including a single study of prenatal exposure. In CHAMACOS, prenatal methyl- and propyl-paraben concentrations (average of two prenatal measurements) were not associated with timing of thelarche, pubarche, or menarche in daughters as assessed via serial Tanner staging from age 9 to 13 [29•]. However, each twofold increase in methylparaben at age 9 was associated with earlier thelarche (mean shift = − 1.10 months, 95% CI: − 2.10, 0.00), pubarche (mean shift = − 1.50 months, 95% CI: − 2.50, − 0.40), and menarche (mean shift = − 0.90 months, 95% CI: − 1.60, − 0.10), while a twofold increase in propyl paraben at age 9 was associated with earlier pubarche only (mean shift = − 0.80 months, 95% CI: − 1.60, − 0.10). By contrast, cross-sectional analysis from NHANES showed no association between total paraben concentrations and age at menarche [41].

Non-specific Chemical Exposures Through PCP Use

Two studies examining hair product use (as a proxy for EDC exposures) suggest that childhood use of certain hair products is associated with earlier age at menarche. In the Greater New York Hair Products Study, the use of hair oils (*RR* = 1.40, 95% CI: 1.10, 1.90) and chemical relaxer/straightening products or perms (*RR* = 1.40, 95% CI: 1.10, 1.80) was associated with menarche onset before age 12 years [53]. Additionally, use of leave-in conditioners was marginally associated with menarche onset before age 12 (*RR* = 1.30, 95% CI: 1.00, 1.60). A second study similarly reported that childhood use of hair oils was associated with menarche onset before age 11 years, although fully adjusted risk estimates included the null (*RR* = 2.32, 95% CI: 0.98, 5.48) [54]. Findings from these studies support the hypothesis that chemical exposures in hair products in particular may impact timing of pubertal outcomes; however, the lack of chemical measurements in biospecimens is a notable limitation. Other studies have reported that hair care products contain a variety of PCP-related chemical additives including DEP, some parabens, and TCS [55, 56]. Additionally, these products likely include other chemicals outside the scope of this review such as other endocrine disruptors.

Discussion

In total, evidence linking phthalates, phenols, and parabens, chemicals commonly found in PCPs to altere timing of pubertal development in girls, is mixed. For phthalates, the most consistent evidence comes from studies examining prenatal exposures as predictors of pubertal development, with several studies suggesting that prenatal MEP exposure may

be associated with earlier timing of pubertal milestones [16•, 27, 29•]. Studies examining peri-pubertal exposures, meanwhile, have primarily observed weak associations, if any. All of the phenols of interest have been associated with measures of girls' pubertal development in one or more studies; however, the associated outcomes (e.g., thelarche, menarche) and direction of association have been inconsistent across studies. In the very limited literature on parabens, there was some indication of earlier pubertal milestones with higher peri-pubertal paraben exposures; however, effect sizes, when observed, were very small. Finally, there was some indication that the use of certain hair products during early childhood (as a proxy for PCP-based chemical exposures) was associated with earlier age at menarche. Overall, the current literature was widely disparate in quality as well as in results, and the current evidence can be best characterized as insufficient and inconsistent.

Strengths and Limitations of the Literature

Several strengths were noted in this literature, particularly among the longitudinal cohort studies. These studies frequently included repeated assessments of pubertal development from the pre- or peri-pubertal stage through adolescence [29•, 33–35, 52•]. Many conducted clinical Tanner staging [27, 28, 29•, 32•, 33, 34, 36, 51, 52•], the gold standard clinical assessment of pubertal development [57] and a preferred outcome measure over self-reported pubertal development or age at menarche, a milestone which shows only moderately reliability even during adolescence [58]. Several studies additionally measured chemical exposures over multiple timepoints, targeting several potential windows of vulnerability to endocrine disruption.

At the same time, several common sources of potential bias were noted, which may contribute to the inconsistency of results. Most case–control studies suffered from missing data on important factors such as race or measures of socioeconomic status (SES) potentially leading to confounding given that race and SES are often associated with chemical exposures and are strong predictors of pubertal timing [59–62]. Additionally, body size was commonly included as confounder or effect modifier which may be appropriate; however, it should also be potentially considered as part of the causal pathway. For example, if body size (e.g., BMI) is on the causal pathway, inclusion in statistical models could be prone to over adjustment or selection bias. Supporting this possibility, some EDCs are associated with childhood adiposity, which in turn has been associated with alterations in the onset of puberty [63, 64]. Additionally, adiposity might impact EDC exposures and not the other way around. Some EDCs have the potential to be stored in adipose tissues and sequestration is greater in individuals with larger body size (i.e., greater adiposity) [65, 66]. As such, BMI might confound and/or mediate associations between EDC exposures from PCP use and pubertal outcomes [67]. This has not been adequately addressed in prior research.

An additional concern for half of the studies in this review, including all cross-sectional and case–control studies, is mistiming of exposure assessment relative to outcome. That is, chemical exposures measured in urine at the time of outcome assessment do not necessarily reflect exposures occurring at the onset of pubertal development or during critical windows of development. It is plausible that girls who develop earlier then begin to use more PCPs, including cosmetics, cleansers, and deodorants. As such, associations between chemical

concentrations and early pubertal outcomes may be a function of girls' natural pubertal timing not the exposure and represent reverse causality. Similarly, some studies conducted a retrospective outcome assessment, which can lead to detection bias.

In addition, several concerns around exposure assessment were identified. First, although the preferred matrix to measure the non-persistent EDCs of interest is urine, some studies measured them in serum or plasma, which typically have much lower concentrations and may be more prone to contamination risks [68–70]. Even urinary measurements pose limitations as the half-lives of the EDCs of interest are roughly several hours up to a day, making concentrations measured in spot samples (as collected by most included studies) potentially a poor indicator of exposure over a longer time frame [71–73]. A single urine sample refects recent short-term exposure (hours or days depending on the phthalate) to the parent compound or the metabolite itself. This concern may be ameliorated if PCP use is stable within individuals (e.g., use of same PCPs on a consistent schedule over extended periods of time) or if serially collected biospecimens can be used. Another factor affecting urinary phthalate measurements is urine dilution. Typically, historically, chemical concentrations in urine have been corrected by creatinine, a skeletal muscle waste product excreted by the kidneys, to account for dilution variation; however, creatinine concentrations may vary by age, gender, race, muscle mass, diet, activity, and time of the day [74]. More recently, epidemiological studies have also used specific gravity, a measure of urine density relative to water, to adjust for dilution [75]. Although specific gravity is not as influenced by individual factors compared to creatinine, it can be affected by mass size and diet [76]. Finally, while exposure to many of these chemicals derives primarily from PCPs, there are additional sources that contribute to body burden. Exposure biomarkers, in this case, phthalate concentrations in human biospecimens, reflect multiple routes of exposure thus attributing risks specific to PCP use is impossible.

Research Gaps and Future Directions

We have identifed several key areas that lend themselves to future research. First, PCP-related phenols and parabens are understudied in this context compared to phthalates; however, given the widespread use of these chemicals in PCPs, additional research is warranted to fully understand their impacts on pubertal development. With environmental epidemiology increasingly moving towards mixtures analyses simultaneously assessing the contributions of multiple exposures to a health outcome, there is great potential to adopt this approach not only to consider chemical mixtures found in PCPs in relation to pubertal development but also mixtures of chemical and non-chemical exposures, such as diet and psychosocial stressors [43•]. Second, timing of exposure may be a critical factor influencing pubertal development. As such, continuous follow-up of children in cohorts is crucial for assessing the influence of prenatal, early childhood, and peri-pubertal exposures on pubertal development. Third, although some studies included hormone measurements as part of their outcome assessment, including other physiologic biomarkers such as kisspeptin may help to capture intermediate links between exposure and outcome. Lastly, collecting information on other important factors relevant to both PCP use and puberty development, such as social determinants, nutrition, and physical activity, is crucial to understand these associations.

Clinical and Public Health Relevance and Conclusions

Overall, the evidence supporting associations between the chemical exposures of interest and girls' pubertal development was mixed and when associations were observed, they were typically quite weak, with timing of pubertal milestones marginally altered (e.g., a doubling of prenatal MEP concentrations associated with a 1.3 month acceleration of pubarche) [29•]. Nevertheless even these small effect sizes may be impactful from a clinical and public health perspective when we consider the many additional factors that may contribute to the long-standing decline in age at puberty that has been widely documented and continued even within the last decade [77, 78]. These include obesity, dietary [79–81], and psychosocial factors [82–84], as well as overall improved standards of living [85, 86] and other environmental contaminants [87–89]. These chemical and non-chemical exposures may act synergistically, exerting a greater joint impact on pubertal onset, tempo, and milestones, such as age at menarche. Furthermore, small changes that may have less overt clinical relevance might translate into larger shifts in pubertal milestones on a population level given the ubiquity of these exposures. Ultimately, any factors that accelerate the onset and timing of puberty may merit concern given that earlier development is associated with early age at first intercourse, problem behaviors, and increased risk of depression, self-harm, and psychological symptoms in adolescence and beyond [90–95]. In the long-term, earlier age at menarche may contribute to increased risk of breast cancer, obesity, and cardiometabolic disease [3, 96, 97]. Thus, to the extent that we can identify and intervene on modifiable risk factors for altered pubertal timing — including potentially PCP use — there may be important public health implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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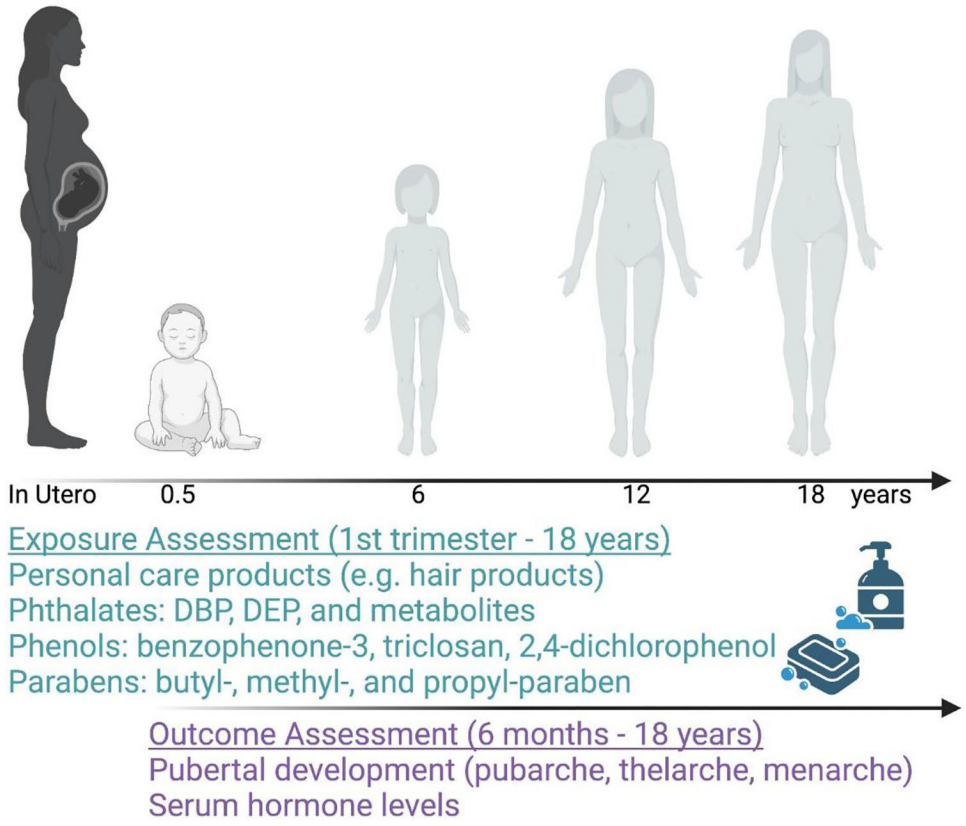

Fig. 1.

Overview of select chemical exposures in PCPs in relation to girls' pubertal development (figure created with BioRender)

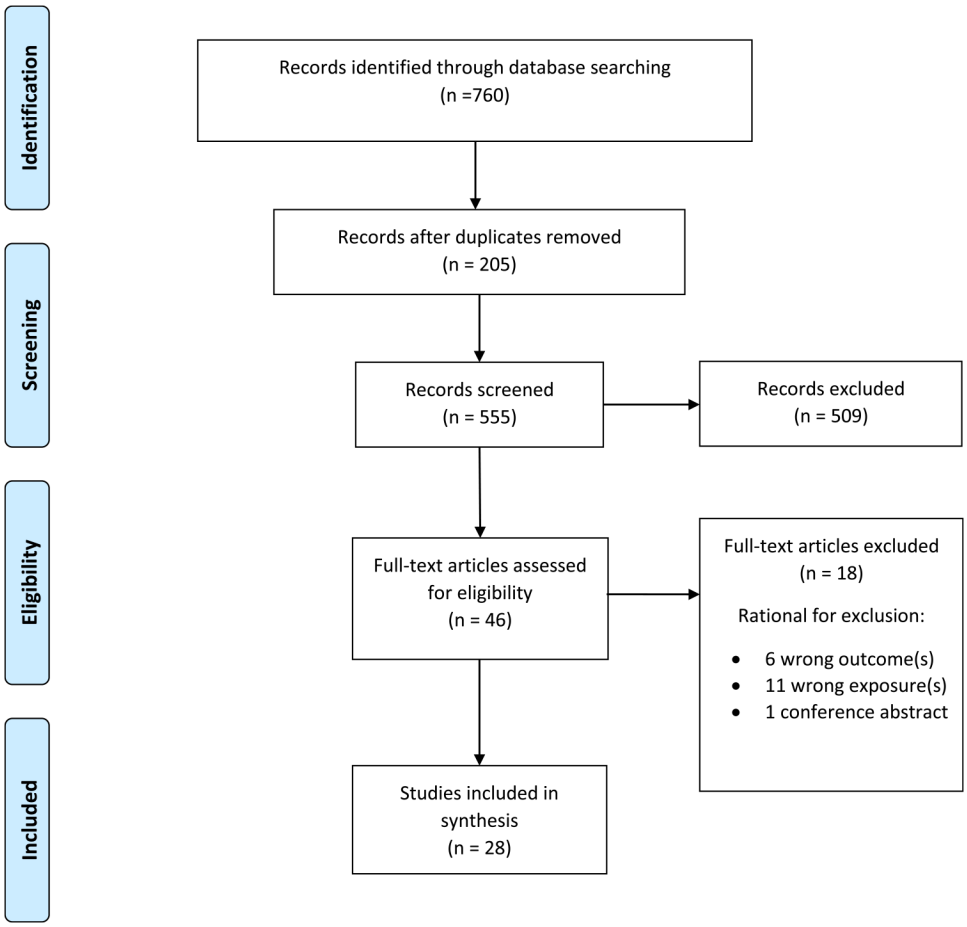

Fig. 2.
Flow chart of study selection

Table 1

Summary of studies investigating the relationship of endocrine-disrupting chemical exposures in personal care products with girls' pubertal development

First author, publication year	Study design and participants	Assessment of chemical exposure	Assessment of outcome(s) of interest	Key findings
Cohort studies				
Berman YE, 2021	Longitudinal cohort of 369 pregnant women and their resulting daughters (up to age 20) in the Western Australia Pregnancy Cohort (Raine) Study Gen2	Serum phthalate metabolites (including MEP, MiBP, MnBP, ΣLMW phthalate metabolites, Σall phthalate metabolites[b]) in samples pooled from 18 and 34/36-week gestation	Age at menarche onset self-reported via questionnaires administered at ages 8, 10, 14,17	• No associations observed between the phthalate metabolites of interest and age at menarche
Binder AM, 2018	GOCS longitudinal cohort of 200 Chilean girls age 2.6–4.0 years at enrollment	Phenols (including 2,4-DCP, BP-3, and TCS), phthalate metabolites (including MBP, MEP, and MiBP), and parabens (including methyl- and propyl-paraben) in urine collected before breast development (B1, ages 6.7–9.6 years) and during adolescence (B4, ages 9.4–13.1 years)	Age at menarche onset self-reported via questionnaire — assessed every 3 months	• Higher BP-3 at the first stage of thelarche (B1) associated with earlier menarche (HR: 1.17; 95% CI: 1.06, 1.29) • Median age at menarche was 4.10 months earlier in girls in the second tertile of BP-3 compared to those in the first tertile (HR 1.58, 95% CI: 1.12, 2.22); no significant difference between first and third tertiles • Higher TCS associated with earlier menarche among overweight or obese girls (HR 1.16, 95% CI: 1.01, 1.34), but not among normal weight girls (HR 0.93, 95% CI: 0.84, 1.02) • Higher MEP associated with earlier age at menarche among overweight or obese girls (HR 1.24, 95% CI: 1.05, 1.47), but not among those of normal weight (HR 1.02, 95% CI: 0.90, 1.17)
Cathey A, 2020	103 pregnant women and their resulting children from the ELEMENT cohort in Mexico	Urinary phthalate metabolites (including MBP, MEP, and MiBP) in each trimester (mean 13.5, 25.1, and 34.4 weeks gestation)	Pubertal development assessed using Tanner staging (physical exam) to assess thelarche and pubarche at two visits between ages 8–18 years. Menarche onset assessed via self-report	• No associations observed between phthalate metabolites of interest and pubertal outcomes • Some associations observed between prenatal phthalates derived from non-PCP related sources (e.g. DEHP metabolites) and pubertal development
Frederiksen H, 2012	Longitudinal cohort of 725 healthy girls (age 5.6–19.1 years) in the Copenhagen Puberty Study and 25 girls with precocious puberty recruited from an outpatient clinic	Urinary phthalate metabolites (including ΣMBP_{i+n}[a], MEP, and total phthalates[b])	Pubertal development assessed using Tanner staging (physical exam) to assess thelarche and pubarche at one study visit. Serum FSH, LH, estradiol, and testosterone used as biomarkers of pubertal development	• MEP higher in older girls at more advanced pubertal stages compared with younger girls at less advanced pubertal stages • $\sum MBP_{i+n}$ significantly higher in younger girls than in older girls • Non-significant positive associations between ΣMBP_{i+n} and total phthalates with age at pubarche • No associations between phthalate metabolites and thelarche observed • No significant association between phthalate concentrations and serum hormone levels observed
Frederiksen H, 2013	Longitudinal cohort of 129 healthy children and adolescents (including 64 girls age 6–21 years) in the Copenhagen Puberty Study	Phenols (including 2,4-DCP, BP-3, and TCS) measured in first morning urine samples	Pubertal development assessed using Tanner staging (physical exam) to assess thelarche and pubarche at one visit	• TCS significantly associated with thelarche (B1 vs. B2 +: $\beta = 3.703$, $p = 0.009$) in older girls • No associations between 2,4-DCP and BP-3 and pubertal development
Harley KG, 2019	Longitudinal cohort of 179 pregnant women and their resulting daughters from the CHAMACOS (U.S) study	Urinary phthalate metabolites (including MEP, MiBP, and MnBP), parabens (butyl-, methyl-, and propyl-paraben) and phenols (including 2,4-DCP,	Pubertal development assessed using Tanner staging (physical exam) to assess thelarche and pubarche every 9 months from	• twofold increase in prenatal TCS and 2,4-dichlorophenol associated with earlier menarche by −0.70 months (95% CI: −1.20, −0.20) and −0.80 months (95% CI: −1.60, 0.00), respectively • twofold increase in prenatal MEP associated with earlier

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First author, publication year	Study design and participants	Assessment of chemical exposure	Assessment of outcome(s) of interest	Key findings
		BP-3, and TCS) at mean 14- and 26.9-week gestation and in children at age 9	age 9–13 years. Menarche onset assessed through self-report	pubarche onset by −1.30 months (95% CI: −2.50, −0.10) • twofold increase in peripubertal propyl paraben associated with earlier thelarche (mean shift = −1.1 months), pubarche (mean shift = −0.9 months) and menarche (mean shift = −0.9 months) • twofold increase in peripubertal methyl paraben associated with earlier pubarche (mean shift = −0.80 months)
Hart R, 2013	Longitudinal cohort of 121 pregnant women and their resulting daughters aged 14–16 in the Raine Study	Serum phthalate metabolites (including MEP, MiBP, MnBP, and total phthalates[b]) at 18- and 34/36-weeks gestation	Age at menarche assessed via questionnaire; serum hormone biomarkers	• No correlations between prenatal phthalate metabolites of interest and age at menarche • Maternal MEP negatively associated with daughters' serum sex hormone binding globulin (SHBG) levels ($r = -0.17$, $p < 0.05$) and positively correlated to free testosterone index (total testosterone/SHBG) ($r = 0.16$, $p < 0.05$)
James-Todd T, 2011	Cohort of 300 African-American, Afro-Caribbean, Hispanic, and White women age 18–77 years	Use of hair products, which might contain the EDCs of interest (hair oils, hair lotions, leave-in conditioners, root stimulators, perms/relaxers, prescription products, and any other types of hair products) before age 13 retrospectively assessed via questionnaire	Age at menarche onset (< 12 years vs ≥ 12 years) assessed via questionnaire	• Childhood use of hair oils (RR 1.40, 95% CI: 1.10, 1.90) and chemical relaxer/straightening products or perms (RR 1.40, 95% CI: 1.10, 1.80) associated with increased risk of menarche onset < 12 years • Childhood use of leave-in conditioners marginally associated with increased risk of menarche < 12 years (RR 1.30, 95% CI: 1.00, 1.60)
Kasper-Sonnenberg M, 2017	Longitudinal cohort of 408 mother-child pairs (including 198 girls) from the Duisburg Birth Cohort and Bochum Cohort studies, in which the children were 8–13 years old at baseline	Urinary phthalate metabolites (including MEP, MiBP, MnBP, and total phthalates[b]) at baseline	Pubertal development (PD) scores were calculated at baseline and three follow-up visits based on two items for girls (pubic hair growth and breast development) using the German version of the "Pubertal Development Scales-PD scales"	• MEP (β −0.118, 95% CI: −0.257, 0.020, $p \leq 0.10$) and ΣDEHP(β −0.195, 95% CI: −0.409, 0.017, $p \leq 0.10$) marginally associated with delayed PD in girls • MEP (OR 0.60, 95% CI: 0.40, 0.88) inversely associated with thelarche in girls • None of the phthalate metabolites were associated with timing of menarche
McDonald JA, 2018	Cohort of 248 adult women (former participants in the National Collaborative Perinatal Project or the New York City Multiethnic Breast Cancer Project)	Use of hair products, which might contain the EDCs of interest (hair oils, hair lotions, leave-in conditioners, root stimulators, perms/relaxers, prescription products, and any other types of hair products) during childhood (< age 13) and adulthood (≥ age 20) retrospectively assessed via questionnaire	Age at menarche assessed via questionnaire	• Ever use of hair oil during childhood marginally associated with an increased risk of menarche onset before age 11 years (RR 2.32, 0.98, 5.48)
Mouritsen A, 2013	Longitudinal cohort of 168 healthy children (including 84 girls age 5.9–12.8 at baseline) from the Copenhagen Puberty Study	Urinary phthalate metabolites (including DBP, DEP, ΣMBP_{i+n}[a], MEP, and MiBP]) at baseline	Pubertal development assessed using Tanner staging (physical exam) every 6 months for 5 years. Age at thelarche and pubarche onset assigned as the mean age between age at first examination in stage 2 and the last examination in stage 1. Hormones measured in blood	• No significant association between urinary phthalate concentrations and age at thelarche or pubarche, but suggested that higher ΣMBP_{i+n} concentrations were associated with increasing age at pubarche • DBP inversely associated with serum FSH, LH, estradiol, and testosterone • Among girls age 13, DHEAS ($p = 0.008$) and adione ($p = 0.001$) concentrations were significantly lower among those in the high excretion group for $\sum MBP_{i+n}$

First author, publication year	Study design and participants	Assessment of chemical exposure	Assessment of outcome(s) of interest	Key findings
Watkins DJ, 2014	113 pregnant women and their resulting daughters (ages 8–13) from the ELEMENT cohort in Mexico	Urinary phthalate metabolites (including MEP, MiBP, and MnBP) in third trimester (mean 34.4 weeks gestation) and in daughters at age 8–13	Pubertal development assessed using Tanner staging (physical exam) at age 8–13 years. Menarche onset assessed via self-report. Daughters' serum hormones measured	• Suggestive associations between MEP (prenatal and peripubertal) and increased odds of having undergone menarche • IQR increase in prenatal MEP and MiBP associated with higher 3rd trimester testosterone %Δ 25.5 (95% CI: 2.1, 54.1) and DHEA-S levels %Δ 19.5 (95% CI: 1.0, 41.3), respectively
Watkins DJ, 2017	120 pregnant women and their resulting daughters (ages 8–13) from the ELEMENT cohort in Mexico	Urinary phthalate metabolites (including MEP, MiBP, MnBP) in each trimester (mean 13.5, 25.1, and 34.4 weeks gestation)	Pubertal development assessed using Tanner staging (physical exam) at age 8–13 years. Menarche onset assessed via self-report. Daughters' serum hormones measured	• IQR increases in mean MEP and MiBP across pregnancy associated with 42% and 44% higher pubertal testosterone, respectively • First trimester MEP associated with higher odds of menarche (OR/IQR: 3.9, 95% CI 1.1, 14.2) • Higher first trimester MBP associated with higher DHEA-S (%Δ/IQR: 25.7, 95% CI: 3.7, 49.5) • IQR increases in mean MEP in each visit associated with pubertal testosterone (1st: %Δ 35.1, 95% CI: 2.6, 78.0; 2nd: %Δ63.0, 95% CI: 20.7, 120; 3rd: %Δ24.2, 95% CI: 2.4, 50.7). Associations were stronger when concentrations were averaged across all trimesters (%Δ40.6, 95% CI: 11.9–76.7) • IQR increase in 3rd trimester MiBP associated with pubertal DHEA-S %Δ 19.4 (95% CI: 0.7, 41.6)
Wolff MS, 2010	Longitudinal cohort of 1,151 girls from the Breast Cancer and Environment Research Program (BCERP – New York City, Cincinnati, and San Francisco) enrolled at age 6–8 years and followed through puberty	Urinary phenols (including BP-3 and TCS), ∑LMW phthalate metabolites[c], and total parabens[d]	Pubertal development assessed using Tanner staging (physical exam) at visit 1 and one year later at visit 2	• Weak, positive associations between LMW phthalate metabolites and prevalence of thelarche (quintile 5 vs. quintile 1: PR 1.06, 95% CI: 0.99, 1.14; *P*-trend = 0.087) and pubarche (quintile 5 vs. quintile 1: PR 1.06, 95% CI: 0.98, 1.13; *P*-trend = 0.08)
Wolff MS, 2014	Longitudinal cohort of 1,170 girls from BCERP	Urinary LMW phthalate metabolites[c] at baseline	Pubertal development assessed using Tanner staging (physical exam) at visit 1 and during up to 6 years of follow-up	• No associations between LMW phthalate metabolites and onset of thelarche (HR 1.02, 95% CI: 0.95, 1.11) or pubarche (HR 0.97, 95% CI: 0.90, 1.05). MBP weakly inversely associated with age at pubarche as a continuous variable (HR 0.92, 95% CI: 0.85, 1.00)
Wolff MS, 2015	Longitudinal cohort of 1,170 girls from BCERP	Urinary phenols (including BP-3 and TCS) and total parabens[d] at baseline	Pubertal development assessed using Tanner staging (physical exam) at visit 1 and during up to 7 years of follow-up	• BP-3 positively associated with age at thelarche (HR 0.95, 95% CI: 0.92, 0.98) but not age at pubarche • TCS inversely associated with age at thelarche (HR 1.05, 95% CI: 1.01, 1.09) but not age at pubarche • Total paraben concentrations were not significantly associated with age at thelarche (HR 1.01, 95% CI: 0.96, 1.06) or pubarche (HR 1.02, 95% CI: 0.97, 1.07)
Wolff MS, 2017	Longitudinal cohort of 1,051 girls from BCERP	Urinary phenols (including BP-3 and TCS), ∑LMW phthalate metabolites[c], and total parabens[d]	Pubertal development assessed using Tanner staging (physical exam) at visit 1 and during up to 11 years of follow-up	• BP-3 associated with older age at menarche (HR 0.95, 95% CI: 0.93, 0.98), but association attenuated after adjustment • TCS not significantly associated with age at menarche onset • Comparing girls in the 5th vs 1st quintiles of BP-3 and TCS concentrations, adjusted median age at thelarche was 6.5 months later and 5 months earlier, respectively • LMW phthalate metabolites (HR 1.15, 1.07, 1.24) and MEP (HR 1.13, 95% CI: 1.07, 1.20) associated with younger age at menarche, but associations attenuated after adjustment

Case–control and cross-sectional studies

First author, publication year	Study design and participants	Assessment of chemical exposure	Assessment of outcome(s) of interest	Key findings
Buttke DE, 2012	Cross-sectional analysis of 440 US girls age 12–16 years from NHANES 2003–2004 and 2005–2008 cycles	Urinary phenols (including 2,4-DCP, BP-3, TCS, and total phenols[e]), total phthalates[b], and total parabens[d]	Age at menarche onset assessed via questionnaires administered when girls were age 12–16 years	• No association between TCS (HR 1.00, 95% CI: 0.91, 1.09) or BP-3 (HR 0.99, 95% CI: 0.91, 1.08) and age at menarche • Inverse association between total phenols (HR 1.10, 95% CI: 1.01, 1.19) and age at menarche • No association observed between total parabens (HR 1.05, 95% CI: 0.93, 1.19) and age at menarche • No association between total phthalate metabolites (HR 0.98, 95% CI: 0.86, 1.12) and age at menarche
Chen C-Y, 2013	Case–control study of 104 girls younger than age 8 in Taiwan: 73 cases with central precocious puberty [CPP] and 31 controls without signs of secondary sexual characteristics	Urinary phthalate metabolites (including MBP and MEP)	Pubertal development assessed using Tanner staging (physical exam). Serum hormones measured	• Association between MBP and kisspeptin-54 observed (R^2 = 0.109; β = 0.148; p = 0.024)
Colon I, 2000	Case–control study of 76 girls in Puerto Rico: 41 cases (age 6 months to 8 years) with premature thelarche (PT) and 35 controls (age 6 months to 10 years) with no evidence of premature sexual development	Serum phthalates (including DBP and DEP)	Clinician diagnosed PT (breast enlargement before age 8)	• Phthalate esters were detected in the serum of 68% of cases (28/41) and < 1 % of controls (1/35)
Durmaz, E, 2018	Case–control study of 54 girls age 4–8 years in Turkey: 29 cases (non-obese girls with premature thelarche but not CPP) and 25 controls with no history of premature thelarche or evidence of secondary sexual characteristics	Urinary phthalate metabolites (including DEP, MEP, MiBP, ΣLMW phthalate metabolites[c]	Cases followed by a physician for one year and controls were assessed at baseline and 12 months later to evaluate pubertal development. PT defined as isolated breast development before age 8 years, with no increase in bone age over one year of chronological age. Serum hormones measured	• PT cases had significantly higher MEP than controls • Basal FSH significantly correlated with MiBP (ρ = 0.323, p = 0.045) • MiBP inversely correlated with fT4 levels (ρ = −0.385, p = 0.002) and BMI (ρ = 0.574, p = 0.002)
Hashemipour M, 2018	Case–control study of 150 girls (mean age 8.12 ± 1.2 years): 87 girls with CPP and 63 age-matched controls) in Iran	Serum phthalate metabolites (including MEP and MBP). Recent exposure to phthalates assessed via questionnaire	CPP confirmed via physical examination and lab tests	• No differences in MEP or MBP observed between CPP cases and healthy controls
Hou J-W, 2015	Cross-sectional study of 270 adolescents (age 6.4–15.0 years) in Taiwan and 38 complainants (age 6.5–8.5 years) who filed a lawsuit after plasticizer contamination scandal	Urinary phthalate metabolites (including MEP and MiBP) and phenols (specifically concentrations of NP)	Pubertal development assessed via a structured questionnaire on secondary sexual characteristics and date at menarche onset	• No associations between MEP, MiBP or NP concentrations and secondary sexual characteristics including onset of thelarche, pubarche, and menarche
Lomenick JP, 2010	Case–control study of 56 girls: 28 CPP cases and 28 controls (age- and race-matched) in Kentucky and Ohio	Urinary phthalate metabolites (including MBP, MEP, and MiBP)	CPP confirmed via physical examination and lab tests	• No differences in phthalate metabolites of interest between cases and controls overall or in race-stratified analyses (Black/African American, White)
Oskar S, 2021	Cross-sectional study of 229 girls aged 12–16 from the	Urinary phthalate metabolites (including MBP, MEP, and MiBP), phenols (including	Age at menarche onset assessed via questionnaire; earlier menarche defined as before age	• In a two-step machine learning approach, having both lower MEHP (non-PCP-related phthalate; ≤ 2.36 ng/mL) and lower BP-3 (≤ 24.50 ng/mL) was associated with non-significant

First author, publication year	Study design and participants	Assessment of chemical exposure	Assessment of outcome(s) of interest	Key findings
	NHANES 2005–2006 and 2007–2008 sampling cycles	TCS, BP-3, 2,4-dichlorophenol), parabens (propyl-, methyl-, ethyl-, and butylparaben), with assessment of the impact of exposure combinations on the outcome of interest	12, later menarche defined as age 12 or older	increased risk of early menarche (PR 1.48, 95% CI: 0.96, 2.31) • Having a combination of both lower 2,4-DCP (≤ 0.67 ng/mL) and lower MEHP (≤ 1.00 ng/mL) was associated with non-significant increased risk of early menarche (PR 1.51, 95% CI: 0.66, 3.43) • For girls who did not have lower MEHP, having higher urinary TCS was associated with a non-significant increased risk of early menarche onset (PR 1.14, 0.89, 1.46)
Shi H, 2015	Cross-sectional study of 503 children (including 251 girls) enrolled in the Pubertal Timing and Health Effects in Chinese Children (PTHEC)	Urinary phthalate metabolites (including MBP and MEP)	Pubertal development assessed using Tanner staging (physical exam). Menarche onset assessed via self-report	• No associations between phthalate metabolites of interest and pubertal outcomes in girls
Srilanchakon K, 2017	Case–control study of 136 girls in Thailand: 42 with precocious puberty defined (thelarche < 8 years), 17 with early puberty (thelarche at 8–9 years), and 77 age-matched controls	Urinary phthalate metabolites (including MEP)	CPP was confirmed via physical examination and lab tests	• Higher median MEP in girls with CPP than controls (6105.09 vs. 4633.98 μg/g creatinine; $p < 0.05$) • Non-significantly higher MEP among girls with early puberty compared to normal puberty (5141.41 vs. 4633.98 μg/g creatinine; $p = 0.40$) • No differences by BMI category
Yum T, 2013	Case–control study of 240 girls ages 6–12 years in South Korea: 150 cases with precocious puberty and 90 controls with no evidence of premature sexual development	Plasma phthalates (including DBP and MBP)	Clinician-diagnosed precocious puberty defined as presence of secondary sex characteristics under the age of 8 or menarche that had occurred before 9.5 years	• No significant differences in phthalate and phenol concentrations of interest between cases and controls

Abbreviations: *BP-3* benzophenone-3, *CHAMACOS* Center for the Health Assessment of Mothers and Children of Salinas, *CPP* central precocious puberty, *DBP* di-n-butyl phthalate, *DCP* dichlorophenol, *DEHP* di(2-ethylhexyl) phthalate, *DEP* diethyl phthalate, *DHEAS* dehydroepiandrosterone, *DHEA-S* dehydroepiandrosterone sulfate, *ELEMENT* Early Life Exposure in Mexico to ENvironmental Toxicants, *FSH* follicle stimulating hormone, *fT4* free thyroxine, *GOCS* Growth and Obesity Cohort Study, *LH* luteinizing hormone, *MBP* monobutyl phthalate, *MEP* monoethyl phthalate, *MiBP* mono-isobutyl phthalate, *MnBP* mono-n-butyl phthalate, *NP* nonyl phenol, *PCP* personal care products, *SHBG* sex hormone binding globulin, *TCS*: triclosan. Note: While some of the studies included examined exposure to other chemicals, included other outcomes, and/or examined the associations of interest among boys, the data in this table focus only on the aspects of each study that are relevant to the associations of exposure to PCP-related EDCs and pubertal outcomes among girls.

[a] ΣMBP_{i+n} represents the sum of all the monobutyl phthalate isoforms.

[b] Total phthalates represents the sum of all phthalate metabolites, which also include non-PCP-related metabolites.

[c] ∑LMW phthalate metabolites represents the molar sum of MEP, MBP, and MiBP in the Wolff 2010, Wolff 2014, and Wolff 2017 studies, while in the Durmaz 2018 study ∑LMW phthalate metabolites represented the molar sum of MEP, MiBP, and MnBP.

[d] Total parabens represents the molar sum of methyl-, butyl-, and propyl paraben in the Wolff 2010, Wolff 2015, and Wolff 2017 studies, while in the Buttke 2012 study total parabens included only propyl and methyl paraben.

[e] Total phenols include 2,4-DCP and 2,5-DCP; the latter is a non-PCP-related metabolite

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	Confounding Bias *(Key Element)*	Attrition/Exclusion Bias			Detection Bias (Exposure) *(Key Element)*					Detection Bias (Outcome) *(Key Element)*			Selective Reporting Bias	Other	Risk of Bias Summary Rating
	Did the analysis account for all of the confounders of interest (age, race/ ethnicity or another SES-related variable, and BMI)?	Was the loss to follow-up reported?	Were the losses to the follow-up related to chemical exposures or pubertal outcomes?	Did the authors use appropriate statistical analysis to address missingness or exclusion bias?	Were the chemicals measured (preferred) or were exposures based on questionnaire only?	If measured, were chemicals measured in urine?	Were the chemicals measured more than once?	Was the timing of the exposure assessment biologically appropriate?	Was the exposure assessment prospective?	Was puberty assessed via Tanner staging? If not, was a valid method used?	Was the Tanner staging method utilized? If so, was conducted by a trained professional (preferred) or by parents/ guardians reporting based on diagrams?	Was the outcome assessment prospective (preferred) or retrospective?	If the methods described multiple outcome measures (e.g., breast development, menarche, pubic hair development), were all included in the results section?	Are there any other potential threats to internal validity?	Risk of bias tier (1 to 3; 1=lowest risk of bias; 3=highest risk of bias)
	++	-	-	-	++	++	-	++	++	++	++	++	++	+	1
	-	-	-	-	++	++	+	+	++	++	++	++	++	+	1
	+	-	-	-	++	++	+	++	++	++	++	++	++	+	1
	++	-	-	-	++	++	-	++	++	++	++	++	++	+	1
	++	-	-	-	++	++	-	++	++	++	++	++	++	+	1
	+	+	-	++	++	++	-	++	++	-	NA	++	+	+	1
	++	-	-	-	++	++	+	++	++	++	++	++	++	+	1
	++	-	-	-	++	++	-	++	++	++	++	++	++	+	1
	++	-	-	-	++	++	-	++	++	-	++	++	++	+	1
	++	-	-	-	++	++	++	++	++	++	++	++	++	+	1
	++	-	-	-	++	++	-	+	++	++	++	++	++	+	1
	+	+	-	-	++	--	-	++	++	-	NA	+	++	-	2

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	Confounding Bias *(Key Element)*	Attrition/Exclusion Bias			Detection Bias (Exposure) *(Key Element)*					Detection Bias (Outcome) *(Key Element)*			Selective Reporting Bias	Other	Risk of Bias Summary Rating
	Did the analysis account for all of the confounders of interest (age, race/ ethnicity or another SES-related variable, and BMI)?	Was the loss to follow-up reported?	Were the losses to the follow-up related to chemical exposures or pubertal outcomes?	Did the authors use appropriate statistical analysis to address missingness or exclusion bias?	Were the chemicals measured (preferred) or were exposures based on questionnaire only?	If measured, were chemicals measured in urine?	Were the chemicals measured more than once?	Was the timing of the exposure assessment biologically appropriate?	Was the exposure assessment prospective?	Was puberty assessed via Tanner staging? If not, was a valid method used?	Was the Tanner staging method utilized? If so, was conducted by a trained professional (preferred) or by parents/ guardians reporting based on diagrams?	Was the outcome assessment prospective (preferred) or retrospective?	If the methods described multiple outcome measures (e.g., breast development, menarche, pubic hair development), were all included in the results section?	Are there any other potential threats to internal validity?	Risk of bias tier (1 to 3; 1=lowest risk of bias; 3=highest risk of bias)
												+		+	2
	-	NA	NA	NA	++	++	++	+	--	++	++	++	++	-	2
	-	+	-	+	++	--	-	+	++	--	NA	-	NA	-	2
	-	NA	-	+	--	NA	NA	-	--	--	--	--	NA	+	3
	++	-	NA	-	--	NA	NA	++	--	--	NA	--	++	-	3
	--	NA	NA	NA	++	--	-	--	--	+	-	--	++	+	2
	-	NA	NA	NA	++	++	-	+	--	+	++	-	NA	+	2
	++	+	-	+	++	++	-	-	-	--	NA	-	++	+	2
	--	NA	NA	-	++	++	-	-	--	++	++	--	++	+	2
	--	NA	NA	-	++	--	-	-	--	+	-	-	NA	+	2
	-	NA	NA	-	++	++	+	+	-	-	-	-	-	+	2
	++	++	-	++	++	++	-	+	--	++	++	+	++	+	2
	--	NA	NA	NA	++	++	-	+	--	+	NA	-	NA	+	2
	+	NA	NA	NA	++	++	-	+	--	+	+	-	NA	+	2
	-	NA	NA	NA	++	--	--	+	--	++	++	++	NA	-	2
	++	NA	NA	++	++	++	--	-	-	--	NA	-	++	-	2

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Articles are presented by risk of bias tier (in ascending order), then by year of publication, and alphabetized by first author.

[a] In this study, Tanner stage was used to assess thelarche every 6 months, but the primary outcome (menarche onset) was assessed using questionnaires that asked study participants to report the date of their first menstruation every 6 months before they reached Tanner stage 4 and every 3 months after they reach Tanner stage 4. Notably, the questionnaire attempted to distinguish between other causes of vaginal bleeding (e.g., vaginal infection, urinary tract infection, trauma).

[b] In this study, prenatal urinary phthalate exposures were assessed in pregnant women (mothers of study participants) during pregnancy.

[c] Although it was not clear that loss to follow-up existed in this study, not all eligible cohort members had available data on the exposures of interest.

[d] This study assessed the proportion of study participants with the presence (vs. absence) of concentrations of phthalate esters in their serum, comparing girls diagnosed with premature thelarche to those who were not diagnosed with premature thelarche. As such, this study did not directly assess the impact of phthalate exposures on pubertal timing.

[e] In this study, the authors stated that age at menarche was “prospectively recorded using a purpose-designed questionnaire at ages 8, 10, 14, and 17. If menarche had been reached since previous follow-up, caregivers were asked to contemporaneously report the exact date of onset”