REVIEW PAPER

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ENVIRONMENTAL NON-PERSISTENT ENDOCRINE-DISRUPTING CHEMICALS EXPOSURE AND REPRODUCTIVE HORMONES LEVELS IN ADULT MEN

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Abstract
Non-persistent endocrine-disrupting chemicals (EDCs) are exogenous, man-made substances present in the environment that may interfere with the natural human hormones and may exert adverse consequences on human organism. Endocrine-disrupting chemicals have been suspected to be associated with altered reproductive function in the case of males and females. Environmental endocrine-disrupting non-persistent chemicals like parabens, phthalates, bisphenol A (BPA), synthetic pyrethroids and organophosphate pesticides are found in various products such as metal food cans, plastic bottles, detergents, personal care products or chemicals used for fighting against insects. The widespread distribution of these chemicals causes that humans are permanently exposed through multiple sources. The aim of this review is to summarize data linking non-persistent endocrine-disrupting chemicals exposure, and human, male reproductive hormones levels. The included studies were selected by searched PubMed, Web of Science and MEDLINE, original papers published from 2006 to 2016 and referring to human data were included to the review. The results of reviewed studies were not consistent, however, majority of the studies indicated that non-persistent EDCs may affect male reproductive hormones levels. Most findings suggest that exposure to environmental EDCs is negatively related to the level of testosterone (except for exposure to BPA which is positively associated). In most of the studies negative association was found between exposure to examined EDCs and free androgen index, too. Considering the suggested health effect of exposure to EDCs, more epidemiological data is needed. Int J Occup Med Environ Health 2018;31(5):551–573

Key words:
Organophosphate pesticides, Bisphenol A, Parabens, Phthalates, Pyrethroids, Male reproductive health

INTRODUCTION

Infertility is defined clinically in the case of women and men who cannot achieve a clinical pregnancy after 1 or more of regular unprotected (at least 3 times in week) sexual intercourse [1]. A male factor is exclusively responsible in about 20% of infertile couples and contributes to another 30–40% of couples [2]. There are many hypotheses in the increase of male infertility [3]. One of the hypothesis is the exposure to environmental factors especially substances with hormonal activity. The group of chemicals that could interfere with normal hormonal balance is named endocrine-disrupting chemi-

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cals (EDCs) or endocrine disruptors (EDs). Endocrine-disrupting chemicals constitute a heterogeneous group of substances that interfere with endocrine function [4]. There is a number of official definitions of the EDCs. The most commonly used one is the following: "Endocrine-disrupting chemicals (EDCs) have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes" by the United States Environmental Protection Agency (U.S. EPA) [5].

Toxicological and epidemiological studies on non-persistent environmental chemicals, such as: bisphenol A, phthalates, parabens, synthetic pyrethroids and organophosphate pesticides, which have relatively short half-lives in the human body and do not accumulate significantly, have also been reported to have endocrine-disrupting properties and are suspected to affect human reproduction and development [6]. The EDCs are observed in all places and countries where human biomonitoring studies have been performed. These substances are omnipresent in the environment and in mass-consumption products and food. Endocrine disruptors may be found in many products including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and chemicals used for fighting against insects.

Human environmental exposure to EDCs takes place via ingestion of food, dust and water, via inhalation of gases and particles in the air, and through the skin [7]. Since such toxicants are omnipresent and it's hard to measure the amount of chemicals entering the body that is why there is disagreement about the degree of risk from exposure to EDCs [8]. Reproductive effect of EDCs exposure has been suspected for a long time, based on laboratory experiments and human epidemiological studies [9]. Due to temporal downward trends in semen quality and testosterone levels among adult men, researchers become increasingly concerned regarding potential risk of EDCs to men's reproductive health [10].

This review focuses on the human data regarding the relationship between environmental exposure to selected non-persistent EDCs (bisphenol A, phthalates, parabens, synthetic pyrethroids, organophosphate pesticides) in the case of adult men and male reproductive hormones levels, one of the predictor of male fertility.

MATERIAL AND METHODS

Epidemiological studies focused on the exposure to EDCs and male reproductive hormones levels were identified by means of searching databases. PubMeb, Web of Science and MEDLINE were systematically searched with detailed terms for: "bisphenol A," "phthalate," "parabens," "pyrethroids," "organophosphate pesticides" and "reproductive health," "reproductive hormones levels." Each of the first 5 keywords was combined with the 2 last keywords. The papers published from 2006 to 2016 were selected and only original articles were included. The period was chosen to reflect the finding over the past 10 years during which new techniques of measuring exposures and health effects in epidemiology studies have emerged. Articles focused on the animal and review or report papers were excluded. Studies regarding environmental exposure for adult men were included to the review. Papers concerning prenatal exposure to endocrine disruptors and male reproductive hormones levels were not taken into consideration. We included cohort, case-control cross-sectional, prospective and clinical studies that analyzed the impact of exposure to non-persistent EDCs on male reproductive hormones levels.

Data was independently extracted by 2 investigators who determined eligibility. Discrepancies were resolved by the third independent author. Finally 26 original studies concerning the association of non-persistent endocrine-disrupting chemicals and male reproductive hormones levels were classified to be reviewed. Contextual details of studies included in the systematic review are presented in

the Table 1. The following data information was selected from the eligible papers: authors, the year published, the year studied, the design of study, the kind of endocrine-disrupting chemicals, exposure assessment, type of outcome, study population, the main conclusion, and the confounders or the potential risk factors. At last all the full-text articles were read in-depth to identify the aims of the studies, statistical methods and accurate results.

RESULTS

Details of the results are shown in the Table 2

Bisphenol A and male reproductive hormones

Bisphenol A (BPA) is used in the chemical industry as a monomer in the production of plastic. It is also an important ingredient in the production of epoxy resins [11]. This toxicant could be identified in toys, cans or baby bottles. Four papers concerning exposure to BPA and male reproductive hormones levels were identified and included in this review [12–15]. Two studies were conducted in the USA [12,13], one in Italy [14] and one in Denmark [15]. The most of the studies were cross-sectional, only Lassen et al. [15] performed an on-going prospective study among general population. In the 2 studies participants [12,13] were recruited from medical centers. Galloway et al. (2010) [14] and Lassen et al. (2014) [15] recruited the participants from the general population. In all the reviewed studies total urinary concentrations of BPA (free + conjugated species) and serum reproductive hormones levels were measured.

Galloway et al. (2010) [14] noticed increasing levels of testosterone (T) with increasing BPA concentration ($p = 0.004$). Similar findings were observed in Lassen et al. study (2014) [15] but additionally the authors observed increase in the levels of luteinizing hormone (LH) ($p = 0.005$) and estradiol (E_2) ($p = 0.006$) in the highest quartile of BPA excretion (> 6.44 ng/ml$_{osm}$). Meeker et al. (2010) [13] found a significant positive association between follicle-stimulating hormone (FSH) ($p = 0.0004$) and BPA urinary concentration. An inverse association between inhibin B (INB) ($p = 0.003$) and BPA was found, too. On the other hand Mendiola et al. (2010) [12] did not observe any association between exposure to BPA and FSH and INB concentration but noticed significant association with sex hormone binding globulin (SHBG) ($\beta = 0.07$; 95% CI: 0.007–0.13).

Phthalate and male reproductive hormones

Phthalates constitute a group of industrial chemicals with many commercial uses, including personal-care products, medical devices and plasticizers in the packing materials of food [16]. Several studies addressing links between urinary metabolites of phthalate and reproductive hormones levels in the case of men have been published for a few recent years [17–27]. In the review 12 papers were included. Most of these studies were cross-sectional. Four of the studies were conducted in China [22,26,27], two in the USA and Denmark [18,19], one in Poland [21], in India [23], in Sweden [25] – and Specht et al. (2014) [24] performed a multicenter study where subjects were recruited in Poland, Ukraine and Greenland. Most of these participants were enrolled during visits in medical centers [18,19,21,23,24,26,27]. Reproductive hormones levels were measured in serum in all the presented studies. In the case of exposure assessment the levels of phthalate metabolites were mostly measured in urine [18–22,25,26]. Whereas Pant et al. (2014) [23] and Wang et al. (2016) [27] assessed the seminal concentrations of phthalates and Specht et al. (2014) [24] as well as Janjua et al. (2007) [17] investigated levels of phthalate metabolites in serum.

Mendiola et al. (2011) [19], Joensen et al. (2012) [20] and Pan et al. (2015) [26] found the negative association between phthalate and free androgen index, additionally Mendiola et al. (2011) [19] reported inverse association between some metabolites of phthalate (mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl)

Table 1. Contextual details of studies concerning the association of non-persistent endocrine-disrupting chemicals and male reproductive hormones levels included in the systematic review from 2006 to 2016

Study	Location	Period	Sample	Study design	Age	Definition of exposure	Outcome
Mendiola et al. (2010) [12]	USA	1999–2005	375 men	cross-sectional	18–53 years M±SD = 31.9±1.7 years	total urinary concentration of BPA (free + conjugated species) [μg/l]	serum hormone levels: FSH [IU/l], LH [IU/l], SHBG [nmol/l], T [nmol/l], E_2 [pmol/l], INB [pg/ml] and FAI, FT, FAI:LH ratio, FT:LH ratio, T:E_2 ratio, T:LH ratio
Meeker et al. (2010) [13]	USA	–	167 men from infertility clinic	cross-sectional	18–55 years M±SD = 27±4.6 years	total urinary concentration of BPA (free + conjugated species) [μg/l]	serum hormone levels: T [ng/dl], E_2 [pg/ml], SHBG [nmol/ml], INB [pg/ml], FSH [IU/l], LH [IU/l] and E_2:T ratio, T:LH ratio, FT [ng/dl], FAI, FSH:INB ratio, FAI:LH ratio
Galloway et al. (2010) [14]	Italy	1998–2000	334 men	cross-sectional	20–74 years	total urinary concentration of BPA (free + conjugated species) [μg/l]	serum hormone levels: E_2 [pg/ml], T [ng/ml], FT [ng/dl], SHBG [nmol/ml]
Lassen et al. (2014) [15]	Denmark	2008–2009	308 men	on-going prospective	27–30 years	total urinary concentration of BPA (free + conjugated species) [ng/ml]	serum hormone levels: FSH [IU/l], LH [IU/l], SHBG [nmol/l], T [nmol/l], FT [pmol/l], E_2 [pmol/l], INB [pg/ml]
Janjua et al. (2007) [17]	Denmark	only abstract available	26 men	pilot study	only abstract available	serum levels of BP and 2 phthalate metabolites: MEP, MBP [μg/l]	serum hormone levels: FSH, LH, T, E_2, INB
Meeker et al. (2009) [18]	USA	2000–2004	425 men from infertility clinic	cross-sectional	18–55 years M±SD = 36±5.3 years	urinary phthalate metabolites: MEHP, MBP, MBzP, MEP, MEHHP, MEOHP [ng/ml]	serum hormone levels: T [ng/dl], E_2 [pg/ml], SHBG [nmol/ml], FSH [IU/l], LH [IU/l], INB and T:LH ratio, FAI, E_2:T ratio
Mendiola et al. (2011) [19]	USA	1999–2005	425 men	cross-sectional	M±SD = 32.2±6.2 years	urinary phthalate metabolites: MEHP, MEHHP, MEOHP, MECPP, MCPP, MEP, MBzP, MBP, MCNP, MCOP, MiBP [ng/ml]	serum hormone levels: FSH [IU/l], LH [IU/l], SHBG [nmol/l], T [nmol/l], FT, E_2 [pmol/l], INB [pg/ml] and FAI, FAI:LH ratio, FT:LH ratio, E_2:T ratio, T:LH ratio
Joensen et al. (2012) [20]	Denmark	2007–2009	881 men	on-going study	M±SD = 19.5±1.3 years	urinary phthalate metabolites: MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MOP, MCPP, MiNP, MHiNP, MOiNP, MCiOP [ng/ml]	serum hormone levels: T [nmol/l], E_2 [pmol/l], SHBG [nmol/l], LH [IU/l], FSH [IU/l], INB [pg/ml], FAI, FT [ng/dl], FT:LH ratio, T:LH ratio, FSH:INB ratio

Jurewicz et al. (2013) [21]	Poland	–	269 men from infertility clinic	cross-sectional	22–57 years M±SD = 32±4.6 years	urinary phthalate metabolites: 5OH-MEHP, MEHP, MEP, MBP, MBzP, MINP [µg/ml]	plasma hormone levels: T [ng/ml], FSH [IU/l], E_2 [pg/ml]
Han et al. (2013) [22]	China	2007	232 men	cross-sectional	20–40 years M = 32 years	urinary phthalate metabolites: MBP, MEP, MEHP, MBzP, PA [µg/ml]	serum hormone levels: T [nmol/l], LH [IU/l], FSH [IU/l], E_2 [pg/ml] and FAI
Pant et al. (2014) [23]	India	–	60 men from infertility clinic	cross-sectional	21–40 years M±SD = 31.81±5.27 years	seminal concentration of phthalate: DEHP, DBP, DEP [µg/ml]	serum hormone levels: FSH [mIU/ml], LH [mIU/ml], T [ng/ml]
Specht et al. (2014) [24]	Greenland, Poland, Ukraine	2002–2004	Greenland – 196 men Poland – 190 men Ukraine – 203 men	cross-sectional	18.5–51.3 years	serum phthalate metabolites: 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP, 7OH-MMeOP, 7oxo-MMeOP, 7cx-MMeOP [ng/ml]	serum hormone levels: LH [IU/l], FSH [IU/l], E_2 [pmol/ml], T [nmol/ml], SHBG [nmol/ml], INB [ng/l] and FAI, T:LH ratio
Axelsson et al. (2015) [25]	Sweden	2008–2010	314 men	cross-sectional	17–20 years M±SD = 18.4±0.36 years	urinary phthalate metabolites: MEP, MBP, MBzP, MEHP, MECPP, MEOHP, MEHHP, MCiOP, MOiNP, MHiNP [ng/ml]	serum hormone levels: FSH [IU/l], LH [IU/l], SHBG [nmol/l], T [nmol/l], E_2 [pmol/l], FT [nmol/l]
Pan et al. (2015) [26]	China	2012–2014	1066 men from infertility clinic	cross-sectional	M±SD = 29.1 years	urinary phthalate metabolites: MMP, MEP, MCPP, MBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCMHP, MOP, MiNP, MCiOP [ng/ml]	serum hormone levels: T [nmol/l], LH [IU/l], FSH [IU/l], E_2 [pmol/l], SHBG [nmol/l], FAI
Wang et al. (2016) [27]	China	2013	342 men from infertility clinic	cross-sectional	M±SD = 32±5.4 years	semen phthalate metabolites: MMP, MEP, MBP, MBzP, MEHP, MEHHP, MEOHP, MOP [ng/ml]	serum hormone levels: E_2 [pg/ml], FSH [mIU/ml], LH [mIU/ml], SHBG [nmol/l], T [ng/dl], FT [ng/dl] and FAI
Qing et al. (2017) [28]	China	2013–2014	796 men	prospective cohort study	20–21 years	urinary phthalate metabolites: MMP, MEP, MiBP, MnBP, MCHP, MCPP, MnOP, MEHHP, MECPP, MEOHP, MEHP, MBzP, MiNP [ng/ml]	serum hormone levels: E_2 [pg/ml], FSH [mIU/ml], LH [mIU/ml], PRL [ng/ml], T [ng/ml]
Meeker et al. (2011) [30]	USA	2000–2004	167 men from infertility clinic	cross-sectional	18–55 years M±SD = 36.7±5.4 years	urinary concentration of parabens and markers: MP, PP, BP, conjugated BPA [µg/l]	serum hormone levels: E_2 [pg/ml], SHBG [nmol/ml], INB [pg/ml], FSH [IU/l], LH [IU/l], PRL [ng/ml], T [ng/dl], FT [ng/dl] and FSH:INB ratio, FAI, T:LH ratio, E_2:T ratio

Table 1. Contextual details of studies concerning the association of non-persistent endocrine-disrupting chemicals and male reproductive hormones levels included in the systematic review from 2006 to 2016 – cont.

Study	Location	Period	Sample	Study design	Age	Definition of exposure	Outcome
Jurewicz et al. (2017) [31]	Poland	2008–2011	315 men from infertility clinic	cross-sectional	M±SD = 32.14±4.2 years	urinary concentration of parabens: MP, EP, PP, BP, iBuP [µg/l]	serum hormone levels: T [ng/ml], E_2 [pg/ml], FSH [IU/l]
Han et al (2008) [33]	China	2004–2006	212 men from infertility clinic	cross-sectional	20–41 years M±SD = 29.37±4.232 years	urinary concentration of metabolite of pyrethroids: 3-PBA [µg/l]	serum hormone levels: FSH [IU/l], LH [IU/l], E_2 [pg/ml], T [ng/ml]
Meeker et al. (2009) [34]	USA	2000–2003	161 men from infertility clinic	cross-sectional	18–54 years M±SD = 36±5.8 years	urinary concentration of metabolites of pyrethroids: 3-PBA, cis-DCCA, trans-DCCA [ng/ml]	serum hormone levels: T [ng/dl], SHBG [nmol/ml], INB [pg/ml], LH [IU/l], FSH [IU/l], E_2 [pg/ml] and FAI
Radwan et al. (2014) [35]	Poland	2008–2011	334 men from infertility clinic	cross-sectional	22–44.8 years M±SD = 32.24±4.43 years	urinary concentration of metabolites of pyrethroids: 3-PBA, cis-DCCA, trans-DCCA, BDCA [µg/l]	plasma hormone levels: T [ng/ml], FSH [IU/l], E_2 [pg/ml]
Yoshinaga et al. (2014) [36]	Japan	1999–2000 and 2002–2003	322 men	cross-sectional	18–24 years	urinary concentration of metabolite of pyrethroid: 3-PBA [ng/ml]	serum hormone levels: FSH [IU/l], LH [IU/l], T [nmol/l], SHBG [nmol/l], INB [pg/ml], FT [pmol/l] and T:LH ratio
Meeker et al. (2006) [38]	USA	2000–2003	268 men from infertility clinic	cross-sectional	M±SD = 36.1±5.4 years	urinary metabolites of insecticides: TCPY (metabolite of chlorpyrifos and chlorpyrifos-methyl), 1N (metabolite of carbaryl and naphthalene) [µg/l]	serum hormone levels: T [ng/dl], SHBG [nmol/ml], INB [pg/ml], LH [IU/l], FSH [IU/l] and FAI
Meeker et al. (2007) [39]	USA	2000–2003	322 men from infertility clinic	cross-sectional	20–54 years	urinary metabolites of insecticides: TCPY (metabolite of chlorpyrifos and chlorpyrifos-methyl), 1N, 2N ((metabolites of carbaryl and naphthalene) [µg/l]	serum hormone levels: E_2 [pg/ml], PRL [ng/ml]
Omoike et al. (2015) [40]	USA	1999–2002	356 men	cross-sectional	20–55 years Me = 37 years	urinary concentrations of organophosphate insecticides metabolites: TCPY, DEPH, DETP, DEDTP, DMP, DMTP, DMDTP [ng/ml]	serum hormone levels: T [% change], E_2 [% change]
Melgarejo et al. (2015) [37]	Spain	2012–2013	116 men from infertility clinic	cross-sectional	25–38 years M±SD = 35.1±4.6 years	urinary concentrations of organophosphate pesticides metabolites: DMP, DMTP, DMDTP, DEPH, DETP, DEDTP [µg/l]	serum hormone levels: FSH [mIU/ml], LH [mIU/ml], T [nmol/l], E_2 [pmol/l], E_2:T ratio, T:LH ratio

2N – 2-naphthol; 3-PBA – 3-phenoxybenzoic acid; 5cx-MEPP – 5-carboxy-mono-2-ethylpenty phthalate; 5OH-MEHP – mono-(2-ethyl-5-hydroxyhexyl)phthalate; 5oxo-MEHP – 2-ethyl-5-oxyhexyl phthalate; 7cx-MmeOP – mono-4-methyl-7-carboxyheptyl phthalate; 7OH-MmeOP – mono-4-methyl-7-hydroxy-octyl phthalate; 7oxo-MmeOP – mono-4-methyl-7-oxooctyl phthalate; BDCA – cis-2;2-dibromovinyl-2;2-dimethylcyclopropane-1-carboxylic acid; BP – butyl paraben; BPA – bisphenol A; cis-DCCA – cis-3-2;2-dichlorovinyl-2;2-dimethylcyclopropane carboxylic acid; DBP – dibutyl phthalate; DEDTP – diethyldithiophosphate; DEHP – di(2-ethylhexyl) phthalate; DEP – diethyl phthalate; DEPH – diethylphosphate; DETP – diethylthiophosphate; DMDTP – dimethyldithiophophate; DMP – dimetylphosphate; DMTP – dimethylthiophosphate; E_2 – estradiol; EP – ethyl paraben; PP – propyl paraben; FAI – free androgen index; FSH – follicle-stimulating hormone; FT – free testosterone; iBuP – iso-butyl paraben; INB – inhibin B; LH – luteinizing hormone; MBP – mono(n-butyl) phthalate; MBzP – monobenzyl phthalate; MciOP – mono(carboxy-isooctyl) phthalate; MCMHP – mono-(2-carboxymethyl) hexyl phthalate; MCHP – monocyclohexyl phthalate MCNP – monocarboxyisononyl phthalate; MCOP – monocarboxyisooctyl phthalate; MCPP – mono(3-carboxypropyl) phthalate; MECPP – mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP – mono(2-ethyl-5-hydroxylhexyl) phthalate; MEHP – mono(2-ethylhexyl) phthalate; MEOHP – mono(2-ethyl-5-oxohexyl) phthalate; MEP – monoethyl phthalate; MHiNP – mono-(hydroxy-iso-nonyl) phthalate; MiBP – monoisobutyl phthalate; MINP – monoisononyl phthalate; MiNP – mono(hydroxyl-isononyl) phthalate; MMP – monomethyl phthalate; MnBP – mono-n-butyl phthalate; MnOP – mono-n-octyl phthalate; MoiNP – mono(oxo-isononyl) phthalate; MOP – mono-n-octyl phthalate; MP – methyl paraben; PA – phthalic acid; PRL – prolactin; SHBG – sex hormone-binding globulin; T – testosterone; TCPY – 3;5;6-trichloro-2-pyridinol; 1N – 1-naphthol; trans-DCCA – trans-3-2;2-dichlorovinyl-2;2-dimethylcyclopropane carboxylic acid.

Table 2. The main findings of studies concerning the association of non-persistent endocrine-disrupting chemicals and male reproductive hormones levels included in the systematic review from 2006 to 2016

Source	Exposure	Main findings
Mendiola et al. (2010) [12]	BPA	BPA was significantly associated with SHBG (β = 0.07; 95% CI: 0.007–0.13); there was a significant inverse association between urinary BPA concentration and both FAI and FAI/LH ratio (β = –0.05; 95% CI: –0.09–(–0.004); and β = –0.11; 95% CI: –0.18–(–0.03), respectively)
Meeker et al. (2010) [13]	BPA	in the model using only BPA concentrations measured in the single urine sample collected on the same day as the serum sample there was a positive association between BPA and FSH (β = 1.23; 95% CI: 1.1–1.4) and a suggestive inverse association between BPA and INB (β = –16.8; 95% CI: –33.8–0.22); in the model using geometric mean BPA concentrations from multiple urine samples there were a positive association between BPA and FSH (β = 1.18; 95% CI: 1.04–1.34) and between BPA and E_2:T ratio (β = 0.86; 95% CI: 0.75–0.97)
Galloway et al. (2010) [14]	BPA	higher daily BPA excretion was associated with higher T concentrations in men (β = 0.046; 95% CI: 0.015–0.076; p = 0.004)
Lassen et al. (2014) [15]	BPA	men in the highest quartile (> 6.44 ng/ml$_{(osm)}$) of BPA excretion had an average 18% higher T (95% CI: 8–28%), 22% higher LH (95% CI: 6–39%), and 13% higher E_2 (95% CI: 4–24%)
Janjua et al. (2007) [17]	BP, MEP, MBP	minor differences in INB, LH and E_2 were observed between the 2 weeks but these were not related to exposure
Meeker et al. (2009) [18]	MEHP, MBP, MBzP, MEP, MEHHP, MEOHP	T was inversely associated with SG-adjusted urinary MEHP – increase IQR in MEHP was associated with a 14.9 ng/dl decrease in T (95% CI: –27.5–(–2.3) ng/dl; p-value = 0.02); SG-adjusted MEHP was inversely associated with E_2 – increase IQR in MEHP was associated with a 6.8% decline in E_2 (95% CI: –11.2–(–2.4)%); no relationship among MEP, MBP, MBzP with any of the measured hormones
Mendiola et al. (2011) [19]	MEHP, MEHHP, MEOHP, MECPP, MCPP, MEP, MBzP, MBP, MCNP, MCOP, MiBP	SHBG was positive associated with MEHP (β = 0.05; 95% CI: 0.02–0.09); FAI/LH ratio was inversely associated with urinary MEHP concentrations (β = –0.06; 95% CI: –0.1–(–0.01))

Table 2. The main findings of studies concerning the association of non-persistent endocrine-disrupting chemicals and male reproductive hormones levels included in the systematic review from 2006 to 2016 – cont.

Source	Exposure	Main findings
Joensen et al. (2012) [20]	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MOP, MCPP, MiNP, MhiNP, MoiNP, MciOP	LH was positively associated with MnBP (9% higher LH in the highest MnBP quartile compared with the lowest, 95 CI%: 1–18%; p = 0.03) and this association was confirmed when MnBP was modeled as a continuous variable; % MiNP was negatively associated with FAI, with a 15% lowest (95% CI: –23–(–8)) FAI for the highest (8.31–27.38) vs. lowest (0.28–3.17) quartile of % MiNP; T/LH ratio and FAI/LH ratio were 9% lower (95% CI: –18–(–0.4)%) and 19% lower (95% CI: –30–(–8)%) in the highest compared with the lowest % MiNP quartile; SHBG was 10% higher in the highest quartile (95% CI: 2–18%); % MEHP was negatively associated with total testosterone (–7% for the highest (11.28–28.97) vs. lowest (0.93–5.38) % MEHP quartile; 95% CI: –13–(–1)%), free testosterone (–7%; 95% CI: –12–(–0.3)%) and FAI (–9%; 95% CI: –16–(–1)%)
Jurewicz et al. (2013) [21]	5OH-MEHP,MEHP, MEP, MBP, MBzP, MINP	in adjusted analysis there was a negative relationship between MEHP and T level (p = 0.038)
Han et al. (2013) [22]	MBP, MEP, MEHP, MBzP, PA	E_2 was correlated with MBP, MEHP and total PA in the preliminary analysis (R = –0.12, p < 0.05; R = –0.13; p < 0.05; R = 0.18; p < 0.05, respectively) but not in adjusted analysis; there were a significant positive correlation between LH and MBP (R = 0.14, p < 0.05) and between FSH and total PA (R = 0.15, p < 0.05) in uncontrolled analysis; there were no associations after adjusted for potential risk factors
Pant et al. (2014) [23]	DEHP, DBP, DEP,	DBP/DEHP showed negative association with testosterone (DBP β = –0.61, p < 0.04; DEHP β = –0.96, p < 0.02); DEHP/DBP was not significantly associated with FSH and LH but the trend of regression coefficient was negative
Specht et al. (2014) [24]	5OH-MEHP, oxo-MEHP, 5cx-MmeOP, 7OH-MmeOP, 7oxo-MmeOP, 7cx-MmeOP	proxy-MEHP and – MiNP were negatively associated with T, and for proxy-MiNP, SHBG; SHBG was negatively associated with 7cx-MmeHP, and the T/LH ratio was negatively associated with 5OH-MEHP
Axelsson et al. (2015) [25]	MEP, MBP, MBzP, MEHP, MECPP, MEOHP, MEHHP, MciOP, MoiNP, MhiNP	continuously treated urinary % MEHP was negatively associated with testosterone and free testosterone (p = 0.022, η^2 = 1.7%; p = 0.027, η^2 = 1.7%) in adjusted analysis; in categorized urinary exposure there were no differences in reproductive hormones between man in the highest quartile and those in the lowest quartile of any of examined urinary phthalate metabolites
Pan et al. (2015) [26]	MMP, MEP, MCPP, MBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCMHP, MOP, MiNP, MciOP	MBP was negatively associated with T (p = 0.007), FT (p < 0.001), LH (p = 0.002) and FAI (p = 0.001); MiBP was also negatively associated with T (p = 0.02), FT (p = 0.001), FAI (p = 0.012) and LH (p < 0.001); for E_2, a significant negative relationship with MEHP (p = 0.04) and suggestive relationship with % MEHP (p = 0.055) was observed; no significant associations between SHBG and any phthalate metabolites
Wang et al. (2016) [27]	MMP, Mep, MBP, MBzP, MEHP, MEHHP, MEOHP, MEP	in univariate analysis $E_2$was positively associated with MMP (3.3 pg/ml higher estradiol in the highest MMP tertile compared with the lowest tertile, 95% CI: 0.24–6.4 pg/ml; p for trend = 0.03); LH was positively associated with MEP (12% higher LH in the highest MEP tertile compared with the lowest tertile, 95% CI: 0.9–25%; p for trend = 0.03); T was negatively associated with MEOHP (10% lower T in the highest MEOHP tertile compared with the lowest tertile, 95% CI: –21(–0.6)%; p for trend = 0.04); in multivariate analysis no association between semen phthalate metabolites and serum reproductive hormones levels

Qing et al. (2017) [28]	MMP, MEP, MiBP, MnBP, MCHP, MCPP, MnOP, MEHHP, MECPP, MEOHP, MEHP, MBzP, MiNP	all hormone outcomes were associated with at least one phthalate metabolite; all metabolites (except MEHP) declines after relocations of men ($p < 0.001$ respectively), at the same time E_2 and LH increased (by 34.2% and 10%, respectively) and T decreased (by 7%)
Meeker et al. (2011) [30]	MP, PP, BP, BPA	there were no association between urinary parabens and hormones levels
Jurewicz et al. (2017) [31]	MP, EP, PP, BP, iBuP	in multivariate linear regression models the negative association was observed between urinary concentration of BP and T level ($p = 0.031$)
Han et al. (2008) [33]	3-BPA	there was significant association between 3-BPA and LH, E_2 ($p = 0.013$, $p = 0.022$, respectively), but no associations was found in the other detected hormones
Meeker et al. (2009) [34]	3-BPA, cis-DCCA, trans-DCCA	men in the highest 3BPA category (> 75th) had significantly higher FSH levels ($p = 0.001$; p for trend among low (< 50th), medium (50th–75th) and high (> 75th) categories $p = 0.002$); additionally cis-DCCA and trans-DCCA were inversely associated with INB (p for trend = 0.03 and $p = 0.02$ respectively)
Radwan et al. (2014) [35]	3-BPA, CDCCA, TDCCA, BDCA	the level of TDCCA greater than 50th was negatively related to the level of T ($p = 0.04$)
Yoshinaga et al. (2014) [36]	3-BPA	no association between urinary 3-BPA and serum hormone levels
Meeker et al. (2006) [38]	TCPY, 1N	an interquartile range increase in TCPY was association with a decline of 25 ng/dl (95% CI: –40–(–10)) in T concentration; the highest TCPY quintile was associated with a T decline of 83 ng/dl (–128–(–39)) compared with the lowest TCPY quintile; positive association between TCPY and FAI ($\beta = 0.93$; 95% CI: 0.89–0.98) and inverse association between 1N concentrations and decreased T levels ($\beta = –24.3$; 95% CI: –43.3–(–5.21))
Meeker et al. (2007) [39]	TCPY, 1N, 2N	an interquartile range increase in TCPY was associated with a 1.36 pg/ml decline (95% CI: –2.91–(–0.22)) in E_2 concentration
Omioke et al. (2015) [40]	TCPY, DEP, DETP, DEDTP, DMP, DMTP, DMDTP	in adjusted models there was an association between DEP and T (–2.5; 95% CI: –3.5–(–1.4)%)
Melgarejo et al. (2015) [37]	DMP, DMTP, DMDTP, DEP, DETP, DEDTP	there was a positive association between DEDTP concentration and LH and FSH levels ($\beta = 11.4$; 95% CI: 0.81–22.1; $p < 0.05$; $\beta = 3.2$; 95% CI: 0.08–6.2; $p < 0.05$, respectively); there was a negative association between the DEDTP and T/LH ratio ($\beta = –9.6$; 95% CI: –18.7–(–0.5); $p < 0.05$)

CI – confidence interval; SG – specific gravity; IQR – interquartile range; proxy-MEHP – total serum concentrations of the DEHP metabolites.
Other abbreviations as in Table 1.

phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP) and free testosterone. The study conducted by Axelsson et al. (2015) [25] indicated that % MEHP was negatively associated with testosterone (T) ($p = 0.022$, $\eta^2 = 1.7\%$) and free testosterone (FT) ($p = 0.027$, $\eta^2 = 1.7\%$) in the adjusted model. In the prospective ongoing study conducted by Qing [28] all hormone outcomes were associated with at least one phthalate metabolite. A comparison of phthalate metabolites between baseline and the follow-up showed that all but MEHP substantially declined after the relocation ($p < 0.001$ respectively). At the same time E_2 and LH increased (by 34.2%, 10%, respectively), and T decreased (by 7%). In all the remaining studies exposure to phthalate was negatively associated with testosterone levels [18–21,23–26], too. Whereas Wang et al. (2016) [27] and Han et al. (2013) [22] didn't find any significant association between phthalate exposure and serum reproductive hormones levels. Janjua et al. [17] conducted the clinical study on 26 healthy young male volunteers which were assigned to daily whole body topical application of 2 mg/cm^2 basic cream formulation each without and with the 2% compounds. Authors did not reveal any short-term influence on the reproductive hormones levels in the case of the examined men.

Parabens and male reproductive hormones

Parabens are extensively used as antimicrobial preservatives in food, cosmetics, toiletries and pharmaceuticals [29]. According to our knowledge only 3 studies examine the association between exposure to parabens and reproductive hormones in the case of men [17,30,31]. The studies were conducted in Poland, Denmark and USA. Jurewicz et al. (2017) [31] and Meeker et al. (2011) [30] assessed urinary concentrations of parabens whereas Janjua et al. (2007) [17] assessed serum level of butyl paraben (BP). In all the remaining studies reproductive hormones levels were measured in serum. Jurewicz et al. [31] showed that BP was negatively associated with the level of testosterone ($p = 0.031$). While Janjua et al. [17] and Meeker et al. [30] did not reveal any association between exposure to parabens and serum hormone levels. Further studies are necessary to clarify the association between environmental exposure to parabens and reproductive hormones levels in the case of adult men.

Synthetic pyrethroids and male reproductive hormones

Synthetic pyrethroids constitute the class of insecticides and are found in many formulations used in agriculture for controlling insect pests in crops, forestry and in gardens. They are also widely used as insecticides in household and public buildings [32]. Synthetic pyrethroids are most common insecticides used nowadays [32]. These chemicals possess hormonal activities and have also been classified as endocrine disruptors [33]. In the review 4 original papers concerning the relationship between synthetic pyrethroids and male reproductive hormones were included [33–36]. The studies were conducted in China [33], USA [34], Poland [35] and Japan [36]. All the participants were recruited from medical centers except for Yoshinaga et al. (2014) [36] where the participants were students from Kawasaki.

Exposure to synthetic pyrethroids was assessed by measuring pyrethroids metabolites in urine: 3-phenoxybenzoic acid (3-PBA) [33–36], cis-3-(2,2-dichlorovinyl)-2,2-dimethylocyclopropane carboxylic acid (CDCCA), trans-3-(2,2-dichlorovinyl)-2,2-dimethylocyclopropane carboxylic acid (TDCCA) [34,35] and cis-2,2-dibromovinyl-2,2-dimethylcyclopropane-1-carboxylic acid (DBCA) [35]. Radwan et al. (2014) [35] showed that the level of TDCCA greater than 50th was negatively related to the level of T ($p = 0.04$) but there was no association between reproductive hormones and other pyrethroids metabolites (CDCCA, 3PBA, DBCA). In the study performed by Han et al. [33] significant association was found between 3-PBA and LH, E_2 ($p = 0.013$, $p = 0.022$, respec-

tively). These results are similar to those of Meeker et al.'s study (2009b) [34], where suggestive positive association with LH was also found (p = 0.054). Additionally, men in the highest 3-PBA category (≥ 75th percentile) had significantly higher FSH levels (p = 0.001) and had a suggestive decline in free androgen index (FAI) (p = 0.08), too. Furthermore, cis-DCCA and trans-DCCA were negatively associated with inhibin B (p for trend = 0.03 and p for trend = 0.02, respectively). On the other hand Yoshinaga et al. (2014) [36] revealed that there was no associations between urinary 3-BPA and reproductive hormones levels.

Organophosphate pesticides and male reproductive hormones

Organophosphate pesticides are used in agricultural and household for pest control [37]. These chemicals are widely used in agriculture and commerce [38]. Due to extensive use of such pesticides, a large proportion of the population is exposed to these chemicals or their environmental degradation products. Four original papers referring to exposure to organophosphate pesticides and levels of reproductive hormones were included in the review [37–40]. Three of the studies were conducted in the USA [38–40] and one in Spain [37]. All of the studies were cross-sectional. Participants were male partners in couples presenting to an infertility clinics, except for Omoike et al. (2015) [40] who derived data (subset of men (N = 356)) from the cross-sectional US National Health and Nutrition Examination Survey (NHANES).

In all reviewed studies serum hormones levels and urinary concentrations of metabolites of pesticides were measured. Meeker et al. (2006, 2007) [38,39] assessed the metabolites of chlorpyrifos, carbaryl, naphthalene: 3,5,6-trichloro-2-pyridinol (TCPY), 1-naphthol (1N), 2-naphthol (2N) whereas Omoike et al. (2015) [40] and Melgarejo et al. (2015) [37] measured 6 non-specific urinary metabolites of chlorpyrifos and chlorpyrifos-methyl: diethylphosphate (DEPH), diethylthiophosphate (DETP), diethyldithiophosphate (DEDTP), dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP). Both studies performed by Meeker et al. (2006, 2007) [38,39] indicated that there was an inverse association between urinary metabolites of non-persistent insecticides and reproductive hormones levels. Negative association between TCPY and testosterone concentration was found [38]. Interquartile range increase in TCPY was associated with a decline of 25 ng/dl (95% CI: –40–(–10)) in testosterone level and the highest TCPY quintile was associated with a testosterone decline of 83 ng/dl (95% CI: –128–(–39)) as compared with the lowest TCPY quintile [38]. The next study performed by Meeker et al. (2007) [39] revealed that an interquartile range increase in TCPY was associated with a 1.36 pg/ml decline (95% CI: –2.91–(–0.22)) in E_2 concentration. Whereas Omoike et al. (2015) [40] observed a statistically significant inverse association between DEPH and testosterone (–2.5; 95% CI: –3.5–(–1.4)) when exposure was modeled as both a continuous or a categorical variable. The results are not consistent with Melgarejo et al. (2015) [37], where only DEDTP concentration was positively associated with serum LH and FSH concentrations levels (β = 11.4; 95% CI: 0.81–22.1; $p < 0.05$; β = 3.2; 95% CI: 0.08–6.2; $p < 0.05$, respectively).

DISCUSSION

Main findings

The results of the reviewed original papers suggest that environmental exposure to non-persistent endocrine-disrupting chemicals may affect reproductive hormones levels. The summary of the results is presented in the Table 3. The results of studies analyzing the association between exposure to bisphenol A and male reproductive hormones levels (T, LH, FSH, SHBG, E_2, INB, prolactin (PRL)) are not consistent. When some results suggest that BPA was positively associated with some reproductive hormones levels, other studies didn't find such associations. Mendio-

Table 3. The summary of the results of reviewed studies from 2006 to 2016 concerning environmental exposure to non-persistent endocrine-disrupting chemicals that may affect reproductive hormones levels

Outcome	Endocrine disruptors				
	bisphenol A (BPA)	phthalates	parabens	pyrethroids	organophosphate insecticides
Testosterone (T)	(–) Mendiola et al. (2010) [12] (–) Meeker et al. (2010) [13] (+) Galloway et al. (2010) [14] (+) Lassen et al. (2014) [15]	(+) Meeker et al. (2009) [18] (+) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (+) Jurewicz et al. (2013) [21] (–) Han et al. (2013) [22] (+) Pant et al. (2014) [23] (+) Specht et al. (2014) [24] (+) Axelsson et al. (2015) [25] (+) Pan et al. (2015) [26] (–) Wang et al. (2016) [27] (–) Januja et al. (2007) [17] (+) Qing et al. (2017) [28]	(–) Meeker et al. (2011) [30] (+) Jurewicz et al. (2017) [31] (–) Janjua et al. (2007) [17]	(–) Han et al. (2008) [33] (+) Meeker et al. (2009) [34] (+) Radwan et al. (2014) [35] (–) Yoshinaga et al. (2014) [36]	(+) Meeker et al. (2006) [38] (+) Omoike et al. (2015) [40] (–) Melgarejo et al. (2015) [37]
Free testosterone (fT)	(–) Mendiola et al. (2010) [12] (–) Meeker et al. (2010) [13] (–) Galloway et al. (2010) [14] (+) Lassen et al. (2014) [15]	(+) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (+) Axelsson et al. (2015) [25] (–) Pan et al. (2015) [26] (–) Wang et al. (2016) [27]	(–) Meeker et al. (2011) [30]	(–) Yoshinaga et al. (2014) [36]	
Sex hormone-binding globulin (SHBG)	(+) Mendiola et al. (2010) [12] (+) Meeker et al. (2010) [13] (–) Galloway et al. (2010) [14] (–) Lassen et al. (2014) [15]	(+) Meeker et al. (2009) [18] (+) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (+) Specht et al. (2014) [24] (–) Axelsson et al. (2015) [25] (–) Pan et al. (2015) [26] (–) Wang et al. (2016) [27]	(–) Meeker et al. (2011) [30]	(–) Meeker et al. (2009) [34]	(–) Meeker et al. (2006) [38] (–) Meeker et al. (2007) [39] (–) Omoike et al. (2015) [40]

Follicle-stimulating hormone (FSH)	(–) Mendiola et al. (2010) [12] (+) Meeker et al. (2010) [13] (–) Lassen et al. (2014) [15]	(–) Meeker et al. (2009) [18] (–) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (–) Jurewicz et al. (2013) [21] (–) Han et al. (2013) [22] (–) Pant et al. (2014) [23] (–) Specht et al. (2014) [24] (–) Axelsson et al. (2015) [25] (–) Pan et al. (2015) [26] (–) Wang et al. (2016) [27] (–) Janjua et al. (2007) [17] (–) Qing et al. (2017) [28]	(–) Meeker et al. (2011) [30] (–) Jurewicz et al. (2017) [31] (–) Janjua et al. (2007) [17]	(–) Han et al. (2008) [33] (+) Meeker et al. (2009) [34] (–) Radwan et al. (2014) [35] (–) Yoshinaga et al. (2014) [36]	(–) Meeker et al. (2006) [38] (+) Melgarejo et al. (2015) [37]
Luteinizing hormone (LH)	(–) Mendiola et al. (2010) [12] (–) Meeker et al. (2010) [13] (+) Lassen et al. (2014) [15]	(–) Meeker et al. (2009) [18] (–) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (–) Han et al. (2013) [22] (–) Pant et al. (2014) [23] (–) Specht et al. (2014) [24] (+) Axelsson et al. (2015) [25] (+) Pan et al. (2015) [26] (–) Wang et al. (2016) [27] (–) Janjua et al. (2007) [17] (+) Qing et al. (2017) [28]	(–) Meeker et al. (2011) [30] (–) Janjua et al. (2007) [17]	(+) Han et al. (2008) [33] (+) Meeker et al. (2009) [34] (–) Yoshinaga et al. (2014) [36]	(–) Meeker et al. (2006) [38] (+) Melgarejo et al. (2015) [37]
Estradiol (E_2)	(–) Mendiola et al. (2010) [12] (–) Meeker et al. (2010) [13] (–) Galloway et al. (2010) [14] (+) Lassen et al. (2014) [15]	(+) Meeker et al. (2009a [18] (–) Mendiola et al. (2011) [19] (–) Joensen et al. (2012) [20] (–) Jurewicz et al. (2013) [21] (–) Han et al. (2013) [22] (–) Specht et al. (2014) [24] (–) Axelsson et al. (2015) [25] (+) Pan et al. (2015) [26] (–) Wang et al. (2016) [27] (–) Janjua et al. (2007) [17] (+) Qing et al. (2017) [28]	(–) Meeker et al. (2011) [30] (–) Jurewicz et al. (2017) [31] (–) Janjua et al. (2007) [17]	(+) Han et al. (2008) [33] (–) Meeker et al. (2009) [34] (–) Radwan et al. (2014) [35]	(–) Meeker et al. (2007) [39] (–) Omoike et al. (2015) [40] (–) Melgarejo et al. (2015) [37]

Table 3. The summary of the results of reviewed studies from 2006 to 2016 concerning environmental exposure to non-persistent endocrine-disrupting chemicals that may affect reproductive hormones levels – cont.

Outcome	Endocrine disruptors				
	bisphenol A (BPA)	phthalates	parabens	pyrethroids	organophosphate insecticides
Inhibin B (INB)	(–) Mendiola et al. (2010) [12] (+) Meeker et al. (2010) [13] (–) Lassen et al. (2014) [15]	(–) Meeker et al. (2009) [18] (–) Mendiola et al. (2011) [19] (–) Joensen et al. (2012) [20] (–) Specht et al. (2014) [24] (–) Janjua et al. (2007) [17]	(–) Meeker et al. (2011) [30] (–) Janjua et al. (2007) [17]	(+) Meeker et al. (2009) [34] (–) Yoshinaga et al. (2014) [36]	(–) Meeker et al. (2006) [38]
Free androgen index (FAI)	(+) Mendiola et al. (2010) [12] (+) Meeker et al. (2010) [13]	(+) Meeker et al. (2009) [18] (+) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (–) Han et al. (2013) [22] (–) Specht et al. (2014) [24] (+) Pan et al. (2015) [26] (–) Wang et al. (2016) [27]	(–) Meeker et al. (2011) [30]	(+) Meeker et al. (2009) [34]	(+) Meeker et al. (2006) [38]
FAI/LH ratio	(+) Mendiola et al. (2010) [12] (–) Meeker et al. (2010) [13]	(+) Mendiola et al. (2011) [19]			
fT/LH ratio	(–) Mendiola et al. (2010) [12]	(–) Mendiola et al. (2011) [19] (–) Joensen et al. (2012) [20]			
T/LH ratio	(–) Mendiola et al. (2010) [12] (–) Meeker et al. (2010) [13]	(–) Meeker et al. (2009) [18] (–) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20] (+) Specht et al. (2014) [24]	(–) Meeker et al. (2011) [30]	(–) Meeker et al. (2009) [34] (–) Yoshinaga et al. (2014) [36]	(+) Melgarejo et al. (2015) [37]
E_2/T ratio	(–) Mendiola et al. (2010) [12] (+) Meeker et al. (2010) [13]	(+) Meeker et al. (2009) [18] (–) Mendiola et al. (2011) [19] (+) Joensen et al. (2012) [20]	(–) Meeker et al. (2011) [30]		(+) Melgarejo et al. (2015) [37]
FSH/INB ratio	(+) Meeker et al. (2010) [13]	(–) Joensen et al. (2012) [20]	(–) Meeker et al. (2011) [30]		

"–" – no association; "+" – significant association.
Abbreviations as in Table 1.

la et al. (2010) [12] and Meeker et al. (2010) [13] revealed that BPA was positively associated with SHBG but in Galloway et al.'s (2010) [14] and Lassen et al.'s (2014) [15] studies there were no similar associations. Likewise, the results of studies referring to phthalates and male reproductive hormones are not consistent. Three [27,22] of the 10 studies did not find any association between the exposure to phthalates and the level of reproductive hormones in the case of men in adjusted models. The rest of the studies [18–21,23–26] revealed that at least one of the phthalate metabolites was associated with decline in the level of testosterone. Some authors [18,20,26] also revealed that exposure to phthalate was inversely associated with E_2 and free androgen index. Three studies [17,30,31] assess the relationship between exposure to parabens and male reproductive hormones levels and only in the study performed by Jurewicz et al. [31] the level of urine BP was negatively associated with testosterone. Two of the studies [17,30] found no evidence for this association. However, it is possible that intraindividual variability in exposure and small sample size could have limited ability to reveal subtle associations.

The results of studies analyzing the associations between exposure to synthetic pyrethroids and male reproductive hormones have some differences in results as well. While Yoshinaga et al. (2014) [36] revealed no evidence for those associations, other authors suggested that environmental pyrethroids exposure may have affected the level of reproductive hormones. Han et al. (2008) [33] and Meeker et al. (2009b) [34] noticed positive associations between 3-PBA and LH concentration, additionally Meeker et al. (2009b) [34] revealed positive associations with FSH and negative association with inhibin B and free androgen index. Radwan et al. (2014) [35] indicated that TDCCA was negatively related to the level of testosterone. Finally, the studies concerning the association between organophosphate pesticides and male reproductive hormones levels suggest that environmental exposure to pesticides may interfere with the male endocrine system. Meeker et al. (2006, 2007) [38,39] revealed the negative association between urinary metabolites of insecticides and testosterone, estradiol and free androgen index. Omoike et al. (2015) [40] showed such associations only with testosterone. In contrast Melgarejo et al. (2015) [37] revealed the positive association between urinary concentrations of organophosphate pesticide metabolites and LH and FSH.

There are possibly numerous factors contributing to the divergent results between studies. The various reproductive hormones levels used may be a possible explanation for the varied results. The use of different biomarkers to ascertain exposure may have some bearing on the statistical association, too. Other factors that may affect the differences may be the study population (general or from the infertility clinics) and number of participants in each of the study. Additionally, the choice of confounding factors included in the statistical analysis may also impact the results.

The results of the epidemiological studies concerning the exposure to EDCs are similar to those of animal studies [33], however, it must be noted that most animal studies to date have used dose levels that are much higher than what is encountered by environmentally exposed humans [17].

Exposure assessment

The exposure assessment in almost all reviews was based on the biomarkers of exposure. In the case of exposure to BPA, total urinary concentration (free + conjugated) was measured [12–15]. Phthalates were measured in urine [18–22,25,26], semen [23,27] and serum [24]. Parabens, synthetic pyrethroids and organophosphate pesticides were measured in urine samples [30,33–40]. In most of the studies only one urine or various biological fluid samples were used for the exposure assessment purposes. One urine sample as a biomarker of exposure to EDCs may have resulted in substantial measurement error and attenuation of associations [41]. Janjua et al. (2007) [17] and Qing et al. (2017) [28]

assessed 2 samples to evaluate the levels of phthalate. Meeker et al. (2010, 2011) [13,30] used 3 samples of urine to measure the concentration of BPA and parabens but the group of subjects with 2 or more urine samples was small. Whereas Galloway et al.'s (2010) [14] analyses were based on the 24-h urine specimens which is likely to be more accurate (participants were asked to collect the urine for 24 h in a vessel with a preservative) [14]. Non-persistent endocrine-disrupting chemicals are rapidly metabolized and excreted, and urinary metabolite concentrations only reflect exposure in the preceding 1 or 2 days [18]. However, despite within-person variability in urinary concentrations of endocrine-disrupting chemicals, a single spot is predictive of long-term exposure and provides good sensitivity to classify individuals [42].

Confounders and potential risk factor

The results of these studies were adjusted to many well-known factors. Details of potential risk factors are shown in the Table 4. In the studies the age and body mass index (BMI) was usually controlled. Smoking status was included as a potential risk factor in all the studies. Only in 3 studies [21,31,40] the smoking status was controlled by measuring the level of nicotine. The time of the day of blood/urine sample collection was adjusted in nearly a half of the studies [12,13,15,18,19,25,26,30,33,37,39], too. Several studies during which participants provided urine samples, urinary creatinine concentration was also considered to be a potential confounder [12,14,19,21,22,37,40]. Other factors such as ethnicity, medicine intake and chronic diseases were used as confounders in some studies [12,19,21,22,35,39,40]. Only Han et al. [22] and Melgarejo et al. [37] adjusted their study models by psychological tension and the number of stressful life events.

Mechanism

Endocrine-disrupting chemicals may interfere with the production, secretion, transportation, metabolism, receptor binding, mediation of effects, and excretion of endogenous hormones which support endocrine homeostasis in the organism [5,43]. These chemicals may have anti-oestrogenic, oestrogenic, antigestagenic and antiandrogenic properties and are thought to mimic endogenous estrogens by entering the cell, binding to the receptor and activating transcription and may also antagonize normal androgen action [44]. In general, there is the number of information on the effect of exposure to EDCs on male reproductive hormones levels, indeed a considerable number of *in vitro* (sub-cellular or cellular) and *in vivo* (animal) screening tests for hormonal-activities of these substances have been developed [45]. Nonetheless, it is known that hormonal disruption alters the hypothalamic-pituitary endocrine function [37].

It was proven that BPA behaved similarly to natural estrogen-17-β estradiol by inducing estrogen receptors but in the concentrations about one thousand higher (10^{-6} to 10^{-4}M) in comparison to estradiol [46]. Estrogenic activity of BPA has been well documented in the investigations on animals [47,48]. Additionally, BPA was proven to affect functions of androgens and prolactin [49]. On the other hand, phthalate esters act as agonists and/or antagonists of estrogen and androgen receptors via one or more hormonal receptors, although interaction of phthalate esters with the estrogen and androgen receptors requires certain size and bulkiness with alkyl groups [50]. Likewise, these endocrine disruptors may exhibit their activities by altering pregnane X receptor-regulated (PXR) steroid hormone metabolism [8]. Activation of PXR may increase the levels of endocrine-disrupting metabolites while at the same time altering the local bioavailability of endogenous androgens and estrogens [8]. Animals models documented that parabens possessed very weak estrogenic properties which may have resulted in alternations to male reproductive functions including testosterone secretion [51] but it had been hypothesized that the combination of several weakly acting substances may be additive or even synergistic and

Table 4. The confounder and/or risk factors disturbed the relation between endocrine-disrupting chemicals and reproductive hormones in studies from 2006 to 2016 concerning evnironmental exposure to non-persistent endocrine-disrupting chemicals that may affect reproductive hormones levels

Source	Exposure	Potential risk factors and/or confounder
Mendiola et al. (2010) [12]	BPA	age, age squared, BMI, smoking status, ethnicity, study center, urinary creatinine concentration, time of sample collection
Meeker et al. (2010) [13]	BPA	specific gravity, age, BMI, smoking status, season, time of day blood/urine samples were collected
Galloway et al. (2010) [14]	BPA	age, study site, smoking, BMI, weight, waist circumference, urinary creatinine concentration
Lassen et al. (2014) [15]	BPA	BMI, smoking, time of day of blood sampling
Janjua et al. (2007) [17]	BP, MEP, MBP	–
Meeker et al. (2009a) [18]	MEHP, MBP, MBzP, MEP, MEHHP, MEOHP	age, BMI, current smoking, season, time of day blood sample collection
Mendiola et al. (2011) [19]	MEHP, MEHHP, MEOHP, MECPP, MCPP, MEP, MBzP, MBP, MCNP, MCOP, MiBP	age, age square, BMI, smoking status, ethnicity, urinary creatinine concentration, time of sample collection, time of collection squared
Joensen et al. (2012) [20]	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MOP, MCPP, MiNP, MHiNP, MoiNP, MciOP	age, BMI, smoking, alcohol intake, time of day of blood sample
Jurewicz et al. (2013) [21]	5OH-MEHP, MEHP, MEP, MBP, MBzP, MINP	age, smoking, past diseases and creatinine in urine
Han et al. (2013) [22]	MBP, MEP, MEHP, MBzP, PA	BMI, smoking status, age
Pant et al. (2014) [23]	DEHP, DBP, DEP	lead, cadmium, DEP, DBP, DEHP, age, BMI, tabacco chewing, smoking, alcohol, diet
Specht et al. (2014) [24]	5OH-MEHP, 5oxo-MEHP, 5cx-MmeOP, 7OH-MmeOP, 7oxo-MmeOP, 7cx-MmeOP	age, BMI, study site
Axelsson et al. (2015) [25]	MEP, MBP, MBzP, MEHP, MECPP, MEOHP, MEHHP, MciOP, MoiNP, MhiNP	BMI, current own cigarette smoking, maternal and paternal smoking during pregnancy, time of day at sampling
Pan et al. (2015) [26]	MMP, MEP, MCPP, MBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCMHP, MOP, MiNP, MciOP	age, BMI, smoking, alcohol drinking status, time of blood collection
Wang et al. (2016) [27]	MMP, MBP, MBzP, MEHP, MEHHP, MEOHP, MEP	age, BMI, alcohol use, smoking status
Qing et al. (2017) [28]	MMP, MEP, MiBP, MnBP, MCHP, MCPP, MnOP, MEHHP, MECPP, MEOHP, MEHP, MBzP, MiNP	age, abstinence period, BMI, smoking, alcohol consumption

Table 4. The confounder and/or risk factors disturbed the relation between endocrine-disrupting chemicals and reproductive hormones – cont.

Source	Exposure	Potential risk factors and/or confounder
Meeker et al. (2011) [30]	MP, PP, BP, BPA	specific gravity, age, BMI, current smoking status, time of day of blood/urine sample collection
Jurewicz et al. (2017) [31]	MP, EP, PP, BP, iBuP	sexual abstinence, age, smoking, alcohol consumption, past disease
Han et al. (2008) [33]	3-PBA	creatinine, smoking, passive smoking, drinking status, medicine intake, history of operation, psychological tension, sleep quality
Meeker et al. (2009b) [34]	3-PBA, cis-DCCA, trans-DCCA	age, BMI, smoking status, timing of blood sample collection by season and time of day
Radwan et al. (2014) [35]	3-PBA, cis-DCCA, trans-DCCA, BDCA	sexual abstinence, age, smoking, past diseases, alcohol consumption
Yoshinaga et al. (2014) [36]	3-PBA	age, smoking, frequency of soy product consumption
Meeker et al. (2006) [38]	TCPY, 1N	age, BMI, smoking status, time of day that blood was collected, SHBG
Meeker et al. (2007) [39]	TCPY, 1N, 2N	age, BMI, smoking status, race, timing of blood sample by season
Omoike et al. (2015) [40]	TCPY, DEPH, DETP, DEDTP, DMP, DMTP, DMDTP	age, BMI, race/ethnicity, education, serum SHBG, serum cotinine, urinary creatinine
Melgarejo et al. (2015) [37]	DMP, DMTP, DMDTP, DEPH, DETP, DEDTP	urinary creatinine, time of blood drawn

BMI – body mass index.
Other abbreviations as in Table 1.

thereby yet produce adverse effects on the organism [45]. Whereas synthetic pyrethroids may affect estrogen receptors in Sertoli cells and have antiandrogenic properties by antagonizing the androgen receptor [52]. Some pyrethroids demonstrated deleterious effect on testosterone synthesis by the activity of enzyme for testosterone biosynthesis [36]. Finally, potential mechanisms for the association between organophosphate pesticides and reproductive hormones levels remain unclear [39]. The observed associations could be due to: impaired Leydig cell function [53], inhibited secretion of FSH or LH [54], reduced expression of steroidogenic enzymes or proteins [55].

The effect of endocrine-disrupting chemicals mediated through the activation or the inhibition of androgen and estrogen receptors are of primary concern for male reproductive health. Nevertheless, action through the aryl hydrocarbon receptor, which is cytosolic transcription factor with roles in developmental processes, xenobiotic metabolism and immunological responsiveness may also be important [4]. Estrogenic endocrine-disrupting chemicals may also exert more general effects through the induction of oxidative stress [56,57].

Strengths and limitations of the studies

The presented studies had several methodological strengths. The advantage of the studies includes the use of a detailed questionnaire information on demographic, medical, and life style risk factors performed among study participants. The filled-in questionnaires allowed to control the potential confounders in the statistical models. Furthermore, stringent criteria were used for excluding the subjects with drug treatment, occupational chemical exposures and medical history, which are related to reproductive hormones levels. In reviewed studies the sensitive immunoassay methods were used for measuring the levels of reproductive hormones. Additionally, exposure assessment based on biomarkers of exposure was the methodological strengths of the studies.

The limitations of the studies included the use of a single urine/semen sample to assess EDs exposure and a single serum sample to describe reproductive hormones levels. Endocrine disruptors are rapidly metabolized and excreted, therefore metabolite concentrations in urine/semen only reflect exposure status shortly before sampling. In most of the reviewed studies the reproductive hormones were measured in one serum sample. However, requiring multiple blood samples from participants may results in a reduced participation rate and lower statistical power. Another limitation is that subjects were selected mainly from an infertility clinics and the ability to generalize the results to the general population may be limited. The cross-sectional design of the presented studies restricted the ability to make conclusions regarding the relationship between EDs and reproductive hormones and didn't allow to rule out reverse causation, either. Finally, the temporal variability in metabolites of EDs from environmental exposure might have led to a bias during the studies.

CONCLUSIONS

The available epidemiology-related literature on the association of non-persistent endocrine-disrupting chemicals exposure with male reproductive hormones was reviewed. The results of 26 original papers are not consistent and demonstrate variability in study findings. Nonetheless, the results suggest that environmental exposure to non-persistent endocrine-disrupting chemicals may affect male reproductive hormones levels.

The widespread distribution of environmental chemicals and the detection of these substances within human body indicate that humans are continually exposed to a variety of endocrine-disrupting chemicals through multiple sources. Data is alarming and although the association between EDs exposure and human disorders is difficult to establish, there is growing evidence to suggest a potential interference. In future more related studies should be conducted to confirm the associations.

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