Environmental Research 142 (2015) 486–494

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Human urinary/seminal phthalates or their metabolite levels and semen quality: A meta-analysis

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ARTICLE INFO

Article history:
Received 26 October 2014
Received in revised form
13 July 2015
Accepted 13 July 2015

Keywords:
Phthalates
Urinary metabolite levels
Semen quality
Meta-analysis
Epidemiology

ABSTRACT

Health concerns surrounding human exposure to phthalates include diminished semen quality. Epidemiological findings remain inconsistent. We have performed a quality appraisal and meta-analysis to quantitatively summarize evidence for associations between phthalate exposures and human semen quality. Pubmed and Web of Science were searched for pertinent studies through October 2014. Cited references were reviewed to identify secondary studies. Studies that reported quantitative estimates of the association between phthalates or their metabolite levels in humans and semen quality were eligible. Random effects models were used to calculate pooled effects estimates. Overall, 20 studies met our inclusion criteria. Subsequently, 14 studies were included in the meta-analysis. Urinary monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP) were associated with reduced sperm concentration (MBP [7.4–25.3 μg/L], pooled odds ratio [OR]=2.60, 95% confidence interval [CI]=1.32–5.15; MBzP [14.0–540.2 μg/L], pooled OR=2.23, 95% CI=1.16–4.30). Both MBP (24.6–14,459.0 μg/L) and MEHP (3.1–208.1 μg/L) were inversely associated with straight line velocity (VSL; MBP, pooled β=−2.51, 95% CI=−4.44, −0.59; MEHP, pooled β=−1.06, 95% CI=−1.99, −0.12). An IQR increase in MBzP and MEP levels (MBzP, IQR=11.35 μg/L; MEP, IQR=449.4 μg/L) was associated with an increase in comet extent (CE; MBzP, pooled β=3.57, 95% CI=0.89–6.25; MEP, pooled β=4.22, 95% CI=1.66–6.77). No associations were observed between monomethyl phthalate and any semen parameters. Our meta-analysis strengthens the evidence that specific phthalates or their metabolite levels may affect semen quality.

1. Introduction

Exposure to specific phthalates might cause adverse changes in the male reproductive system (Burton, 2013; Toppari et al., 1996). Epidemiologic investigations have reported associations between phthalate exposures at environmental levels and impaired testicular function, such as aberrant genital development in neonates, abnormal sex hormone function, and an impairment of semen quality in adults (Huang et al., 2012; Meeker et al., 2009). Animal studies have confirmed that fetal testis development is exceptionally sensitive and that exposure to certain phthalates in utero, including the phthalates: di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and butylbenzyl phthalate (BBzP), could lead to reproductive tract malformations in rats and decreased semen quality in their offspring (Kay et al., 2014; Foster et al., 2001). However, current studies have not clearly revealed the mode of action and molecular mechanisms for phthalate effects on

Abbreviations: BBzP, butylbenzyl phthalate; CE, Comet extent; CI, confidence interval; CMR, carcinogenic, mutagenic and toxic to reproduction; DBP, dibutyl phthalate; DEP, diethyl phthalate; DEHP, di (2-ethylhexyl) phthalate; DIDP, diisodecyl phthalate; DINP, diisononyl phthalate; DnOP, di-n-octyl phthalate; DnPP, di-n-pentyl phthalate; EU, the European Union; HMW, high molecular weight; LIN, linearity; LMW, low molecular weight; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono [2-ethyl-5-hydroxyhexyl] phthalate; MEOHP, mono [2-ethyl-5-oxohexyl] phthalate; MMP, monomethyl phthalate; OR, odds ratio; PVC, polyvinyl chloride; Tail%, percent of DNA in tail; ROS, reactive oxygen species; TDM, tail distributed moment; TRI, toxics release inventory; U.S.EPA, United States Environmental Protection Agency; VSL, straight line velocity; VCL, curvilinear velocity; WHO, World Health Organization

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http://dx.doi.org/10.1016/j.envres.2015.07.008
0013-9351/

semen quality (Kay et al., 2014). Some studies found that decreased testosterone biosynthesis of Leydig cells probably resulted from changes in reactive oxygen species (ROS), expression of steroidogenic proteins or growth factor, along with germ cell apoptosis are thought to be implicated in the phthalate-induced testicular toxicity though the mode of action have not been clearly elucidated (Chauvigne et al., 2011; Lin et al., 2008, 2010; Zhao et al., 2012). Given the public health concern over these compounds, the European Union (EU) has banned DEHP, DBP, and BBzP in toys, food wrappings, and cosmetics; the United States Environmental Protection Agency (U.S.EPA) has placed DEHP, DBP, BBzP, di-n-pentyl phthalate (DnPP), di-n-octyl phthalate (DnOP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP) on the Toxics Release Inventory (TRI) (U.S. EPA, 1996; CPSC, 2010; National Research Council, 2008).

Phthalates, primarily used as plasticizers, are classified into two groups based on carbon molecular number in their alcohol backbone, i.e., low molecular weight phthalates (LMW phthalates; 3–6 Carbons; DEHP, DBP, BBzP, etc.) and high molecular weight phthalates (HMW phthalates; 7–13 Carbons; DIDP, DINP, etc.) (ECPI, 2014). LMW phthalates, widely used in medical devices and general purpose polyvinyl chloride (PVC), are classified as Category 1B reproductive agents and CMR (carcinogenic, mutagenic and toxic to reproduction) under the EU risk assessment regulation (ATSDR, 1995, 2002). HMW phthalates which have more durability and are commonly used in PVC-related products (flooring and wall-coverings, automotive applications, and wire and cables), are considered non-CMR and promoted in the market as safe alternatives to LMW phthalates (ECPI, 2014). As they are not chemically bound to products and are therefore constantly released into the environment, humans are exposed to phthalates via ingestion, inhalation, and dermal contact (Guo et al., 2011). Phthalates are extensively metabolized in the body and metabolites are excreted in urine. The monoester metabolites or their oxidative metabolites serve as good biomarkers of phthalate exposure (Frederiksen et al., 2013; Guo et al., 2011; Hauser et al., 2004; Martino-Andrade and Chahoud, 2010; Wu et al., 2013). These metabolite levels only represent very recent exposure.

Many epidemiological studies have been conducted on the association between phthalates or their metabolite levels in humans and semen quality in the last decade. Quite a number of them demonstrate that some LMW phthalates are associated with the adverse effects on human sperm concentration and motility (Hauser et al., 2006; Kranvogl et al., 2014; Pant et al., 2014), but the existing studies remain inconsistent (Herr et al., 2009; Jonsson et al., 2005). Although several articles have reviewed epidemiological research into the detrimental effects on human semen of specific phthalate exposure (Huang et al., 2012; Meeker et al., 2009; Swan, 2008), the epidemiologic evidence on the association between phthalates exposure and semen quality has never undergone a formal quality appraisal or been quantitatively summarized. Therefore, the purpose of the present study is to analyze and confirm the effects of phthalate exposure on human semen quality by a quality appraisal and a meta-analysis based on human epidemiological studies. We first conducted an appraisal to evaluate the quality of relevant studies. Subsequently, a meta-analysis was performed to quantitatively analyze the association of phthalates or metabolite levels in humans and measures of semen quality.

2. Materials and methods

2.1. Study selection

Two independent investigators searched Pubmed (from January 1, 1966, to October 20, 2014) and Web of Science (from January 1, 1898, to October 20, 2014) using combinations of the following words: phthalate, phthalates, phthalic acid, humans, males, men, semen, sperm, sperm production parameters (semen volume, total sperm count, sperm concentration), sperm quality parameters (sperm motility, sperm morphology, sperm motion, straight line velocity [VSL], curvilinear velocity [VCL], linearity [LIN]), and sperm DNA damage parameters (comet assay, comet extent [CE], percent of DNA in tail [Tail%], tail distributed moment [TDM]). We reviewed the cited references to identify secondary studies.

2.2. Inclusion criteria

Studies were included if they (1) evaluated environmental exposure rather than occupational exposure of humans to phthalates; (2) provided concentrations of phthalates or their metabolites in human biological specimens (urine, semen, serum, etc.); and (3) had quantitative estimates of the association between phthalates exposure, e.g., phthalates or their metabolite levels, and human semen quality. Studies lacking original data or ones not published as full reports were excluded.

2.3. Data abstraction

For each publication, we extracted publication year, original country, study design, characteristics of subjects, sample size, the specific phthalates or metabolites analyzed, semen indices, main results, detection limit, statistical methods, and potential confounders. We also checked whether the identified studies conducted exposure-response analysis.

2.4. Quality appraisal

To evaluate the consistency of the association between phthalates or metabolite levels in humans and semen quality, a formal quality evaluation of the published studies using a systematic and standardized approach was conducted. We added a point for each methodological strength and subtracted a point for each evident weakness (Goodman et al., 2004; Salay and Garabrant, 2009). Discrepancies of all uncertain issues were resolved by discussion, consensus, and arbitration by two epidemiological experts. The quality scoring was performed according to the following criteria (Elwood, 1998):

1. Study design – sampling system: survey=−1; cohort and case control=0.
2. Study design – time relationship: cross sectional=−1; retrospective, prospective=0.
3. Study population: subfertile couples=0; general population=1.
4. Information about the subject selection process: limited=−1; sufficient=0.
5. Measurement of phthalate concentrations: non-specific=0; specific parent compound or metabolite=1.
6. Intra-individual exposure variability: no=0; yes=1.
7. Detection limit for phthalate determination: approx. 15 ng/mL or higher=−1; approx. 1 ng/mL=0; approx. 0.4 ng/mL or lower=1.
8. Sample size: $<100=-1$; 100–300=0; $>300=1$.
9. Age adjustment: no=−1; yes=0.
10. Abstinence time adjustment: no=−1; yes=0.
11. Smoking adjustment: no=−1; yes=0.
12. Alcohol adjustment: no=−1; yes=0.
13. Confounding by other chemicals: likely=−1; possible but not clearly evident=0; unlikely/addressed=1.