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Phthalate exposure, even below US EPA reference doses, was associated with semen quality and reproductive hormones: Prospective MARHCS study in general population

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ABSTRACT

Background: Environment-Protection-Agency Reference Doses (EPA RfDs) for phthalate intakes are based on limited evidence, especially regarding low-dose male-reproductive toxicity. This study investigates the association between phthalate exposure and semen parameters and reproductive hormones in a general population with low phthalate exposure compared to the EPA RfDs.

Methods: The MARHCS (Male-Reproductive-Health-in-Chongqing-College-Students) cohort recruited 796 male students, who experienced a relocation of campuses and shifting environmental exposure. Urine, semen and blood before and after the relocation was collected and investigated for: (1) the associations between 13 urinary phthalate metabolites and 11 semen/hormone outcomes (five semen parameters including semen volume, sperm concentration, total sperm number, progressive motility, normal morphology) and six serum reproductive hormones including estradiol, follicle-stimulating hormone, luteinizing hormone, prolactin, progesterone, testosterone; (2) re-analysis of the metabolite-outcome associations in the subjects with estimated phthalate intakes below the RfDs; (3) a change in phthalate metabolites and change in semen/hormone outcomes after the relocation; (4) the association between these changes.

Results: (1) All but two semen/hormone outcomes were associated with at least one phthalate metabolite, e.g., each quartile monoethyl phthalate was associated with a 5.3%, 5.7% and 2.6% decrease of sperm concentration, total sperm number and progressive motility respectively. (2) In the subjects with phthalate intakes below the RfDs, these metabolite-outcome associations remained significant. (3) All metabolites except mono(2-ethylhexyl) phthalate declined after relocation ($P < 0.001$ respectively); at the same time, semen volume, normal morphology, estradiol and luteinizing hormone increased (by 5.9%, 25.0%, 34.2% and 10.0%) and testosterone decreased (by 7.0%). (4) The changes in semen volume, normal morphology, estradiol and testosterone, but not the change in luteinizing hormone after relocation, were associated with the changes in the phthalate metabolites.

Conclusions: Phthalate exposure is associated with interrupted semen quality and reproductive hormones in the human population even with a dose given below the RfDs. These effects, however, may only partially revert back when exposure decreases, thus emphasizing the urgency of stricter phthalate administration.

Abbreviations: BBzP, butyl benzyl phthalate; BMI, body mass index; CI, confidential interval; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiNP, di-*n*-nonyl phthalate; DnBP, di-*n*-butyl phthalate; EPA, Environment Protection Agency; LC-MS/MS, chromatography tandem mass spectrometry; LODs, limits of detection; MARHCS, Male Reproductive Health in Chongqing College Students; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MCHP, monocyclohexyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-81 5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono (2-isobutyl) phthalate; MiNP, monoisononyl phthalate; MMP, mono-methyl phthalate; MnBP, mono-*n*-butylphthalate; MnOP, mono-*n*-octyl phthalate; RfDs, reference doses; ΣDEHPm, DEHP metabolites; ΣHMWP, high-molecular-weight phthalates; ΣLMWP, low-molecular-weight phthalates

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1. Introduction

Phthalates are globally produced at the huge amount of nearly 11 billion pounds each year and are regularly added in shampoos, toys, building supplies and medical devices (CDC, 2015; LCSP, 2011), leading to widespread distribution and potential contamination. The chemicals are detected in water, soil and indoor dust worldwide and their metabolites are detected in the blood, urine and semen of many populations. Phthalates, with two ester groups on a benzene ring, can interact with various receptors in the human body (Lovekamp-Swan et al., 2003; Wang et al., 2016). This raises a global concern about the potential hazardous effects of phthalates on human health (Heudorf et al., 2007).

To address this risk, the U.S. Environment Protection Agency (EPA) has set reference doses (RfDs) for four phthalates — diethyl phthalate (DEP), di-*n*-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP) (EPA, 1988, 2002a, 2002b, 2003). RfDs are an estimate of the daily exposure that is likely to have no appreciable risk of deleterious effects during a lifetime in the human population, i.e., doses less than the RfD are thus anticipated as not being of regulatory concern (Barnes and Dourson, 1988). To be noted, since the EPA RfDs are also cited in other regions such as China and European Union, their influence go far beyond the health of American population (Guo et al., 2011a; Koch et al., 2003; Yang et al., 2013; Zhuang et al., 2014). However, the phthalate RfDs were based on inadequate studies and with little consideration of male reproductive toxicity. Thus, the EPA ranked their confidence in the RfDs for phthalates as low (for DEP, DnBP and BBzP) to medium (for DEHP).

Recently, several studies have reported that phthalates induced testis and spermatozoa injuries and interrupted reproductive hormones in animals (Aly et al., 2015; Buteau-Lozano et al., 2008). However, the studies in human beings have shown only controversial results as summarized in one review (Kay et al., 2014). All of these epidemiological studies were case-control or cross-sectional, inherently having weak power to infer any causation relationship between phthalate exposure and semen/hormone outcomes. Most of the studies were also performed in infertility clinics patients whose reproductive systems were already more vulnerable. Hence it is doubtful whether the results derived from these special subjects can be logically generalized to the general population. Moreover, these researchers usually measured the metabolites of phthalates in urine as exposure biomarkers, but they rarely estimated the phthalate intakes based on the metabolites. According to our knowledge, estimation of phthalate intake was only performed for one phthalate (DEHP) in one study, in which the DEHP exposure substantially exceeded the EPA RfD in some of the occupationally-exposed subjects (Pan et al., 2006). So it is impossible to know whether the EPA RfDs for phthalate were safe enough for male reproductive health using these studies. These issues indeed emphasize the necessity to prospectively investigate the relationship of phthalate exposure and semen/hormone outcomes in a general population receiving phthalate intakes lower than the EPA RfDs.

To address this gap, we report here a prospective investigation of semen/hormone outcomes in a cohort (Male Reproductive Health in Chongqing College Students, MARHCS) from the general population, and analyze the association of that with phthalate exposure. Especially, we also estimate the phthalate intakes for the subjects and analyze these associations in the subjects receiving phthalate intakes lower than the EPA RfDs.

2. Materials and methods

2.1. Study design

We performed a prospective investigation of phthalate exposure and related semen/hormone outcomes in the MARHCS cohort with 796 healthy males, 656 of whom received a second investigation when a substantial change in environmental exposure occurred between the two separate investigations. We estimated the phthalate intakes of these subjects in comparison to the EPA RfDs, and analyzed the relation between phthalates and semen/hormone outcomes to respond to our four research questions. These questions are: (1) Are the urinary phthalate metabolites in a subject associated with his semen/hormone outcomes? (2) After a change in environmental exposure, are there also changes of semen/hormone outcomes in that population? (3) Do the changes in semen/hormone outcomes in a subject correlate with the changes of that subject's phthalate exposure? (4) More importantly, do these associations also exist in males whose phthalate exposure was below the RfDs? This study was approved by the Ethics Committee of Third Military Medical University, and written informed consent was gained from all the participants.

2.2. Participant interviews

To investigate the effect of environmental pollutants on male reproductive health, we designed the MARHCS study based on a common phenomenon in China—the relocation of students to different university campuses. Chinese universities are facing shortages of space due to an increasing number of students. The Chongqing government thus assigned a region for local universities to build an additional campus far from the original one. Most students in these universities thus experience relocation when achieving higher grades. They then live in the new environment for the remainder of their college career. These two regions have distinct water supplies (Yangtze River before relocation and Jialing River after relocation). In wet seasons the phthalate concentration substantially increases in both rivers, and the contamination in the Yangtze River, which could be attributed to the industrial emissions, is even higher (Du, 2012; Luo et al., 2009). As water is a predominant sources of phthalate intakes for the Chinese (Ji et al., 2014), the phthalate exposures were expected to be different for the two distinct regions. We, therefore, established the MARHCS cohort in those students and measured their exposure and semen/hormone outcomes before and after the relocation, as described in details in previous publication (Yang et al., 2015).

In brief, after excluding those having urogenital disease history and those failing to supply semen samples at appropriate abstinence period (2–7 days), we recruited 796 out of 872 Chinese male students living in the University Town of Chongqing (the new campus) in June of 2013 (as a baseline) while they stayed at the old campus. Urine, semen and peripheral blood were collected to measure phthalate metabolites, semen quality and reproductive hormones. The subjects completed a composite questionnaire on specific socio-psycho-behavioral factors, including tobacco smoking and alcohol drinking. Body weight and height were measured to evaluate their body mass index (BMI). One month later, the campus relocation occurred. The students moved to the old campus and stayed there until graduation. In June 2014, 656 (82.4%) of these subjects were successfully followed up and bio-samples were collected from them again for a precise comparison to the earlier baseline.

2.3. Measurement of semen/hormones outcomes

We measured five semen parameters (semen volume, sperm concentration, total sperm number, progressive motility, and normal morphology) following the World-Health-Organization-recommended methodology (WHO, 2010). We also measured six serum reproductive hormones (estradiol, follicle-stimulating hormone, luteinizing hormone, prolactin, progesterone, and testosterone) using the Unicel Dxi 800 Immunology Analyzer (Beckman Coulter Inc., Brea, CA). Details are available in Supplementary method 1 and in previous publication (Chen et al., 2016). The analysts had no idea of the individual identity of any of the subjects.

2.4. Measurement of phthalate metabolites

We supplied a glass tube for each subject to use to collect 20 mL of urine sample which was then stored at −20 °C until the analysis. We established a liquid chromatography tandem mass spectrometry (LC-MS/MS) method to measure 13 phthalate metabolites: mono-methyl

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