**Table 2. Study Characteristics examining fecundity and BFRs (N=5)**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, and publication** | **Country** | **Sample** | **Total sample size (N)** | **Age range of study population (years)** | **Chemical type/Health effects** | **Methods of assessing fecundity or time to pregnancy** | **Study results** | **Adjustment for confounders** | **Exposure assessment matrix/analysis** | **Chemical concentration** | **Study type (analytical method)** |
| **Female (N=3)** | | | | | | | | | | | |
| Harley et al. 2010 | USA | Pregnant women enrolling in the center for the health assessment of Mothers and Children of Salinas | 223 | 21.5-27.3 years | PBDEs/ Fecundability | In person interview | Association with longer TTP and increasing levels of BDEs 47, 99, 100, 153, and sumPBDEs,  Reduce fORs for BDE-100, and the sum of the PBDEs | Paternal [1], smoking, work in agriculture, years of residence in US, history of gynecologic conditions, hormonal contraceptive use in the year before conception, breast-feeding in the 2 months before conception, caffeine consumption in the 3 months before pregnancy | Blood/GC, GC-IDHRMS | Geometric mean (ng/g lipid)  BDE-47  14.9 (12.9-17.2)  BDE-99 4.4  (3.9-5.1)  BDE-100  2.8 (2.4-3.2)  BDE-153  2.5 (2.2-2.8) | Retrospective cohort |
| Chevrier et al. 2013 | Canada | Pregnant women in three districts of Brittany | 396 among 2956 eligible women | 25 -  ≥35 | PBDE209/  fecundability | Questionnaire, clinical check up | No associations between PBDE209 and fecundability | Maternal [1] (continuous), [2] (<18.5 kg/m², 18.5–24.9 kg/m², ≥25 kg/m²), smoking status when first attempting the pregnancy (smoker, nonsmoker), and oral contraceptives used before attempting pregnancy | Cord blood  /GC-MS | PBDE209  <LOD (<0.050 μg/L)b  ≥LOD (≥0.050 μg/L) | Retrospective Cohort |
| Gao et al. 2016 | China | Pregnant women living in Shandong province (2010-2017) | 207 | ≥ 18 | PBDE/Time to pregnancy | Interview with questionnaires, medical records | Association between BDE 28 and longer TTP (adjusted OR = 1.34, 95%CIs = 1.03 – 1.76).  PBDE congeners and time to pregnancy  BDE 47  (adjusted OR = 1.03, 95%CIs = 0.95 – 1.12).  BDE 85 (adjusted OR = 0.33, 95%CIs = 0.07 – 1.57).  BDE 99 (adjusted OR = 1.01, 95%CIs = 0.09– 1.12).  BDE 100 (adjusted OR = 0.60, 95%CIs = 0.31 – 1.12).  BDE 153 (adjusted OR = 0.91, 95%CIs = 0.66– 1.25).  BDE 154  (adjusted OR = 0.28, 95%CIs = 0.04– 1.83).  BDE 183  (adjusted OR = 0.90, 95%CIs = 0.60– 1.34).  Sum of PBDEs (28-183) (adjusted OR = 1.01, 95%CIs = 0.97 – 1.04). | Paternal age, maternal education level, parental occupations, mother passive smoke history (during pregnancy), father smoke history (during pregnancy), father alcohol consumption (during pregnancy), mother’s BMI, parity and family income | Blood/ GC-MS | Median level (ng/g lipid)  BDE-28 1.99  BDE-47 2.08  BDE-85 0.90  BDE-99 3.45 BDE-100 1.95 BDE-153 4.67  BDE-154 0.40 BDE-183 1.89  Total PBDEs 16.27 | Prospective Cohort (Cross-sectional approach) |
| **Male (N=1)** | | | | | | | | | | | |
| Den Hond et al. 2015 | Belgium | Males from four academic fertility clinics in Belgium | 120 (80 controls, 40 cases) 163 men eligibility | Age <50 years | PBDEs, HBCD/ subfertility | Self-assessment questionnaires | Association between BDE 209 in serum and increased risk of subfertility (adjusted OR = 7.22, 95%CIs = 1.03 – 50.6)  No significant OR observed for other PBDEs, or HBCD | Age, BMI, smoking, Environmental tobacco Smoke (ETS) exposure, and educational level | Serum/ GC-MS | Geometric means of (25th percentile, 75th percentile) BDE-47 1.5-4.0 (ng/L)  BDE-153 3.0-5.0  BDE-99 <LOQvs≥LOQ BDE-100 <LOQvs≥LOQ BDE-154 <LOQvs≥LOQ BDE-209 <LOQvs≥LOQ  HBCD <LOQvs≥LOQ | Case-control study |
| **Both gender (N=1)** | | | | | | | | | | | |
| Buck Louis et al. 2013 | USA | Couples discontinuing contraception for the pregnant purpose in the Life Study  (2005-2007) | 501 | Female -Female 40  Male Not Given18 Male ≥ 18 | PBDE 183/  Fecundity | Completion of daily journals, and clinical pregnancy test | Association between PBDE 183 and reduction in fecundability | Time off contraception before enrollment and sum of all other chemicals in the class of compounds, [1] (categorized), [2] (continuous), continue (continuous), lipids (continuous) except in PFCs models, and site (Michigan/Texas) | Blood/IDHRMS for PBDEs | GMs (95%CI)  Males PBDE 183 Achieved pregnancy (n=347) 0.002 (0.002-0.002) when p<0.01 Withdrew/Not pregnant (n=154) 0.003(0.002-0.003) | Prospective cohort |

**Abbreviation:**

Body mass index (BMI)

**Adjustment for confounders:**

[1] Age, [2] BMI

**Exposure assessment:**

Gas chromatograph mass spectrometer (GC–MS), Gas chromatograph isotope dilution high-resolution mass spectrometry (GC-IDHRMS), Liquid chromatography (LC), Liquid chromatography tandem mass spectrometry (LC-TMS), Gas chromatograph high resolution mass spectrometer (GC-HRMS), Isotope dilution tandem mass (IDTMS), Liquid chromatograph mass spectrometry, mass spectrometry (LC-MS/MS), Isotope dilution high-resolution mass spectrometry (IDHRMS)

**Chemical concentration:**

Mean concentration of the selected POPs were reported, or median levels were reported if there is no mean.

**Study design:**

Harley et al. (2010) used a cross sectional investigation using a cohort of adult males

**Table 3. Study characteristics of Phthalates and time to pregnancy (N=10)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, and publication** | **Country** | **Sample/ study period** | **Total sample size (N)** | **Age range of study population (years)** | **Chemical type/Health effects** | **Methods of assessing fecundity and time to pregnancy** | **Study results** | **Adjustment for confounders** | **Exposure assessment matrix/analysis** | **Chemical concentration** | **Study type (analytical method)** |
| Modigh et al., 2002 | Sweden | Men working in three plants with DEHP exposure 1997-1998 | 193 fathers of the 326 pregnancies | <29-≥34 | Phthalate-DHEP/ time to pregnancy | Postal questionnaires, telephone interview | No association between paternal DEHP exposure and a prolonged time to pregnancy. Fecundability.  Low exposure and time to pregnancy: (FR=1.07: 95%CI 0.84-1.35), high exposure and time to pregnancy: (FR=0.97: 95%CI 0.70-1.33) | Father’s age, mother’s age, and length of recall. | Air samples from three plants/High-performance liquid chromatography and ultraviolet detection at 224 nanometers | DEHP: Ranged from <0.1 to 2.1 mg/m3  Mean <0.5mg/m3 | Retrospective Cohort Study |
| Burdorf et al., 2011 | Netherlands | The generation R study, 2002-2006 | 3 719 for time to pregnancy among 6 302 | 15.8-46.4 (mean: 30.2) | Phthalates/time to pregnancy | Questionnaires, physical exam, interviews, biological samples at different stages during pregnancy. | Association between job exposure assessment based maternal occupational exposure to phthalates and prolonged TTP (OR=2.16: 95%CI 1.01-4.57) | Age, height, weight, education, minority, parity, smoking and alcohol use | Job exposure assessment ,self-reported exposure | NG | Prospective Cohort Study |
| Buck Louis et al., 2014 | USA | LIFE study 2005-2009 | 501 couples | Women 18-44 (mean; 30.0)  Men ≥18 (mean; 31.8) | Phthalates/ Couple fecundity | Completion of daily journals, and clinical pregnancy test | Association between urinary concentrations of some phthalates and a longer TTP in men.  Monomethyl and a longer TTP (FOR=0.80: 95%CI 0.70-0.93)  Mono-n-butyl and a longer TTP (FOR=0.82: 95%CI 0.70-0.97)  Monobenzyl phthalates and a longer TTP (FOR=0.77: 95%CI 0.65-0.92).  No association between women and urinary exposure of phthalates. | Age, BMI, cotinine, creatinine, and research site while accounting for time off contraception. | Urine/ high-performance liquid chromatography with electrospray triple-quadrupole mass spectrometer (HPLC-MS/MS). | Female and male partner | Prospective Cohort Study |
| Buck Louis et al., 2018 | USA | LIFE study 2005-2009 | 339 male partners | Males participant by couple’s pregnancy status  Pregnant (n=246)  Mean: 31.4  Not pregnant (n=93) Mean: 32.2 | Phthalates/ Couple fecundity | Completion of daily journals, and clinical pregnancy test | No relationship found with couple fecundability and phthalates | Male model: male age, male BMI, male serum cotinine, and research site (Michigan/Texas)  Couple model: female age, difference in couple’s ages, both partner’s BMI, both partners’s serum cotinine concentrations, and research site (Michigan/Texas) | Seminal plasma, Urine/ high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), gas chromatography-mass spectrometry (GC-MS) | **Phthalates metabolites**  Median in semen ranged <below limit of detection – 10.61ng/ml  **Phthalates dieters**  Median in semen ranged 0.00-4.20 ng/ml | Prospective Cohort Study |
| Den Hond et al., (2015) | Belgium | Males from four academic fertility clinics in Belgium | 120 (80 controls, 40 cases) from 163 men eligibility | Age <50 years | Phthalates/ Male subfertility | Self-assessment questionnaires | No significant OR between urinary phthalates exposure and subfertility  MEPH 1.5–5.8 (OR=0.94: 95%CI 0.56-1.58)  5OH-MEHP  (μg/L) 5.8–19.0 (OR=0.84: 95%CI 0.42-1.67)  5oxo-MEHP (μg/L) 4.1–14.0 (OR=0.83: 95%CI 0.38-1.80)  MEP (μg/L) 19–106 (OR=0.80: 95%CI 0.40-1.59)  MiBP (μg/L) 29–109 (OR=1.09: 95%CI 0.58-2.05)  MnBP (μg/L) 12.0–38.0  (OR=1.27: 95%CI 0.64-2.51)  MBzP (μg/L) 2.1–9.5 (OR=1.03: 95%CI 0.57-1.87) | Age, BMI, smoking, ets exposure and education level | Urine/ UPLC-MS | Geometric means of (25th percentile, 75th percentile) (μg/L)  MEPH 1.5–5.8  5OH-MEHP  (μg/L) 5.8–19.0  5oxo-MEHP (μg/L) 4.1–14.0  MEP (μg/L) 19–106  MiBP (μg/L) 29–109  MnBP (μg/L) 12.0–38.0  MBzP (μg/L) 2.1–9.5 | Case-Control Study |
| Specht et al.,. 2015 | Three countries: Greenland, Poland, and Ukraine | INUENDO cohort (2002-2004) | 1,239 (938 pregnant (women/ 401 male spouses) | Mean age (years)  Greenland: women (26), men (31)  Poland: women (28), men (31)  Ukraine:  Women (23), men (27) | Phthalates: DEHP metabolites, DiNP metabolites/ TTP | Face to face interview with a structured interview questions | Shorter TTP in women with high levels of DEHP (FR=1.14, 95%CI: 1.0-1.30), No relations found between DiNP in women. Longer TTP in first time pregnancy women from Greenland with high serum DiNP. | For female: Maternal age, smoking in pregnancy, frequency of sexual, parity status, maternal BMI, gestational week of interview, blood sampling and frequency of sexual intercourse.  For male: paternal age, paternal BMI and maternal age. | Serum/ Liquid chromatography-tandem mass spectrometry system (LC-MS/MS) | Pooled median concentration  **Women (pM)**  Proxy-MEHP: 4.98  Proxy-MiNP: 1.40  Men  Proxy-MEHP: 7.97  Proxy-MiNP: 2.63 | Retrospective Cohort (Cross-Sectional approach) |
| Snijder et al., 2011 | Netherlands | Generation R study | 2, 774 women  2, 728 men | Age at start TTP  period, mean (SD)  Maternal age: 30.57 (4.13) Paternal age: 32.67 (5.04) | Phthalates/ time to pregnancy | Self-report TTP | Association between maternal occupational exposed to phthalate and prolonged TTP (FR=1.14, 95%CI: 1.0-1.30) | Age, height, weight, education, country of origin, parity,  smoking habits, and alcohol use | Job exposure assessment | NG | Prospective Cohort Study (Cross – Sectional approach) |
| Velez et al., 2015 | Canada | MIREC Study (2008-2011) | 1, 597 | Mean age (years)  Women (32.85), men (34.74) | Phthalates/TTP | A detailed questionnaires (demographics, present medical and obstetric history and lifestyle characteristics) | Suggestive evidence of shorter TTP in participants with phthalates exposure | Specific gravity, maternal age, maternal smoking, education, income, BMI. | Urine/ Liquid chromatography-tandem mass spectrometry system (LC-MS/MS) with ultra-performance liquid chromatography couples with tandem mass spectrometry (UPLC-MS/MS) | **Phthalate metabolites (n ¼ 1,597, ng/mL)**  **Low molecular weight**  Mono-n-butyl phthalate (MnBP) : 12  Mono-ethyl phthalate (MEP): 28  Mono-benzyl phthalate (MBzP): 5  Mono-methyl phthalate (MMP);2.5  **Intermediate molecular weight**  Mono-cyclo-hexyl phthalate (MCHP): 0.1  **High molecular weight**  Mono-isononyl phthalate (MiNP): 0.2  Mono-n-octyl phthalate (MnOP)  : 0.35  Mono-(3-carboxypropyl) phthalate (MCPP): 0.93  Mono-(2-ethylhexyl) phthalate (MEHP)  : 2.2  Mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP); 6.5  Mono--(2-ethylhexyl) (MEHH): 9.4 | Retrospective Cohort Study |
| Jukic et al., 2016 | USA | The North Carolina Early Pregnancy Study (EPS) (1982-1986) | 221 | 26-31 years of age | Phthalates/Fecundability | In person interview, clinical pregnancy | No association between phthalate exposure and TTP. | Age, age at menarche, current smoking, alcohol intake, BMI, caffeine consumption, and education. | Urine/ high-performance liquid chromatography-isotope dilution tandem mass spectrometry (HPLC-IDTMS) | (Ng/mL)  MnBP: 80.0  MEP: 134  MBzP: 39.5  MEHP: 6.6  MEHHP: 50.4  MEOHP: 30.3  MECPP: 66.0  MCNP: 3.4  MCOP: 3.3  MCPP: 13.5  MiBP: 3.1 | Prospective Cohort Study |
| Tomsen et al., 2017 | Denmark | Danish cohort study (1992-1994) | 229 women | 20-35 | Phthalates/TTP | Self-reported with Questionnaires | Association between female exposure to MEP and a longer TTP (FR=0.79: 95%CI 0.63-0.99)  No association between MBP (FR=1.03: 95%CI 0.76-1.39)  , MBzP (FR=0.88: 95%CI 0.64-1.19)  , or MBHP (FR=0.99: 95%CI 0.72-1.35)  and a longer TTP. | Age, BMI, and the time-varying variables alcohol and smoking. | Urine/ liquid chromatography tandem-mass spectrometry (LC-MS/MS) | Median concentrations of both pregnancy and no pregnancy phthalate metabolites (ng/ml)  MEP: 225  MBP: 178  MBzP: 14.9  MEHP: 11.2 | Prospective Cohort Study |

**Sample:** Longitudinal Investigation of Fertility and the Environment (LIFE) Study, (INUENDO). Maternal-Infant Research on Environmental Chemicals (MIREC)

**Exposure assessment matrix/analysis**: high-performance liquid chromatography with electrospray triple-quadrupole mass spectrometer (HPLC-MS/MS), liquid chromatography tandem-mass spectrometry (LC-MS/MS), gas chromatography high-resolution mass spectrometry (GC-HRMS), ultra-performance liquid chromatography couples with tandem mass spectrometry (UPLC-MS/MS), high-performance liquid chromatography-isotope dilution tandem mass spectrometry (HPLC-IDTMS), high-performance liquid chromatography with electrospray triple-quadrupole mass spectrometer (HPLC-TQ/MS).

**Study results:** MEP, monoethyl phthalate; MBP, monobutyl phthalate; MBzP, monobenzyl phthal-ate; MEHP, monoethylhexyl phthalate; FR, Fecundability ratio.