**Paternal and Maternal Phthalate Exposure and Birth Weight**

**Supplementary Appendix**

**Table 1A**. Pearson correlations coefficients of loge phthalate metabolite concentrations across windows of exposure.

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| --- | --- |
| **Phthalate Metabolite** | **Windows of Exposure** |
|  | Paternal PreconceptionxMaternal Preconception | Maternal PreconceptionxMaternal Prenatal | Paternal PreconceptionxMaternal Prenatal |
|  | Pearson’s *r* | Pearson’s *r* | Pearson’s *r* |
| ∑DEHP1 | 0.55 | 0.58 | 0.56 |
| MEHP | 0.40 | 0.47 | 0.38 |
| MEHHP | 0.51 | 0.55 | 0.51 |
| MEOHP | 0.50 | 0.56 | 0.50 |
| MECPP | 0.56 | 0.60 | 0.57 |
| MEP | 0.30 | 0.61 | 0.09 |
| MBP | 0.43 | 0.52 | 0.44 |
| MiBP | 0.51 | 0.54 | 0.48 |
| MBzP | 0.41 | 0.55 | 0.37 |
| MCPP | 0.31 | 0.33 | 0.24 |
| MCOP | 0.54 | 0.51 | 0.46 |
| MCNP | 0.43 | 0.38 | 0.32 |
| ∑AAPhthalates2 | 0.50 | 0.58 | 0.48 |

Abbreviations: DEHP: di(2-ethylhexyl) phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: mono(2-ethyl-5-oxohexyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MiBP: mono-isobutyl phthalate; MBzP: monobenzyl phthalate;MCPP: mono(3-carboxypropyl) phthalate; MCOP: monocarboxyisooctyl phthalate; MCNP: monocarboxyisononyl phthalate.

1 ∑DEHP: is the weighted molar sum of DEHP metabolites MEHP (molecular weight=272), MEHHP (molecular weight=294), MEOHP (molecular weight=292) and MECPP (molecular weight=308) concentrations expressed in µmol/L. We multiplied the molar sum by the molecular weight of MECPP (308 g/mol) to express ∑DEHP as ng/ml.

2 ∑AAPhthalates: was calculated by multiplying the specific gravity adjusted concentration of each of these seven individual phthalate metabolites by their anti-androgenic potency and summing the weighted concentrations: ΣPhthalates = MBP + (0.24\*MiBP) + (0.26\*MBzP) + (0.61\*MEHP) + (0.61\*MEHHP)+(0.61\*MEOHP)+ (0.61\*MECPP).

**Table 2A**. Sensitivity analysesfor paternal ∑DEHP metabolites and anti-androgenic phthalate metabolites (∑AAPhthalates): all IVF-conceived singletons, stratified by infant sex, and excluding preterm births.1

|  |  |  |  |
| --- | --- | --- | --- |
| **Phthalate Metabolite** | **All Singletons** | **All Singletons, by sex** | **Excluding Preterm Births** |
| **N=116** | **Girls, n=56**  | **Boys, n=60** |  | **N=106** |
| Beta (95% CI) | Beta (95% CI) | Beta (95% CI) | p-value2 | Beta (95% CI) |
| ∑DEHP3 | -90 (-165, -15) | -122 (-237, -7) | -86 (-182, 9) | 0.63 | -84 (-167, -1) |
| ∑AAPhth.4 | -113 (-188, -37) | -142 (-251, -33) | -104 (-204, -4) | 0.61 | -99 (-184, -15) |

1 All paternal models adjusted for: paternal and maternal age (continuous), Body Mass Index (continuous), and smoking (ever/never), maternal education (<college, college, graduate degree), infertility treatment (male, female, unexplained), and gestational age (continuous, except in model excluding preterm births).

2 p-value is for the interaction term: loge[phthalate]\*sex.

3 ∑DEHP: is the weighted molar sum of DEHP metabolites MEHP (molecular weight=272), MEHHP (molecular weight=294), MEOHP (molecular weight=292) and MECPP (molecular weight=308) concentrations expressed in µmol/L. We multiplied the molar sum by the molecular weight of MECPP (308 g/mol) to express ∑DEHP as ng/ml.

4 ∑AAPhthalates: was calculated by multiplying the specific gravity adjusted concentration of each of these seven individual phthalate metabolites by their anti-androgenic potency and summing the weighted concentrations: ΣAAPhthalates = MBP + (0.24\*MiBP) + (0.26\*MBzP) + (0.61\*MEHP) + (0.61\*MEHHP)+(0.61\*MEOHP)+ (0.61\*MECPP).

**Table 3A.** Difference in gestational-age-standardized birth weight Z-scores with loge-unit increase in paternal preconception *∑*DEHP and anti-androgenic phthalate metabolites (∑AAPhthalates): adjusted analysis among IVF-conceived singletons.

|  |  |  |
| --- | --- | --- |
| **Phthalate Metabolite** | **Paternal Preconception****Adjusted Model 21** | **Paternal Preconception****Adjusted Model 32** |
| **N=116** | **N=105** |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| *∑DEHP* 3 | -0.23 (-0.40, -0.06) | 0.009 | -0.24 (-0.46, -0.03) | 0.03 |
| MEHP | -0.17 (-0.33, 0.005) | 0.04 | -0.14 (-0.31, 0.04) | 0.12 |
| MEHHP | -0.19 (-0.35, -0.03) | 0.02 | -0.20 (-0.39, -0.02) | 0.03 |
| MEOHP | -0.22 (-0.39, -0.05) | 0.01 | -0.24 (-0.44, -0.04) | 0.02 |
| MECPP | -0.24 (-0.40, -0.06) | 0.007 | -0.26 (-0.48, -0.04) | 0.02 |
| ∑AAPhthalates4 | -0.28 (-0.45, -0.11) | 0.002 | -0.24 (-0.45, -0.03) | 0.02 |
|  |  |  |  |  |

1 Paternal models adjusted for: paternal and maternal age (continuous), Body Mass Index (continuous), and smoking (ever/never), maternal education (<college, college, graduate degree), and infertility treatment (male, female, unexplained).

2 Paternal models adjusted for: maternal and paternal age (continuous), maternal and paternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal and paternal smoking (ever/never), infertility treatment (male, female, unexplained), and maternal prenatal phthalate concentrations.

3 ∑DEHP: is the weighted molar sum of DEHP metabolites MEHP (molecular weight=272), MEHHP (molecular weight=294), MEOHP (molecular weight=292) and MECPP (molecular weight=308) concentrations expressed in µmol/L. We multiplied the molar sum by the molecular weight of MECPP (308 g/mol) to express ∑DEHP as ng/ml.

4 ∑AAPhthalates: was calculated by multiplying the specific gravity adjusted concentration of each of these seven individual phthalate metabolites by their anti-androgenic potency and summing the weighted concentrations: ΣPhthalates = MBP + (0.24\*MiBP) + (0.26\*MBzP) + (0.61\*MEHP) + (0.61\*MEHHP)+(0.61\*MEOHP)+ (0.61\*MECPP).

**Table 4A (Data for Figure 1).** Association of loge-unit increase in paternal preconception, maternal preconception, and maternal prenatal phthalate concentrations and birthweight (g) **among IVF-conceived singletons**: Unadjusted (Model 1), covariate-adjusted (Model 2), and covariate- and partners’ exposure-adjusted (Model 3) models.

|  |  |  |  |
| --- | --- | --- | --- |
| **Model 11** | **Paternal Preconception** | **Maternal Preconception** | **Maternal Prenatal** |
| N=119 |  N=204  |  N=174  |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **Metabolite** |  |  |  |  |  |  |
| *∑DEHP* 6 | -113 (-195, -32) | 0.006 | -22 (-102, 57) | 0.58 | -108 (-186, -32) | 0.006 |
| MEHP | -79 (-154, -3) | 0.04 | -35 (-109, 40) | 0.36 | -112 (-181, -44) | 0.001 |
| MEHHP | -95 (-170, -20) | 0.01 | -4 (-75, 68) | 0.92 | -84 (-156, -12) | 0.02 |
| MEOHP | -109 (-188, -30) | 0.007 | -20 (-96, 55) | 0.60 | -91 (-165, -16) | 0.02 |
| MECPP | -118 (-199, -36) | 0.005 | -28 (-108, 52) | 0.49 | -114 (-191, -36) | 0.004 |
| MEP | -18 (-90, 53) | 0.61 | 12 (-45, 70) | 0.67 | 18 (-42, 78) | 0.56 |
| MBP | -124 (-219, -30) | 0.01 | -33 (-116, 49) | 0.43 | -136 (-219, -53) | 0.001 |
| MiBP | -94 (-193, 6) | 0.07 | 18 (-65, 101) | 0.67 | -47 (-139, 45) | 0.31 |
| MBzP | -100 (-190, -10) | 0.03 | -38 (-103, 28) | 0.26 | -72 (-144, 1) | 0.05 |
| MCPP | -19 (-119, 81) | 0.71 | 66 (-7, 139) | 0.07 | -103 (-177, -28) | 0.007 |
| MCOP | 20 (-59, 99) | 0.62 | 34 (-25, 93) | 0.26 | -61 (-126, 4) | 0.07 |
| MCNP | -4 (-103, 95) | 0.94 | -2 (-84, 81) | 0.97 | -104 (-197, -13) | 0.03 |
| **Model 2** | **Paternal Preconception2** | **Maternal Preconception3** | **Maternal Prenatal3** |
| N=116 | N=195 | N=169 |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **Metabolite** |  |  |  |  |  |  |
| *∑DEHP* 6 | -90 (-165, -15) | 0.02 | -22 (-102, 58) | 0.59 | -122 (-199, -44) | 0.002 |
| MEHP | -66 (-136, 3) | 0.06 | -17 (-94, 59) | 0.66 | -114 (-183, -46) | 0.001 |
| MEHHP | -75 (-143, -5) | 0.03 | -5 (-77, 68) | 0.90 | -100 (-172, -28) | 0.006 |
| MEOHP | -86 (-160, -13) | 0.02 | -19 (-95, 58) | 0.63 | -102 (-176, -27) | 0.007 |
| MECPP | -91 (-166, -16) | 0.02 | -28 (-108, 52) | 0.49 | -124 (-200, -47) | 0.002 |
| MEP | -10 (-75, 55) | 0.77 | 4 (-55, 64) | 0.89 | -9 (-72, 54) | 0.77 |
| MBP | -135 (-218, -52) | 0.002 | -30 (-113, 52) | 0.47 | -133 (-213, -51) | 0.001 |
| MiBP | -114 (-203, -24) | 0.01 | 49 (-35, 133) | 0.25 | -39 (-128, 50) | 0.40 |
| MBzP | -96 (-177, -14) | 0.02 | -43 (-112, 25) | 0.22 | -89 (-160, -18) | 0.01 |
| MCPP | -50 (-139, 38) | 0.26 | 65 (-8, 139) | 0.08 | -91 (-166, -16) | 0.02 |
| MCOP | -12 (-86, 63) | 0.76 | 37 (-23, 97) | 0.23 | -59 (-124, 5) | 0.07 |
| MCNP | -15 (-110, 79) | 0.75 | 2 (-82, 87) | 0.96 | -108 (-200, -16) | 0.02 |
| **Model 3** | **Paternal Preconception4** | **Maternal Preconception5** | **Maternal Prenatal5** |
| N=105 | N=115 | N=105 |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **Metabolite** |  |  |  |  |  |  |
| *∑DEHP* 6 | -107 (-199, -14) | 0.02 | 90 (-33, 213) | 0.15 | -16 (-135, 103) | 0.79 |
| MEHP | -58 (-133, 16) | 0.12 | 24 (-78, 126) | 0.64 | -47 (-138, 44) | 0.31 |
| MEHHP | -92 (-172, -12) | 0.02 | 75 (-32, 182) | 0.17 | -23 (-126, 81) | 0.67 |
| MEOHP | -104 (-188, -20) | 0.01 | 70 (-44, 184) | 0.23 | -21 (-128, 86) | 0.70 |
| MECPP | -109 (-204, -14) | 0.02 | 89 (-36, 215) | 0.16 | -10 (-132, 112) | 0.87 |
| MEP | 6 (-58, 71) | 0.84 | 32 (-51, 116) | 0.45 | -4 (-92, 85) | 0.94 |
| MBP | -111 (-203, -19) | 0.02 | 29 (-94, 153) | 0.64 | -111 (-232, 10) | 0.07 |
| MiBP | -139 (-240, -37) | 0.007 | 110 (-13, 234) | 0.08 | 39 (-86, 163) | 0.54 |
| MBzP | -93 (-182, -3) | 0.04 | 47 (-56, 149) | 0.37 | -54 (-156, 48) | 0.30 |
| MCPP | -49 (-139, 42) | 0.29 | 159 (49, 269) | 0.005 | 30 (-73, 133) | 0.57 |
| MCOP | 28 (-60, 98) | 0.65 | 79 (-18, 175) | 0.11 | -25 (-118, 68) | 0.60 |
| MCNP | -6 (-100, 88) | 0.90 | 33 (-85, 152) | 0.58 | -32 (-157, 91) | 0.61 |

**Abbreviations**: ∑DEHP: di(2-ethylhexyl) phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: mono(2-ethyl-5-oxohexyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MiBP: mono-isobutyl phthalate; MBzP: monobenzyl phthalate;MCPP: mono(3-carboxypropyl) phthalate; MCOP: monocarboxyisooctyl phthalate; MCNP: monocarboxyisononyl phthalate.

**1** Model 1: unadjusted analysis.

**2** Model 2: Paternal models adjusted for: maternal and paternal age (continuous), maternal and paternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal and paternal smoking (ever/never), gestational age (days), infertility diagnosis (male, female, unexplained).

**3** Model 2: Maternal models adjusted for: maternal age (continuous), maternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal smoking (ever/never), and infertility diagnosis (male, female, unexplained).

**4** Model 3: Paternal models adjusted for: maternal and paternal age (continuous), maternal and paternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal and paternal smoking (ever/never), gestational age (days), infertility diagnosis (male, female, unexplained), and maternal prenatal phthalate concentrations.

**5** Model 3: Maternal models adjusted for: maternal age (continuous), maternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal smoking (ever/never), infertility diagnosis (male, female, unexplained), and paternal preconception phthalate concentrations.

6 ∑DEHP: Is the weighted molar sum of DEHP metabolites MEHP (molecular weight=272), MEHHP (molecular weight=294), MEOHP (molecular weight=292) and MECPP (molecular weight=308) concentrations expressed in µmol/L. We multiplied the molar sum by the molecular weight of MECPP (308 g/mol) to express ∑DEHP as ng/ml.

**Table 5A (Data for Figure 2).** Association of loge-unit increase in paternal preconception, maternal preconception, and maternal prenatal phthalate concentrations and birthweight (g) among **non-IVF conceived singletons:** Unadjusted (Model 1), covariate-adjusted (Model 2), and covariate- and partners’ exposure-adjusted (Model 3) models.

|  |  |  |  |
| --- | --- | --- | --- |
| **Model 11** | **Paternal Preconception** | **Maternal Preconception** | **Maternal Prenatal** |
|  N=76  | N=155 | N=147 |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **Metabolite** |  |  |  |  |  |  |
| *∑DEHP* 6 | 20 (-81, 121) | 0.70 | -24 (-112, 65) | 0.60 | 39 (-56, 134) | 0.42 |
| MEHP | 1 (-84, 87) | 0.98 | -14 (-107, 78) | 0.76 | 22 (-63, 109) | 0.61 |
| MEHHP | 17 (-78, 112) | 0.72 | -32 (-113, 49) | 0.44 | 29 (-60, 119) | 0.52 |
| MEOHP | 28 (-72, 128) | 0.58 | -25 (-107, 56) | 0.54 | 39 (-51, 129) | 0.40 |
| MECPP | 16 (-82, 113) | 0.75 | -15 (-104, 74) | 0.74 | 47 (-50, 144) | 0.35 |
| MEP | -17 (-107, 73) | 0.71 | -83 (-155, -10) | 0.02 | -88 (-160, -16) | 0.02 |
| MBP | -48 (-197, 100) | 0.52 | -32 (-121, 56) | 0.47 | 36 (-68, 141) | 0.50 |
| MiBP | -70 (-219, 79) | 0.36 | -24 (-122, 75) | 0.64 | 39 (-73, 151) | 0.50 |
| MBzP | -56 (-185, 74) | 0.40 | -27 (-127, 73) | 0.60 | 44 (-64, 152) | 0.43 |
| MCPP | -16 (-116, 84) | 0.75 | -27 (-117, 63)  | 0.56 | 8 (-72, 88) | 0.84 |
| MCOP | -19 (-102, 64) | 0.65 | 6 (-63, 75) | 0.86 | -13 (-80, 54) | 0.71 |
| MCNP | -16 (-115, 123) | 0.82 | 2 (-97, 102) | 0.96 | 9 (-93, 110) | 0.86 |
| **Model 2** | **Paternal Preconception2** | **Maternal Preconception3** | **Maternal Prenatal3** |
| N=72 |  N=143  |  N=135  |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **Metabolite** |  |  |  |  |  |  |
| *∑DEHP* 6 | 18 (-76, 113) | 0.70 | -48 (-140, 44) | 0.30 | 64 (-14, 143) | 0.11 |
| MEHP | -2 (-82, 79) | 0.97 | -46 (-141, 49) | 0.35 | 38 (-32, 108) | 0.29 |
| MEHHP | 13 (-77, 104) | 0.77 | -51 (-134, 33) | 0.23 | 53 (-20, 126) | 0.16 |
| MEOHP | 24 (-72 119) | 0.62 | -45 (-130, 39) | 0.29 | 68 (-5, 142) | 0.07 |
| MECPP | 26 (-63, 115) | 0.56 | -40 (-133, 53) | 0.40 | 69 (-11, 150) | 0.09 |
| MEP | -9 (-88, 70) | 0.82 | -89 (-165, -13) | 0.02 | -61 (-123, 2) | 0.06 |
| MBP | -35 (-167, 96) | 0.60 | -53 (-142, 35) | 0.24 | 54 (-32, 140) | 0.22 |
| MiBP | -50 (-186, 86) | 0.47 | -35 (-137, 66) | 0.49 | 23 (-74, 120) | 0.64 |
| MBzP | -34 (-146, 77) | 0.55 | -87 (-190, 15) | 0.10 | 38 (-52, 129) | 0.41 |
| MCPP | -28 (-120, 64) | 0.55 | -70 (-164, 25) | 0.15 | 1 (-65, 67) | 0.97 |
| MCOP | -16 (-97, 65) | 0.70 | -20 (-89, 50) | 0.58 | -5 (-64, 54) | 0.86 |
| MCNP | -21 (-155, 113) | 0.76 | -50 (-152, 51) | 0.33 | -28 (-120, 63) | 0.54 |
|  |  |  |  |  |  |  |
| **Model 3** | **Paternal Preconception4** | **Maternal Preconception5** | **Maternal Prenatal5** |
|  N=69  | N=72 | N=69 |
| Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **Metabolite** |  |  |  |  |  |  |
| *∑DEHP* 6 | -14 (-122, 94) | 0.81 | -10 (-142, 123) | 0.89 | 73 (-74, 220) | 0.33 |
| MEHP | -4 (-85, 77) | 0.93 | -99 (-231, 33) | 0.14 | 38 (-74, 150) | 0.51 |
| MEHHP | -16 (-120, 87) | 0.76 | -9 (-128, 109) | 0.88 | 57 (-81, 196) | 0.42 |
| MEOHP | -15 (-122, 93) | 0.78 | -1 (-122, 121) | 0.99 | 77 (-63, 217) | 0.28 |
| MECPP | -3 (-106, 99) | 0.95 | 4 (-131, 139) | 0.95 | 84 (-68, 236) | 0.28 |
| MEP | 4 (-74, 83) | 0.91 | -87 (-179, 5) | 0.06 | -70 (-163, 23) | 0.14 |
| MBP | -111 (-248, 26) | 0.11 | 45 (-80, 170) | 0.48 | 131 (5, 258) | 0.04 |
| MiBP | -99 (-251, 53) | 0.20 | 88 (-52, 227) | 0.22 | 155 (19, 292) | 0.02 |
| MBzP | -62 (-189, 65) | 0.34 | -35 (-179, 109) | 0.63 | 174 (13, 334) | 0.03 |
| MCPP | -33 (-129, 63) | 0.50 | -30 (-158, 98) | 0.65 | 41 (-64, 145) | 0.45 |
| MCOP | 22 (-76, 120) | 0.66 | -69 (-182, 44) | 0.23 | 17 (-92, 125) | 0.76 |
| MCNP | 44 (-114, 202) | 0.58 | -213 (-379, -47) | 0.01 | -2 (-158, 154) | 0.98 |

**Abbreviations**: ∑DEHP: di(2-ethylhexyl) phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: mono(2-ethyl-5-oxohexyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MiBP: mono-isobutyl phthalate; MBzP: monobenzyl phthalate;MCPP: mono(3-carboxypropyl) phthalate; MCOP: monocarboxyisooctyl phthalate; MCNP: monocarboxyisononyl phthalate.

**1** Model 1: unadjusted analysis.

**2** Model 2: Paternal models adjusted for: maternal and paternal age (continuous), maternal and paternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal and paternal smoking (ever/never), infertility diagnosis (male, female, unexplained).

**3** Model 2: Maternal models adjusted for: maternal age (continuous), maternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal smoking (ever/never), and infertility diagnosis (male, female, unexplained).

**4** Model 3: Paternal models adjusted for: maternal and paternal age (continuous), maternal and paternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal and paternal smoking (ever/never), infertility diagnosis (male, female, unexplained), and maternal prenatal phthalate concentrations.

**5** Model 3: Maternal models adjusted for: maternal age (continuous), maternal Body Mass Index (continuous), maternal education (<college, college, graduate degree), maternal smoking (ever/never), infertility diagnosis (male, female, unexplained), and paternal preconception phthalate concentrations.

6 ∑DEHP: Is the weighted molar sum of DEHP metabolites MEHP (molecular weight=272), MEHHP (molecular weight=294), MEOHP (molecular weight=292) and MECPP (molecular weight=308) concentrations expressed in µmol/L. We multiplied the molar sum by the molecular weight of MECPP (308 g/mol) to express ∑DEHP as ng/ml.