Supplemental Tables

The association between urinary concentrations of phosphorous-containing flame retardant metabolites and semen parameters among men from a fertility clinic

Mary E. Ingle a, Lidia Mínguez-Alarcón b, Courtney C. Carignan c, d, Craig M. Butt e, Heather M. Stapleton e, Paige L. Williams f, g, Jennifer B. Ford b, Russ Hauser b, g, h, John D. Meeker a, \*, for the EARTH Study Team

a Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

b Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

c Department of Food Science and Nutrition, Michigan State University, East Lansing, Michigan, USA

d Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan, USA

e Nicholas School of the Environment, Duke University, Durham, North Carolina, USA

f Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

g Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

h Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

\* Corresponding author: 1835 SPH 1, 1415 Washington Heights, Ann Arbor, MI USA 48109. Telephone: 734-764-7184. Email: meekerj@umich.edu

Supplemental Table 1. Crude bivariate associations with PFR and semen parameters among (n=220) men

|  |  |
| --- | --- |
|  | Metabolite |
|  | BDCIPP | DPHP | ip-PPP | tb-DPHP |
| Semen parameters | r | 25th, 75th % | p-Value | r | 25th, 75th % | p-Value | r | 25th, 75th % | p-Value | r | 25th, 75th % | P-Value |
|  Total sperm count | 0.06 |  | 0.36 | 0.08 |  | 0.34 | 0.07 |  | 0.37 | 0.08 |  | 0.67 |
|  Concentration (mil/mL) | 0.10 |  | 0.14 | 0.06 |  | 0.36 | 0.07 |  | 0.83 | 0.11 |  | 0.56 |
|  Motility (P+NP) (%) | **0.16** |  | 0.02 | 0.08 |  | 0.23 | 0.04 |  | 0.61 | 0.11 |  | 0.55 |
|  Progressive motility | **0.15** |  | 0.04 | 0.04 |  | 0.61 | 0.06 |  | 0.46 | 0.13 |  | 0.51 |
|  Morphology (%norm) | 0.09 |  | 0.21 | -0.02 |  | 0.82 | 0.05 |  | 0.55 | 0.29 |  | 0.12 |
|  Sample volume (mL) | -0.05 |  | 0.45 | -0.05 |  | 0.43 | 0.004 |  | 0.96 | 0.14 |  | 0.45 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  Total sperm count  <39 mill a Yes No  | 0.500.62 |  0.35, 0.76 0.35, 1.46 | 0.13 | 0.720.76 | 0.34, 1.860.41, 1.47 | 0.81 | 0.350.36 | 0.12, 0.830.21, 0.62 | 0.55 | 0.130.12 | 0.13, 0.130.12, 0.22 | 0.51 |
|  Sperm concentration  <15 mil/mL a Yes No | 0.460.62 | 0.35, 0.790.35, 1.16 | 0.21 | 0.670.77 | 0.29, 0.930.42, 1.48 | 0.21 | 0.300.37 | 0.13, 0.640.21, 0.64 | 0.26 | 0.380.16 | 0.38, 0.380.12, 0.20 | 0.22 |
|  Percent motile sperm (P+NP) <40 a  Yes No | 0.550.72 | 1.111.67 | 0.08 | 0.730.74 | 0.37, 1.370.42, 1.47 | 0.68 | 0.360.39 | 0.21, 0.590.19, 0.64 | 0.69 | 0.160.16 | 0.12, 0.200.12, 0.25 | 0.80 |
|  Percent morph.  Sperm <4 a Yes No | 0.620.61 | 0.36, 1.260.34, 1.45 | 0.92 | 0.770.74 | 0.44, 1.320.41, 1.47 | 0.82 | 0.360.40 | 0.20, 0.790.21, 0.64 | 0.95 | 0.150.18 | 0.13, 0.160.13, 0.24 | 0.21 |

r= spearman coefficient; a r = median values, p-value for 2-tailed test

Supplemental Table 2. Bivariate associations of PFR metabolite (uncorrected) and demographic characteristics (n=220 men)

|  |  |
| --- | --- |
|  | Metabolite |
|  | BDCIPP | DPHP | ip-PPP | tb-DPHP |
| Demographic characteristic | r | 25th, 75th % | P-value | r | 25th, 75th % | P-value | r | 25th, 75th % | P-value | r | 25th, 75th % | P-value |
| Age | -0.04 |  | 0.54 | -0.01 |  | 0.81 | 0.03 |  | 0.69 | -0.15 |  | 0.38 |
| BMI | 0.21 |  | **0.0005** | 0.08 |  | 0.15 | 0.04 |  | 0.49 | -0.09 |  | 0.59 |
| Abstinence period | 0.07 |  | 0.27 | 0.01 |  | 0.89 | 0.08 |  | 0.26 | 0.14 |  | 0.45 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Race a White Black Asian Other | 0.600.990.521.65 | 0.30, 1.290.76, 1.060.38, 2.500.81, 2.34 | 0.08 | 0.740.531.231.02 | 0.41, 1.280.25, 0.650.55, 1.690.73, 1.48 | 0.20 | 0.350.970.240.30 | 0.20, 0.610.08, 1.510.13, 0.400.15, 0.62 | 0.38 | 0.160.230.160.18 | 0.09, 0.200.23, 0.230.09, 0.260.18, 0.18 | 0.71 |
| Smoking Status a Never smoke Past smoker Current smoker | 0.620.550.58 | 0.30, 1.460.37, 1.410.30, 0.83 | 0.71 | 0.740.760.79 | 0.39, 1.280.53, 1.500.46, 1.26 | 0.67 | 0.340.360.35 | 0.19, 0.620.20, 0.640.23, 0.52 | 0.91 | 0.160.18- | 0.10, 0.200.07, 0.23 | 0.75 |
| Education a <High school HS grad  1 or 2 yr. college 3 or 4 yr. college College grad Graduate degree | 2.660.930.480.740.600.48 | 0.56, 3.300.22, 1.520.26, 0.810.43, 1.450.38, 1.150.27, 0.13 | 0.15 | 0.581.501.300.680.740.73 | 0.58, 1.020.48, 4.320.54, 2.190.47, 1.080.41, 1.240.34, 1.22 | 0.51 | 0.360.450.380.470.300.33 | 0.24, 0.480.35, 0.620.31, 0.470.19, 0.630.16, 0.520.18, 0.54 | 0.61 | --0.16-0.160.19 | --0.16, 0.16-0.13, 0.170.07, 0.26 | 1.00 |
| Season a Winter Spring Summer Fall | 0.540.441.040.60 | 0.22, 0.980.29, 0.750.52, 1.810.28, 1.12 | **<0.0001** | 0.890.710.750.72 | 0.54, 1.940.34, 1.260.45, 1.540.37, 1.03 | 0.05 | 0.380.340.340.35 | 0.17, 0.540.19, 0.630.21, 0.770.20, 0.54 | 0.80 | 0.150.170.160.17 | 0.10, 0.230.10, 0.230.09, 0.200.12, 0.22 | 0.96 |

r= Spearman coefficient; a r = median values; Winter: December-February, Spring: March-May; Summer: June-August; Fall: September-November

|  |  |
| --- | --- |
|  | Metabolite a |
|  | BDCIPP | DPHP | ip-PPP | ∑ PFR |
| Sperm Parameter  | β | 95%CI | p-Value | β | 95%CI | p-Value | β | 95%CI | p-Value | β | 95%CI | p-Value |
| Total sperm count a, b | -0.04 | (-0.14, 0.07) | 0.49 | 0.05 | (-0.07, 0.17) | 0.42 | -0.0001 | (-0.11, 0.00) | 1.00 | 0.07 | (-0.07, 0.21) | 0.33 |
| Concentration (mil/mL) a, c | -0.001 | (-0.11, 0.10) | 0.91 | 0.06 | (-0.05, 0.17) | 0.28 | 0.04 | (-0.07, 0.14) | 0.49 | 0.09 | (-0.04, 0.23) | 0.17 |
| Motility (P+NP) (%) a, c | 0.07 | (-0.02, 0.17) | 0.11 | 0.07 | (-0.04, 0.16) | 0.22 | 0.04 | (-0.06, 0.14) | 0.40 | 0.14 | (-0.02, 0.29) | 0.08 |
| Progressive motility a, d | 0.07 | (-0.04, 0.17) | 0.21 | 0.06 | (-0.06, 0.17) | 0.32 | 0.06 | (-0.05, 0.17) | 0.29 | 0.11 | (-0.03, 0.25) | 0.12 |
| Morphology (%norm) e | 0.32 | (-0.07, 0.72) | 0.11 | 0.22 | (-0.26, 0.70) | 0.36 | 0.26 | (-0.19, 0.711) | 0.25 | 0.41 | (-0.17, 0.99) | 0.16 |
| Sample volume (mL) f | -0.10 | (-0.26, 0.06) | 0.20 | -0.08 | (-0.26, 0.11) | 0.42 | -0.06 | (-0.24, 0.11) | 0.47 | -0.16 | (-0.39, 0.06) | 0.16 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Odds Ratio | OR |  |  | OR |  |  | OR |  |  | OR |  |  |
| Total sperm count <39 mill b  | 0.85 | (0.63, 0.85) | 0.33 | 0.90 | (0.59, 1.39) | 0.65 | 1.01 | (0.55, 1.84) | 0.98 | 0.71 | (0.45, 1.12) | 0.39 |
| Sperm concentration <15 mil/mL c  | 0.88 | (0.64, 1.22) | 0.44 | 0.91 | (0.57, 1.48) | 0.70 | 0.98 | (0.53, 1.79) | 0.94 | 0.74 | (0.41, 1.34) | 0.39 |
| Percent motile sperm (P+NP) <40 b  | 0.94 | (0.72, 1.22) | 0.64 | 0.92 | (0.67, 1.27) | 0.62 | 0.92 | (0.66,1.28) | 0.64 | 0.76 | (0.52, 1.12) | 0.17 |
| Percent morph. Sperm <4 e  | 0.89 | (0.65, 1.20) | 0.43 | 1.00 | (0.72, 1.39) | 0.99 | 0.92 | (0.65, 1.31) | 0.64 | 0.81 | (0.51, 1.27) | 0.34 |

Supplemental Table 3. Regression coefficients and odds ratios (95% CI) for semen parameters of men contributing (1-5) urine samples restricting 1.01 ≤ SG ≤ 1.03. Adjusted for specific gravity, age, BMI, smoking status & abstinence period

a natural log transformation; b n=168; c n=188; d n=185; e n=204; f n=214

Supplemental Table 4. Intraclass correlation coefficients (95% CI) for repeated semen parameters

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Subjects | Observations | ICC | 95% CI |
| Total sperm count (mill) | 174 | 235 | 0.52 | (0.36, 0.67) |
| Concentration (mil/mL) | 176 | 237 | 0.58 | (0.41, 0.74) |
| Motility (P+NP) (%) | 176 | 237 | 0.79 | (0.69, 0.86) |
| Progressive motility | 173 | 234 | 0.71 | (0.58, 0.81) |
| Morphology (%norm) | 189 | 255 | 0.51 | (0.35, 0.66) |
| Sample volume (mL) | 195 | 267 | 0.58 | (0.43, 0.71) |

Supplemental Table 5. Odds ratios (95% CIs) by quartile of PFR metabolite for males contributing 1-5 samples. Adjusted for

specific gravity, age, BMI, smoking status & abstinence period

|  |  |  |
| --- | --- | --- |
|  |  | Semen parameters |
| PFR a | (quartile range) | Total sperm count (<39 x 106) | Sperm Concentration (<15 million/mL) | Sperm motility (<40% motile sperm) | Morphology (<4% normal) |
| BDCIPP |  |  |
| Q1 | (0.2-0.17) | - | - | - | - |
| Q2 | (0.18-0.51) | 1.99 | (0.65 6.14) | 1.04 | (0.38, 2.86) | 0.69 | (0.34, 1.36) | 1.74 | (0.79, 3.82) |
| Q3 | (0.52-1.11) | 1.24 | (0.03, 59.36) | 2.79 | (0.05, 144.68) | 0.21 | (0.02, 2.96) | 1.38 | (0.08, 23.06) |
| Q4 | (1.12-10.30) | 0.16 | (0.02, 1.42) | 0.35 | (0.05, 2.58) | 0.99 | (0.27, 3.58) | 0.41 | (0.08, 2.03) |
| p-trend |  | 0.14 | 0.25 | 0.91 | 0.38 |
| DPHP |  |  |
| Q1 | (0.07-0.27) | - | - | - | - |
| Q2 | (0.28-0.65) | 1.50 | (0.32, 1.07) | 1.15 | (0.30, 4.42) | 1.48 | (0.57, 3.87) | 0.63 | (0.20, 1.97) |
| Q3 | (0.66-1.21) | 0.55 | (7.90x10-5, 3847.58) | 0.27 | (1.03, 700.36) | 0.13 | (9.42x10-4, 18.52) | 6.79x10-4 | (1.72x10-6, 0.27) |
| Q4 | (1.22-10.57) | 1.04 | (0.20, 5.31) | 0.71 | (0.07, 6.97) | 0.76 | (0.20, 2.95) | 2.33 | (0.40, 13.73) |
| p-trend |  | 0.83 | 0.91 | 0.96 | 0.24 |
| ip-PPP |  |  |
| Q1 | (0.04-0.08) | - | - | - | - |
| Q2 | (0.09-0.18) | 0.78 | (0.43, 1.40) | 1.02 | (0.64, 1.62) | 1.07 | (0.76, 1.49) | 0.89 | (0.60, 1.34) |
| Q3 | (0.19-0.45) | 3.19 | (0.71, 14.36) | 2.70 | (0.76, 9.53) | 0.93 | (0.48, 1.81) | 1.07 | (0.49, 2.36) |
| Q4 | (0.46-4.56) | 0.15 | (8.92x104, 26.62) | 1.33 | (0.01, 150.55) | 1.53 | (0.08, 31.26) | 2.02 | (0.08, 52.44) |
| p-trend |  | 0.97 | 0.60 | 0.93 | 0.50 |
| ∑PFR |  |  |
| Q1 | (0.17-0.79) | - | - | - | - |
| Q2 | (0.80-1.86) | 1.60 | (0.01, 502.90) | 1.87 | (0.01, 298.90) | 1.02 | (0.04, 29.15) | 2.06 | (0.04, 104.27) |
| Q3 | (1.87-3.21) | 1.57 | (0.32, 7.71) | 1.74 | (0.42, 7.26) | 0.71 | (0.27, 1.85) | 1.48 | (0.45, 4.83) |
| Q4 | (3.22-15.56) | 0.79 | (0.33, 1.86) | 0.54 | (0.20, 1.50) | 0.76 | (0.45, 1.29) | 0.79 | (0.37, 1.71) |
| p-trend |  | 0.70 | 0.32 | 0.24 | 0.50 |

a natural log transformation; Quartile 1=reference