

HUMAN STUDIES OF PHTHALATE EFFECTS

(Emphasis added by NOW on PBS)

1

DEHP, bis(2)-ethylhexyl phthalate, alters gene expression in human cells: possible correlation with initiation of fetal developmental abnormalities.

Hum Exp Toxicol. 2006 Dec;25(12):687-95.

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Diethylhexylphthalate (DEHP) is a widely distributed phthalate, to which humans are exposed to due to its variety of commercial and manufacturing uses. As a plasticiser, it is found in a wide number of products, and metabolites of DEHP have been detected in urine samples from a high percentage of the people screened for phthalates. We utilised DNA microarray analysis to evaluate DEHP for gene expression disrupting activity using the human cell line MCF-7, and found that DEHP significantly dysregulated approximately 34% of the 2400 genes spotted on the NEN2400 chip we used. The results suggest that DEHP, a known estrogen agonist and probable androgen antagonist, alters the expression of a number of genes, many of which are critical for fetal development. Down-regulation of two genes, FGD1 and PAFAH1B1, related in that both are essential for fetal brain development, was corroborated using quantitative real time PCR.

These studies show DEHP to be a highly effective human gene expression-altering chemical, and that, at appropriate concentrations, it has the possibility of altering fetal central nervous system development, resulting in the birth defects lissencephaly and/or faciodigitogenital dysplasia.

2

Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age.

Environ Health Perspect. 2006 Feb;114(2):270-6.

Main KM, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, Schmidt IM, Suomi AM, Virtanen HE, Petersen DV, Andersson AM, Toppari J, Skakkebaek NE.

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Phthalates adversely affect the male reproductive system in animals. We investigated whether phthalate monoester contamination of human breast milk had any influence on the postnatal surge of reproductive hormones in newborn boys as a sign of testicular dysgenesis. DESIGN: We obtained biologic samples from a prospective Danish-Finnish cohort study on cryptorchidism from 1997 to 2001. We analyzed individual breast milk samples collected as additive aliquots 1-3 months postnatally (n = 130; 62 cryptorchid/68 healthy boys) for phthalate monoesters [mono-methyl phthalate (mMP), mono-ethyl phthalate (mEP), mono-n-butyl phthalate (mBP), mono-benzyl phthalate (mBzP), mono-2-ethylhexyl phthalate (mEHP), mono-isononyl phthalate (miNP)]. We analyzed serum samples (obtained in 74% of all boys) for gonadotropins, sex-hormone binding globulin (SHBG), testosterone, and inhibin B. RESULTS: All phthalate monoesters were found in breast milk with large variations [medians (minimum-maximum)]: mMP 0.10 (< 0.01-5.53 microg/L), mEP 0.95 (0.07-41.4 microg/L), mBP 9.6 (0.6-10,900 microg/L), mBzP 1.2 (0.2-26 microg/L), mEHP 11 (1.5-1,410 microg/L), miNP 95 (27-469 microg/L). Finnish breast milk had higher concentrations of mBP, mBzP, mEHP, and Danish breast milk had higher values for miNP (p = 0.0001-0.056). No association was found between phthalate monoester levels and cryptorchidism. However, mEP and mBP showed positive correlations with SHBG (r = 0.323, p = 0.002 and r = 0.272, p = 0.01, respectively); mMP, mEP, and mBP with LH:free testosterone ratio (r = 0.21-0.323, p = 0.002-0.044) and miNP with luteinizing hormone (r = 0.243, p = 0.019). mBP was negatively correlated with free testosterone (r = -0.22, p = 0.033). Other phthalate monoesters showed similar but nonsignificant tendencies. **CONCLUSIONS: Our data on reproductive hormone profiles and phthalate exposures in newborn boys are in accordance with rodent data and suggest that human Leydig cell development and function may also be vulnerable to perinatal exposure to some phthalates. Our findings are also in line with other recent human data showing incomplete virilization in infant boys exposed to phthalates prenatally.**

3

DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites.

Hum Reprod. 2007 Mar;22(3):688-95. Epub 2006 Nov 7

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BACKGROUND: The ubiquitous use of phthalate esters in plastics, personal care products and food packaging materials results in widespread general population exposure. In this report, we extend our preliminary study on the relationship

between urinary concentrations of phthalate metabolites and sperm DNA damage among a larger sample of men and include measurements of mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), two oxidative metabolites of di-(2-ethylhexyl) phthalate (DEHP). METHODS: Among 379 men from an infertility clinic, urinary concentrations of phthalate metabolites were measured using isotope-dilution high-performance liquid chromatography-tandem mass spectrometry. Sperm DNA damage measurements, assessed with the neutral comet assay, included comet extent (CE), percentage of DNA in tail (Tail%) and tail distributed moment (TDM). RESULTS: Monoethyl phthalate (MEP), a metabolite of diethyl phthalate, was associated with increased DNA damage, confirming our previous findings. Mono-(2-ethylhexyl) phthalate (MEHP), a metabolite of DEHP, was associated with DNA damage after adjustment for the oxidative DEHP metabolites. After adjustment for MEHHP, for an interquartile range increase in urinary MEHP, CE increased 17.3% [95% confidence interval (CI) = 8.7-25.7%], TDM increased 14.3% (95% CI = 6.8-21.7%) and Tail% increased 17.5% (95% CI = 3.5-31.5%). **CONCLUSIONS: Sperm DNA damage was associated with MEP and with MEHP after adjusting for DEHP oxidative metabolites, which may serve as phenotypic markers of DEHP metabolism to 'less toxic' metabolites. The urinary levels of phthalate metabolites among these men were similar to those reported for the US general population, suggesting that exposure to some phthalates may affect the population distribution of sperm DNA damage.**

4

Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult male.

Fertil Steril. 2008 Feb;89(2 Suppl):e59-65

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In the field of reproductive environmental health there remain many unanswered questions regarding the impact of the environment on male reproductive health. Suggested needs include studies that target populations with high exposure to chemicals, including phthalates and bisphenol A. We also need to identify susceptibility factors and critical exposure windows (life stages) that may increase a man's risk of infertility. Finally, we need to develop methods to better study mixtures of chemicals and develop methods to assess clinical reproductive outcomes of human exposure to the ever-growing list of chemicals.

5

Phthalate exposure and human semen parameters.

Epidemiology. 2003 May;14(3):269-77.

Duty SM, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z, Herrick RF, Christiani DC, Hauser R. Department of Environmental Health, Occupational Health Program, Harvard School of Public Health, Boston, MA 02115, USA.

BACKGROUND: There is scientific and public concern about commonly used chemicals, including phthalates, that are associated with reproductive toxicity in laboratory animals and are hormonally active. People are exposed to phthalates through diet, consumer products and medical devices. The present study explored whether environmental levels of phthalates are associated with altered semen quality in humans. **METHODS:** We recruited 168 men who were part of subfertile couples and who presented to the Massachusetts General Hospital andrology laboratory for semen analysis between January 2000 and April 2001. Semen parameters were dichotomized based on 1999 World Health Organization reference values for sperm concentration (< 20 million/ml) and motility (< 50% motile), as well as Tygerberg Strict criteria for morphology (< 4% normal). The comparison group was men for whom these semen parameters were all above the reference values. In urine, eight phthalate metabolites were measured with high-performance liquid chromatography and tandem mass spectrometry. Specific gravity-adjusted phthalate metabolite levels were categorized into tertiles. **RESULTS:** There was a dose-response relation between tertiles of mono-butyl phthalate and sperm motility (odds ratio per tertile = 1.0, 1.8, 3.0; P-value for trend = 0.02) and sperm concentration (1.0, 1.4, 3.3; P-value for trend = 0.07). In addition, there was a dose-response relation between tertiles of mono-benzyl phthalate and sperm concentration (1.0, 1.4, 5.5; P-value for trend = 0.02). **CONCLUSIONS: There were dose-response relations for monobutyl phthalate and monobenzyl phthalate with one or more semen parameters, and suggestive evidence for monomethyl phthalate with sperm morphology. The lack of a relation for other phthalates may indicate a difference in spermatotoxicity among phthalates.**

6

Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites.

Epidemiology. 2006 Nov;17(6):682-91.

Hauser R, Meeker JD, Duty S, Silva MJ, Calafat AM.

Epidemiology. 2006 Nov;17(6):682-91. Harvard School of Public Health/Massachusetts General Hospital, Boston, MA 02115, USA. rhauser@hohp.harvard.edu

BACKGROUND: Phthalates are multifunctional chemicals used in a variety of consumer, medical, and personal care products. Previously, we reported dose-response associations of decreased semen quality with urinary concentrations of monobutyl phthalate (MBP) and monobenzyl (MBzP) phthalate, which are metabolites of dibutyl phthalate and butylbenzyl phthalate, respectively. The present study extends our work in a larger sample of men and includes measurements of di(2-ethylhexyl) phthalate (DEHP) oxidative metabolites. **METHODS:** Between January 2000 and May 2004, we recruited 463 male partners of subfertile couples who presented for semen analysis to the Massachusetts General Hospital. Semen parameters were dichotomized based on World Health Organization reference values for sperm concentration (<20 million/mL) and motility (<50% motile) and the Tygerberg Kruger Strict criteria for morphology (<4% normal). The comparison group was men with all 3 semen parameters above the reference values. In a single spot urine sample from each man, phthalate metabolites were measured using solid-phase extraction coupled to high-performance liquid chromatography isotope-dilution tandem mass spectrometry. **RESULTS:** There were dose-response relationships of MBP with low sperm concentration (odds ratio per quartile adjusted for age, abstinence time, and smoking status = 1.00, 3.1, 2.5, 3.3; P for trend = 0.04) and motility (1.0, 1.5, 1.5, 1.8; P for trend = 0.04). There was suggestive evidence of an association between the highest MBzP quartile and low sperm concentration (1.00, 1.1, 1.1, 1.9; P for trend = 0.13). There were no relationships of monoethyl phthalate, monomethyl phthalate, and the DEHP metabolites with these semen parameters. **CONCLUSION: The present study confirms previous results on the relationship of altered semen quality with exposure to MBP at general population levels. We did not find associations between semen parameters and 3 DEHP metabolites.**

7

In utero exposure to di-(2-ethylhexyl)phthalate and duration of human pregnancy.

Environ Health Perspect. 2003 Nov;111(14):1783-5.

Giuseppe Latini, Claudio De Felice, Giuseppe Presta, Antonio Del Vecchio, Irma Paris, Fabrizio Ruggieri, and Pietro Mazzeo Neonatal Intensive Care Unit, Division of Paediatrics, Perrino Hospital, Brindisi, Italy. gilatini@tin.it

Di-(2-ethylhexyl)phthalate (DEHP), the most commonly used plasticizer in flexible polyvinylchloride formulations, is a ubiquitous environmental contaminant. To date, no information exists on the potential health hazards from exposure to DEHP and/or its main metabolite, mono-(2-ethylhexyl)phthalate (MEHP), in high-

risk conditions, such as pregnancy and during the neonatal period. The aim of this study was to evaluate prenatal exposure to DEHP and/or MEHP and its possible biologic effects. We measured serum DEHP and MEHP concentrations in the cord blood of 84 consecutive newborns by high-performance liquid chromatography. Relationships between DEHP/MEHP and infant characteristics were tested using Fisher's exact test, unpaired t-tests, and univariate linear regression analyses, and significant differences on univariate analysis were evaluated using multiple logistic regression analysis. We found detectable cord blood DEHP and/or MEHP concentrations in 88.1% of the samples. Either DEHP or MEHP was present in 65 of 84 (77.4%) of the examined samples. Mean concentrations of DEHP and MEHP were 1.19 +/- 1.15 microg/mL [95% confidence interval (CI), 0.93-1.44, range = 0-4.71] and 0.52 +/- 0.61 microg/mL (95% CI, 0.39-0.66, range = 0-2.94), respectively. MEHP-positive newborns showed a significantly lower gestational age compared with MEHP-negative infants ($p = 0.033$). **Logistic regression analysis results indicated a positive correlation between absence of MEHP in cord blood and gestational age at delivery (odds ratio = 1.50, 95% CI, 1.013-2.21; $p = 0.043$). These findings confirm that human exposure to DEHP can begin in utero and suggest that phthalate exposure is significantly associated with a shorter pregnancy duration.**

8

Phthalate exposure and human semen quality in Shanghai: a cross-sectional study.

Biomed Environ Sci. 2006 Jun;19(3):205-9.

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OBJECTIVE: To monitor the level of phthalates in human semen samples and to analyze the relationship between phthalate levels and semen parameters. **METHODS:** Concentrations of three kinds of commonly used phthalates (di-ethyl phthalate, DEP; di-n-butyl phthalate, DBP; di-2-ethylhexyl phthalate, DEHP) were measured using reversed-phase HPLC. Semen parameters were measured by computer aided sperm analysis (CASA). **RESULTS:** The three phthalates were detected in most of the biological samples, with median levels of 0.30 mg/L (0.08-1.32 mg/L) in semen specimens. There was a significant positive association between liquefied time of semen and phthalate concentrations of semen. The correlation coefficient was 0.456 for DEP, 0.475 for DBP, and 0.457 for DEHP, respectively. There was no significant difference between phthalate concentrations of semen and sperm density or livability, though the correlation coefficients were negative. **CONCLUSION: These results suggest that people who reside in Shanghai are exposed to phthalates, especially to DBP and DEHP. Although the level of phthalates is relatively mild, an association of**

phthalate levels and reduced quality of human semen has been shown in the present study.

9

Identification of Phthalate Esters in the Serum of Young Puerto Rican Girls with Premature Breast Development

Environ Health Perspect. 2000 Sep;108(9):895-900

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Premature breast development (thelarche) is the growth of mammary tissue in girls younger than 8 years of age without other manifestations of puberty. Puerto Rico has the highest known incidence of premature thelarche ever reported. In the last two decades since this serious public health anomaly has been observed, no explanation for this phenomenon has been found. Some organic pollutants, including pesticides and some plasticizers, can disrupt normal sexual development in wildlife, and many of these have been widely used in Puerto Rico. This investigation was designed to identify pollutants in the serum of Puerto Rican girls with premature thelarche. A method for blood serum analysis was optimized and validated using pesticides and phthalate esters as model compounds of endocrine-disrupting chemicals. Recovery was > 80% for all compounds. We performed final detection by gas chromatography/mass spectrometry. We analyzed 41 serum samples from thelarche patients and 35 control samples. No pesticides or their metabolite residues were detected in the serum of the study or control subjects. Significantly high levels of phthalates [dimethyl, diethyl, dibutyl, and di-(2-ethylhexyl)] and its major metabolite mono-(2-ethylhexyl) phthalate were identified in 28 (68%) samples from thelarche patients. Of the control samples analyzed, only one showed significant levels of di-isooctyl phthalate. The phthalates that we identified have been classified as endocrine disruptors. **This study suggests a possible association between plasticizers with known estrogenic and antiandrogenic activity and the cause of premature breast development in a human female population.**

10

Phthalates: toxicology and exposure.

Heudorf U, Mersch-Sundermann V, Angerer J. *Int J Hyg Environ Health*. 2007 Oct;210(5):623-34. Epub 2007 Sep 21.2007 Oct;210(5):623-34. Epub 2007 Sep 21.

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Phthalates are used as plasticizers in PVC plastics. As the phthalate plasticizers are not chemically bound to PVC, they can leach, migrate or evaporate into indoor air and atmosphere, foodstuff, other materials, etc. Consumer products containing phthalates can result in human exposure through direct contact and use, indirectly through leaching into other products, or general environmental contamination. Humans are exposed through ingestion, inhalation, and dermal exposure during their whole lifetime, including intrauterine development. This paper presents an overview on current risk assessments done by expert panels as well as on exposure assessment data, based on ambient and on current human biomonitoring results. **Some phthalates are reproductive and developmental toxicants in animals and suspected endocrine disruptors in humans. Exposure assessment via modelling ambient data give hints that the exposure of children to phthalates exceeds that in adults. Current human biomonitoring data prove that the tolerable intake of children is exceeded to a considerable degree, in some instances up to 20-fold. Very high exposures to phthalates can occur via medical treatment, i.e. via use of medical devices containing DEHP or medicaments containing DBP phthalate in their coating. Because of their chemical properties exposure to phthalates does not result in bioaccumulation. However, health concern is raised regarding the developmental and/or reproductive toxicity of phthalates, even in environmental concentrations.**

11

The association between phthalates in dust and allergic diseases among Bulgarian children.

Kolarik B, Naydenov K, Larsson M, Bornehag CG, Sundell J. *Environmental Health Perspectives* 2008 Jan;116(1):98-103.

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BACKGROUND: Recent studies have identified associations between the concentration of phthalates in indoor dust and allergic symptoms in the airways, nose, and skin. OBJECTIVES: Our goal was to investigate the associations between allergic symptoms in children and the concentration of phthalate esters in settled dust collected from children's homes in Sofia and Burgas, Bulgaria. METHODS: Dust samples from the child's bedroom were collected. A total of 102 children (2-7 years of age) had symptoms of wheezing, rhinitis, and/or eczema in preceding 12 months (cases), and 82 were nonsymptomatic (controls). The dust samples were analyzed for their content of dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), and di-n-octyl phthalate (DnOP). RESULTS: A higher concentration of DEHP was found in homes of case children than in those of controls (1.24 vs. 0.86 mg/g dust). The concentration of DEHP was significantly associated with wheezing in the preceding 12 months ($p = 0.035$) as reported by parents. We found a dose-response relationship between DEHP concentration and case status and between DEHP concentration and wheezing in the preceding 12 months. **CONCLUSIONS: This study shows an association between concentration of DEHP in indoor dust and wheezing among preschool children in Bulgaria.**

12

Controversy: neonatal exposure to plasticizers in the NICU.

Pak VM, Nailon RE, McCauley LA. **MCN Am J Matern Child Nurs. 2007 Jul-Aug;32(4):244-9.**

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This article presents a review of extant literature that informs our current understanding of the effects of di-(2-ethylhexyl) phthalate (DEHP) exposure on neonates. Phthalates such as DEHP add flexibility to plastics. **DEHP is a major component in the manufacturing of polyvinyl chloride devices commonly used in the healthcare setting. Premature and critically ill neonates and infants in the NICU are exposed to DEHP and may be at an increased risk for adverse health outcomes as a result. DEHP has been shown to be a developmental and endocrine disrupting toxicant and is a major component in polyvinyl chloride plastics, which are commonly found in medical equipment used in the NICU. Potential toxicities to infants in the NICU are a concern because infants' small body size and compromised physical condition necessitate a multitude of medical interventions, each increasing exposure levels.** Expanding nurses' knowledge regarding DEHP research is important for implementing a precautionary approach to reduce DEHP exposure among NICU patients.

13

Environmental effects on hormonal regulation of testicular descent.

Toppari J, Virtanen H, Skakkebaek NE, Main KM. **J Steroid Biochem Mol Biol.** 2006 Dec;102(1-5):184-6. Epub 2006 Oct 17

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Regulation of testicular descent is hormonally regulated, but the reasons for maldescent remain unknown in most cases. The main regulatory hormones are Leydig cell-derived testosterone and insulin-like factor 3 (INSL3). Luteinizing hormone (LH) stimulates the secretion of these hormones, but the secretory responses to LH are different: INSL3 secretion increases slowly and may reflect the LH dependent differentiated status of Leydig cells, whereas testosterone response to LH is immediate. Testosterone contributes to the involution of the suspensory ligament and to the inguinoscrotal phase of the descent, while INSL3 acts mainly in transabdominal descent by stimulating the growth of the gubernaculum. INSL3 acts through a G-protein coupled receptor LGR8. In the absence of either INSL3 or LGR8 mice remain cryptorchid. In humans only few INSL3 mutations have been described, whereas LGR8 mutations may cause some cases of undescended testis. Similarly, androgen insensitivity or androgen deficiency can cause cryptorchidism. Estrogens have been shown to down regulate INSL3 and thereby cause maldescent. Thus, a reduced androgen-estrogen ratio may disturb testicular descent. Environmental effects changing the ratio can thereby influence cryptorchidism rate. Estrogens and anti-androgens cause cryptorchidism in experimental animals. In our cohort study we found higher LH/testosterone ratios in 3-month-old cryptorchid boys than in normal control boys, suggesting that cryptorchid testes are not capable of normal hormone secretion without increased gonadotropin drive. This may be either the cause or consequence of cryptorchidism. **Some phthalates act as anti-androgens and cause cryptorchidism in rodents. In our human material we found an association of a high phthalate exposure with a high LH/testosterone ratio. We hypothesize that an exposure to a mixture of chemicals with anti-androgenic or estrogenic properties (either their own activity or their effect on androgen-estrogen ratio) may be involved in cryptorchidism.**

14

Metabolism of phthalates in humans.

Frederiksen H, Skakkebaek NE, Andersson AM. **Mol Nutr Food Res.** 2007 Jul;51(7):899-911.

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Phthalates are synthetic compounds widely used as plasticisers, solvents and additives in many consumer products. Several animal studies have shown that some phthalates possess endocrine disrupting effects. Some of the effects of phthalates seen in rats are due to testosterone lowering effects on the foetal testis and they are similar to those seen in humans with testicular dysgenesis syndrome. **Therefore, exposure of the human foetus and infants to phthalates via maternal exposure is a matter of concern.** The metabolic pathways of phthalate metabolites excreted in human urine are partly known for some phthalates, but our knowledge about metabolic distribution in the body and other biological fluids, including breast milk, is limited. Compared to urine, human breast milk contains relatively more of the hydrophobic phthalates, such as di-n-butyl phthalate and the longer-branched, di(2-ethylhexyl) phthalate (DEHP) and di-iso-nonyl phthalate (DiNP); and their monoester metabolites. Urine, however, contains relatively more of the secondary metabolites of DEHP and DiNP, as well as the monoester phthalates of the more short-branched phthalates. This differential distribution is of special concern as, in particular, the hydrophobic phthalates and their metabolites are shown to have adverse effects following in utero and lactational exposures in animal studies.

15

Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males.

Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. Environ Health Perspect. 2007 Jun;115(6):876-82. Epub 2007 Mar 14.

Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ Health Perspect. 2007 Jun;115(6):876-82. Epub 2007 Mar 14

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BACKGROUND: Phthalates impair rodent testicular function and have been associated with anti-androgenic effects in humans, including decreased testosterone levels. Low testosterone in adult human males has been associated with increased prevalence of obesity, insulin resistance, and diabetes.

OBJECTIVES: Our objective in this study was to investigate phthalate exposure and its associations with abdominal obesity and insulin resistance. **METHODS:** Subjects were adult U.S. male participants in the National Health and Nutrition Examination Survey (NHANES) 1999-2002. We modeled six phthalate metabolites with prevalent exposure and known or suspected antiandrogenic

activity as predictors of waist circumference and log-transformed homeostatic model assessment (HOMA; a measure of insulin resistance) using multiple linear regression, adjusted for age, race/ethnicity, fat and total calorie consumption, physical activity level, serum cotinine, and urine creatinine (model 1); and adjusted for model 1 covariates plus measures of renal and hepatic function (model 2). Metabolites were mono-butyl phthalates (MBP), mono-ethyl phthalate (MEP), mono-(2-ethyl)-hexyl phthalate (MEHP), mono-benzyl phthalate (MBzP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP). RESULTS: In model 1, four metabolites were associated with increased waist circumference (MBzP, MEHHP, MEOHP, and MEP; p-values ≤ 0.013) and three with increased HOMA (MBP, MBzP, and MEP; p-values ≤ 0.011). When we also adjusted for renal and hepatic function, parameter estimates declined but all significant results remained so except HOMA-MBP. CONCLUSIONS: **In this national cross-section of U.S. men, concentrations of several prevalent phthalate metabolites showed statistically significant correlations with abdominal obesity and insulin resistance. If confirmed by longitudinal studies, our findings would suggest that exposure to these phthalates may contribute to the population burden of obesity, insulin resistance, and related clinical disorders.**

16

Associations between urinary phthalate monoesters and thyroid hormones in pregnant women.

Hum Reprod. 2007 Oct;22(10):2715-22. Epub 2007 Aug 17.

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BACKGROUND: Maternal hypothyroidism during pregnancy can cause adverse effects in the fetus. Scientific evidence has shown that probable thyroid-like function of some phthalates in vitro and in vivo, and phthalates exposure, can begin in utero. This study investigated the association between phthalate exposure and thyroid hormones in pregnant women. METHODS: Serum and spot urine samples were collected from 76 Taiwanese pregnant women at second trimester. Thyroid hormones, including thyroid-stimulating hormone (TSH), triiodothyronine (T(3)), thyroxine (T(4)) and free T(4) (FT(4)) were analysed in serum samples, and five urinary phthalate monoesters, including mono butyl phthalate (MBP), monoethyl phthalate (MEP) and mono ethylhexyl phthalate (MEHP), were measured. RESULTS: Urinary MBP, MEP and MEHP, the median levels of which were 81.8, 27.7 and 20.6 ng/ml, respectively, were the predominant substances in the urinary phthalate monoesters. **Significant mild negative correlations were found between T(4) and urinary MBP (R = -**

0.248, $P < 0.05$), and between FT(4) and urinary MBP ($R = -0.368$, $P < 0.05$). After adjusting for age, BMI and gestation, urinary MBP levels showed negative associations with FT(4) and T(4) (FT(4): $\beta = -0.110$, $P < 0.001$; T(4): $\beta = -0.112$, $P = 0.003$). CONCLUSIONS: Exposure to di-n-butyl phthalate (DBP) may affect thyroid activity in pregnant women, but how DBP affects thyroid function is unclear. Further studies are needed to elucidate the mechanism of action and to investigate whether any other factors related to DBP exposure alter the thyroid function.