Environmental Research 111 (2011) 792–796

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Phthalate exposure associated with self-reported diabetes among Mexican women ☆

Katherine Svensson [a,b], Raúl U. Hernández-Ramírez [b], Ana Burguete-García [b], Mariano E. Cebrián [c], Antonia M. Calafat [d], Larry L. Needham [d], Luz Claudio [e], Lizbeth López-Carrillo [b,*]

[a] Graduate School of Public Health, Medical Sciences Campus, University of Puerto Rico, San Juan, PR, USA
[b] National Institute of Public Health, Universidad No. 655, Col. Santa María Ahuacatitlán, Cerrada los Pinos y Caminera, CP. 62100 Cuernavaca, Morelos, Mexico
[c] Departamento de Toxicología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City, Mexico
[d] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA
[e] Division of International Health, Department of Preventive Medicine, Mount Sinai School of Medicine, NY, USA

ARTICLE INFO

Article history:
Received 18 November 2010
Received in revised form
29 April 2011
Accepted 3 May 2011
Available online 21 June 2011

Keywords:
Diabetes
Phthalates
Urinary metabolites
Environmental health
Mexico

ABSTRACT

Background: Phthalates are ubiquitous industrial chemicals used as plasticizers in plastics made of polyvinyl chloride (PVC) to confer flexibility and durability. They are also present in products used for personal-care, industry and in medical devices. Phthalates have been associated with several adverse health effects, and recently it has been proposed that exposure to phthalates, could have an effect on metabolic homeostasis. This exploratory cross-sectional study evaluated the possible association between phthalate exposure and self-reported diabetes among adult Mexican women.

Methods: As part of an on-going case-control study for breast cancer, only controls were selected, which constituted 221 healthy women matched by age (± 5 years) and place of residence with the cases. Women with diabetes were identified by self-report. Urinary concentrations of nine phthalate metabolites were measured by online solid phase extraction coupled to high performance liquid chromatography-isotope-dilution tandem mass spectrometry.

Results: Participants with diabetes had significantly higher concentrations of di(2-ethylhexyl) phthalate (DEHP) metabolites: mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) but lower levels of monobenzyl phthalate (MBzP) a metabolite of benzylbutyl phthalate, compared to participants without diabetes. A marginally significant positive associations with diabetes status were observed over tertiles with MEHHP ($OR_{T3\ vs.\ T1}=2.66$; 95% CI: 0.97–7.33; p for trend $=0.063$) and MEOHP ($OR_{T3\ vs.\ T1}=2.27$; 95% CI; 0.90–5.75; P for trend $=0.079$) even after adjusting for important confounders.

Conclusions: The results suggest that levels of some phthalates may play a role in the genesis of diabetes.

1. Introduction[1]

Phthalates are ubiquitous industrial chemicals used as plasticizers in plastics made of polyvinyl chloride to confer flexibility and durability. Plastics containing phthalates have numerous utilities and may be used to wrap and preserve food, in construction industry, medical devices and pharmaceuticals. Phthalates are also present in daily used products, such as personal-care-products (i.e., perfumes, lotions and cosmetics), paints, lacquers and varnishes (ATSDR, 1995, 1997, 2001, 2002; NTP-CERHS, 2003). Humans metabolize phthalates easily and excrete them in the urine within 24–48 h after exposure. The continuous exposure to phthalates has created interest in their possible effects on human health based on evidence from animal and human studies (Hauser and Calafat, 2005; Swan, 2008).

☆ **Funding sources:** The study was supported by Fondo Sectorial de Investigacion en Salud y Seguridad Social 2005-C02-14373, 2009-01-111384. Additional partial funds were obtained from: Fondo Sectorial de Investigación para la Educación 79912 and the ITREOH program of the Fogarty International Center (TW000640) the MIRT program of the National Center of Minority Health and Health Disparities (MD001452).

* Corresponding author.
E-mail address: lizbeth@insp.mx (L. López-Carrillo).

[1] Centers for Disease Control and Prevention (CDC); diethyl phthalate (DEP); dibutyl phthalate (DBP); diisobutyl phthalate (DiBP); butylbenzyl phthalate (BBzP); di-2-ethylhexyl phthalate (DEHP); monoethyl phthalate (MEP); mono-n-butyl phthalate (MBP); monoisobutyl phthalate (MiBP); monobenzyl phthalate (MBzP); mono(2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOH); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); and mono(3-carboxypropyl) phthalate (MCPP); body mass index (BMI); waist circumference (WC); waist/hip ratio (WH); limit of detection (LOD).

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doi:10.1016/j.envres.2011.05.015

Phthalates have been associated with several adverse human health effects (Swan, 2008; Hauser et al., 2006), and recently it has been proposed that exposure to environmental chemicals, such as phthalates, could have an effect on metabolic homeostasis increasing the risk for obesity (Desvergne et al., 2009). Two recent studies, based on cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 in the United States, suggest that exposure to phthalates could be a risk factor for obesity. One of the first study in humans reported that exposure benzylbutyl phthalate (BzBP) and di(2-ethylhexyl) phthalate (DEHP) as suggested from the urinary concentrations of their corresponding phthalate metabolites, specifically monobenzyl phthalate (MBzP), mono(2-ethyl-5-hydroxylhexyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), was associated with an increase in BMI, and that urinary concentrations of monoethyl phthalate (MEP), monobutyl phthalate (MBP) and MBzP were associated with insulin resistance (HOMA) (Stahlhut et al., 2007). The other study, also found an association between the urinary concentrations of MBzP, with an increase in BMI and waist circumference, as well as positive associations with the urinary concentrations of MEP, MEHHP and MEOHP (Hatch et al., 2008).

A possible way of how phthalates could have an effect on the human metabolism is presented by Grün and Blumberg (2007). This mechanism proposes phthalate exposure could be linked to obesity through nuclear receptors peroxisome-proliferator-activated receptors (PPAR's), specifically with PPARγ, which has an important role in adipogenesis and lipid storage. Given that obesity is a major risk factor for diabetes, the PPAR's could be a link for which phthalates may be a risk for diabetes.

Mexico occupies the fifth position on prevalence of diabetes with 10.7% among the general population (Secretaria de Salud, Encuesta Nacional de Enfermedades Crónicas, 2005). Besides well known risk factors for diabetes, such as genetic predisposition, lack of physical activity, unhealthy diet and obesity (ADA, 2008), and other environmental factors could affect this risk. The current literature leads us to the question of whether phthalate exposure could be a contributing risk factor for diabetes development. Therefore, this exploratory cross-sectional study intends to determine if there is an association between phthalate exposure and self-reported diabetes among adult Mexican women.

2. Material and methods

2.1. Study population

As part of an on-going population based case-control study for breast cancer, the first recruited controls were selected for this report, which constitutes 221 healthy women, with no history of cancer that were individually matched by age (±5 years) and place of residence with the index case. More detailed information about design and methods is published elsewhere (López-Carrillo et al., 2010). Briefly, controls were identified through the master sampling framework used in national health surveys in Mexico. A probabilistic selected list of blocks in the study area was available. Within each block, interviewers randomly identified a household. If there was more than one eligible woman in a home, one participant was randomly chosen. Otherwise, if no eligible woman was found in a household, or if she declined to participate in the study, another home was systematically located according to the survey procedures employed in national surveys (Tapia-Conyer et al., 1992). The response rate (participants/eligible) was 99.55%. This study was approved by the IRB committee from the National Institute of Public Health (INSP) of Mexico.

2.2. Interviews and urine sample collection

After signing the informed consent, participants were interviewed face-to-face by trained personnel to obtain information about socio-demographic characteristics; clinical, reproductive history (parity, lactation, *etc.*) and medical family history; dietary patterns and anthropometric measures. Women with diabetes were identified by self-report to the question *¿Le han diagnosticado alguna vez una o varias de las siguientes enfermedades: Diabetes, enfermedad benigna de mama, etc.?* (*"Have you ever been diagnosed with one or several of the following diseases: Diabetes, benign breast disease, etc.?"*). On the day of the household interview, a first morning void urine sample of each woman was collected in a sterile disposable polypropylene urine collection cup (polypropylene plastics have not been reported to contain detectable levels of phthalates). Samples were refrigerated and shipped to the Mexico National Institute of Public Health where they were stored at −70 °C until they were aliquoted.

2.3. Assessment of urinary phthalate metabolite concentrations

An aliquot of 4-mL was prepared in a cryovial (Simport®) and stored frozen at or below −20 °C until shipment to the US Centers for Disease Control and Prevention (CDC) (approximately 4 months on average).

At the CDC, samples were kept frozen at or below −40 °C until analyzed. The urinary concentrations of nine phthalate metabolites: MEP, mono-*n*-butyl phthalate (MBP), monoisobutyl phthalate (MiBP), MBzP, mono(2-ethylhexyl) phthalate (MEHP), MEHHP, MEOHP, mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono(3-carboxypropyl) phthalate (MCPP), were measured according to the methodology published elsewhere that includes online solid phase extraction coupled to high performance liquid chromatography-isotope-dilution tandem mass spectrometry (Kato et al., 2005). Phthalate metabolite concentrations were adjusted for urine dilution by creatinine levels according to a previously detailed methodology (Barr et al., 2005). Concentrations below the limit of detection (LOD) were assigned a value equal to half the LOD (LOD/2) for the analysis.

2.4. Statistical analysis

The geometric means of the phthalates metabolites concentrations, as well as socio-demographic characteristics and anthropometric measures, were compared between participants with diabetes and without diabetes using the *t*-Student test or Mann–Whitney for continuous variables and χ^2 test for categorical variables. Metabolites concentrations were log-transformed to improve normality and correlations between them were assessed by means of the Spearman correlation coefficients. Also, among women who did not report diabetes, Spearman correlation coefficients were estimated between the phthalate metabolites and BMI, waist circumference (WC), waist/hip (WH) ratio, age and education.

The association between urinary concentrations of phthalates metabolites (continuous) and diabetes was assessed by multivariate logistic regression models that were adjusted by creatinine, as recommended by Barr et al. (2005), as well as the variables that were significantly correlated to the specific phthalate metabolite among healthy women. The analysis was performed using the Stata 10 statistical software (StataCorp., 2005).

3. Results

The average age in the total study population was 54 years and the mean number of school-years was 6 (data not included in the table). From the 221 women selected for this study 39 participants reported having diabetes (17.4%). They were significantly older, less educated and more obese compared to participants without diabetes (age: 60.5 vs. 52.4 years; education 4.1 vs. 6.1 years; WH ratio: 0.94 vs. 0.91) (Table 1).

Phthalate metabolites concentrations were detected in most of the participants with a range of 83% (MEHP) to 100% (MEP, MBP and MECPP). As it was expected, Spearman correlation coefficients indicated moderate to strong associations between the urinary concentrations of the DEHP metabolites (0.66–0.97), and between the major (MBP) and minor (MCPP) metabolites of di-*n*-butyl phthalate (ρ: 0.62) (data not shown). Correlations between age, education and anthropometric measures with phthalate metabolites are shown in Table 2.

Creatinine adjusted urinary concentrations of phthalate metabolites varied by diabetes status. Participants with diabetes had significantly higher concentrations of DEHP metabolites (MEOHP, MECPP and their sum) and MCPP, as well as lower concentrations of MBzP, compared to participants without diabetes (Table 3).

Borderline significant increased risks for diabetes were observed in relation to DEHP metabolites except MEHP in contrast to the decreased risk that resulted with MBzP concentration (Table 4).

Table 1
Selected characteristics of the study population.

Characteristics	Diabetes		*P*-value[a]
	Yes ($n=39$) Mean ± SD	No ($n=182$) Mean ± SD	
Age (years)	60.5 ± 8.5	52.4 ± 12.8	< 0.001
Education (years)	4.1 ± 2.8	6.1 ± 3.4	0.002
Family history of diabetes [*n* (%)]			
No	22 (56.4)	124 (68.1)	
Yes	17 (43.6)	58 (31.9)	0.161
BMI (kg/m^2)	28.9 ± 4.6	29.2 ± 6.2	0.921
BMI categories (kg/m^2) [*n* (%)]			
Normal weight (< 25.0)	11 (28.2)	49 (26.9)	
Overweight (25.0–29.9)	10 (25.6)	60 (33.0)	
Obese (≥ 30.0)	18 (46.2)	73 (40.1)	0.654
WC (cm)	103.0 ± 11.2	98.6 ± 13.3	0.055
WH ratio	0.94 ± 0.07	0.91 ± 0.08	0.001

[a] χ^2 for categorical variables, and Mann-Whitney test for continuous.

Table 2
Spearman correlation coefficients* between phthalate metabolites and obesity indicators in subjects without diabetes ($n=182$).

Parent compounds and metabolites (μg/g creatinine)	BMI (kg/m^2)	WC (cm)	WH ratio	Age (years)	Education (years)
DEP					
MEP	−0.0473	−0.0361	−0.0414	−0.0012	0.1481*
DBP					
MBP	0.0249	−0.0478	−0.0020	0.0111	0.1916*
DiBP					
MiBP	0.0457	0.0151	−0.0156	−0.1281	0.1721*
BBzP					
MBzP	0.0059	−0.0063	0.0883	−0.0750	0.2372*
DOP					
MCPP	−0.0686	−0.0475	0.0728	0.0627	0.0931
DEHP					
MEHP	−0.0668	−0.0236	0.0336	−0.1270	0.1601*
MEHHP	0.0666	0.1843*	0.1982*	0.1726*	−0.1198
MEOHP	−0.0111	0.0865	0.1123	0.0982	−0.0632
MECPP	0.0301	0.1302	0.1235	0.1502*	−0.0652
∑DEHP	0.0354	0.1427	0.1498*	0.1437	−0.0769

* *P*-value < 0.05.

4. Discussion

To our knowledge, this is the first study evaluating phthalate exposure and diabetes status, and suggests that some phthalates might influence diabetes status.

Our results are consistent with previous analyses of a cross-sectional dataset in the United States that found that the urinary concentrations of several phthalate metabolites were associated with metabolic effects (Stahlhut et al., 2007; Hatch et al., 2008). The previous studies suggested exposure to phthalates were related to increased insulin resistance, which is a risk factor for metabolic disorders such as diabetes. Furthermore, it has been seen that exposure to phthalates may reduce the insulin levels in fetal rats (Boberg et al., 2008), which may lead to insulin resistance in adulthood (Holemans et al., 2003) and be a risk for diabetes.

It is widely accepted that obesity is a risk factor for diabetes as well as for other chronic diseases. An increase in obesity affects the balance of metabolism in the body reducing the insulin sensitivity and can finally lead to diabetes (ADA, 2008; Aschner, 2010) The participants in this present study were generally overweight and might have influenced their current diabetes status, however, we did not find significant correlations between phthalate concentrations and obesity, measured by BMI, thus, it is unlikely that obesity be on the casual pathway that may explain our results.

In this regard, it is important to mention that, previous cross-sectional epidemiological studies found that the urinary concentrations of MEHHP and MEOHP were associated with increased

Table 3
Geometric means for creatinine adjusted urinary phthalates metabolites[a] by diabetes status.

Parent compounds and metabolites	Diabetes		*P*-value*
	Yes ($n=39$)	No ($n=182$)	
DEP			
MEP	101.3 ± 2.7	108.0 ± 3.4	0.379
DBP			
MBP	82.3 ± 2.7	82.5 ± 2.6	0.495
DiBP			
MiBP	7.9 ± 2.1	9.1 ± 2.3	0.164
BBzP			
MBzP	3.8 ± 3.9	7.0 ± 2.9	0.001
DOP			
MCPP	4.5 ± 2.0	4.0 ± 2.3	0.011
DEHP			
MEHP	5.3 ± 3.2	5.0 ± 2.5	0.203
MEHHP	62.3 ± 2.1	46.2 ± 2.1	0.382
MEOHP	41.4 ± 2.2	31.9 ± 2.1	0.012
MECPP	100.3 ± 2.1	75.3 ± 2.0	0.021
∑DEHP	213.4 ± 2.1	161.6 ± 2.0	0.012

GM, Geometric mean; SD, Standard deviation.

[a] Metabolite concentration divided by creatinine ($\times 10^{-4}$).
* Student *t*-test, *P*-value < 0.05.

Table 4
Odds ratios for log transformed urinary phthalates metabolites concentration and self-reported diabetes.

Parent compounds and metabolites	Crude[a]			Adjusted[b]		
	OR	(95%CI)	*P* value[a]	OR	(95%CI)	*P* value[a]
DEP						
MEP	0.95	(0.69–1.29)	0.723	1.02	(0.74–1.39)	0.915
DBP						
MBP	0.98	(0.68–1.42)	0.928	1.10	(0.75–1.61)	0.638
DiBP						
MiBP	0.94	(0.62–1.43)	0.776	1.01	(0.65–1.55)	0.977
BBzP						
MBzP	0.73	(0.55–0.97)	0.032	0.74	(0.55–1.00)	0.051
DOP						
MCPP	1.21	(0.80–1.83)	0.367	–	–	–
DEHP						
MEHP	0.96	(0.65–1.41)	0.835	1.01	(0.68–1.49)	0.960
MEHHP	1.62	(1.01–2.59)	0.046	1.40	(0.84–2.33)	0.200
MEOHP	1.58	(0.98–2.54)	0.062	–	–	–
MECPP	1.70	(1.04–2.77)	0.033	1.54	(0.92–2.55)	0.097
∑DEHP	1.66	(1.01–2.73)	0.044	1.64	(0.98–2.73)	0.060

OR, Odds Ratio; 95%CI: 95% Confidence Interval.

[a] Including creatinine concentration as an independent variable.
[b] Adjusted by: creatinine and education (MEP, MBP, MiBP, MBzP, and MEHP): creatinine and age (MEHHP and MECPP); creatinine and WH ratio (MEHHP and ∑DEHP).

BMI and/or waist circumference (WC) in adult males (Stahlhut et al., 2007; Hatch et al., 2008). Results from *in vitro* studies suggest that phthalates have the ability to activate peroxisome-proliferator-activated receptors (PPAR's) and also induce PPARγ-dependent adipogenesis (Hurst and Waxman, 2003; Bility et al., 2004; Feige et al., 2007). The PPARγ plays a major role in the regulation of adipogenesis, insulin sensitivity, and lipid storage (Auwerx, 1999; Desvergne et al., 2009; Casals-Casas et al., 2008). According to the mechanism proposed by Grün and Blumberg (2007), MEHP the hydrolytic metabolite of DEHP can activate the PPARγ and therefore increase the risk for obesity. There is no information that evaluates if the other DEHP metabolites (MEHHP and MEOHP) also activate PPARγ, but recent results consistently suggest that DEHP do not protect against weight gain through PPARα activation, but rather promotes obesity in humanized mice, where the PPARγ plays a fundamental role (Feige et al., 2010).

Also, both Hatch et al. (2008) and Stahlhut et al. (2007), found associations between urinary concentrations of DEHP metabolites and obesity only among the males. The fact that DEHP metabolites are associated with obesity in males may be the consequence of their anti-androgenic effect that reduce levels of free testosterone (Swan, 2008; Pan et al., 2006; Main et al., 2006) and an alteration in adipose tissue (Kapoor et al., 2006). Therefore, the anti-androgenic effect of the DEHP metabolites may explain an increase in weight among men but not in women.

An alternative explanation of our results, would be a direct effect of DEHP metabolites on the glucose homeostasis. It has been seen that rats being administered DEHP at low levels during a short period had changes in their blood, such as decreased serum insulin, cortisol and liver glycogen, and increased blood glucose (Gayathri et al., 2004). A similar effect was seen in liver cells, when they were exposed to DEHP, resulting in reduced insulin receptor concentration and glucose oxidation (Rengarajan et al., 2007). These studies implicate that exposure to DEHP may results in diabetes symptoms. Although these effects have yet been seen among humans it might be another possible explanation for DEHP exposure being associated with diabetes status.

Some methodological considerations should be taken into account to interpret the results of this exploratory study. First, diabetes status was self-reported, and it is likely that some women with pre-diabetes or diabetes were misclassified as non-diabetic, which may underestimate the real prevalence of the disease. However, According to the Mexico Health Nutrition National Survey, the prevalence of diabetes in women 50–69 years of age is 17.7% in the country that is almost the same as the one we obtained in this study sample (Olaiz-Fernández et al., 2006).

Second, the small sample precluded us to find other statistical associations that may in fact exists and also increased the likelihood of detecting chance findings, that might be the case of the higher concentrations of MBzP among participants without diabetes.

Third, phthalate metabolites were measured by one-time urine sample to evaluate exposure, which is the most common way of evaluating phthalates exposure over time. The human body metabolizes phthalates rather quickly (24–48 h) and even if metabolites have been found in other body fluids (i.e., serum, blood, breast milk, saliva, seminal plasma and amniotic fluid) the major part is excreted through urine (Hauser and Calafat, 2005). The variability of phthalate exposure can vary in time from changes in use of personal care products, diet, or daily activities (Hauser and Calafat, 2005; Fromme et al., 2007). Still, most of the studies on variability suggest the exposure patterns are stable enough to permit the measure of exposure through urine and may represent one month exposure (Hoppin et al., 2002; Hauser et al., 2004; Peck et al.,2010). Even with the short half-lives of phthalate, urinary concentrations of phthalate metabolites been proven to be a good biomarker for phthalate exposure over time (Teitelbaum et al., 2008).

However, despite its limitations this study is valuable as a precursor to future studies that could confirm these results. Longitudinal epidemiological studies should take into account the variability of exposure to phthalates over time performing more than one test at 1–3 months in between for more accuracy (Hoppin et al., 2002; Hauser et al., 2004; Fromme et al., 2007; Teitelbaum et al., 2008; Peck et al., 2010; Adibi et al., 2008). It is also recommended that future studies confirm the status of diabetes by standardized test that measure blood glucose levels. Finally, further toxicological studies are needed to clarify the proposed pathways in which phthalate metabolite may influence the development of diabetes.

5. Conclusion

Exposure to DEHP might play a role in diabetogenesis. This is an incipient research that deserves further attention and longitudinal studies are warranted to confirm the relationship between exposure to some phthalates and diabetes.

Disclosure statement

The findings expressed in this paper are the opinions of the authors and do not necessarily reflect the official opinion of the Centers for Disease Control and Prevention. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was limited and determined not to constitute engagement in human subject research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Center or the National Institutes of Health. The authors declare they have no competing financial interests.

Acknowledgments

Authors gratefully acknowledge B.Sc. Verónica López for the overall coordination of field work and, Manori Silva, Tao Jia, Ella Samandar and Jim Preau for their technical assistance in measuring the urinary concentrations of phthalate metabolites. The study was supported by Fondo Sectorial de Investigacion en Salud y Seguridad Social 2005-C02-14373, 2009-01-111384 Additional partial funds were obtained from Fondo Sectorial de Investigación para la Educación 79912. Katherine Svensson is a Mount Sinai International Exchange Program Minority Student participant. Her work was supported by grant MD001452 from the National Center on Minority Health and Health Disparities of the National Institutes of Health. Additional support for this project was provided in part by the Mount Sinai International Training Program in Environmental and Occupational Health (D43TW000640) from the Fogarty International Center.

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