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Exposure to DDT and diabetic nephropathy among Mexican Americans in the 1999–2004 National Health and Nutrition Examination Survey☆

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ABSTRACT

Concentrations of the pesticide DDT (dichlorodiphenyltrichloroethane) and its metabolite DDE (dichlorodiphenyldichloroethylene), in the blood of Mexican Americans, were evaluated to determine their relationships with diabetes and diabetic nephropathy. The data were derived from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 (unweighted N = 1,411, population estimate = 13,760,609). The sample included teens, 12–19 years old, which accounted for 19.8% of the data. The time of the study overlapped the banning of DDT in Mexico in the year 2000, and those participants born in Mexico were exposed to DDT before they immigrated to the US. We sought to better understand the relationship of DDT with diabetes in a race/ethnicity group prone to develop diabetes and exposed to DDT. In this study, nephropathy was defined as urinary albumin to creatinine ratio >30 mg/g, representing microalbuminuria and macroalbuminuria, and total diabetes was defined as diagnosed and undiagnosed diabetes (glycohemoglobin, A1c ≥ 6.5%). The proportion with the isomer *p,p′*-DDT >0.086 ng/g (above the maximum limit of detection) was 13.3% for Mexican Americans born in the US, and 36.9% for those born in Mexico. Levels of *p,p′*-DDT >0.086 ng/g were associated with total diabetes with nephropathy (odds ratio = 4.42, 95% CI 2.23–8.76), and with total diabetes without nephropathy (odds ratio = 2.02, 95% CI 1.19–3.44). The third quartile of *p,p′*-DDE (2.99–7.67 ng/g) and the fourth quartile of *p,p′*-DDE (≥7.68 ng/g) were associated with diabetic nephropathy and had odds ratios of 5.32 (95% CI 1.05–26.87) and 14.95 (95% CI 2.96–75.48) compared to less than the median, respectively, whereas *p,p′*-DDE was not associated with total diabetes without nephropathy. The findings of this study differ from those of a prior investigation of the general adult US population in that there were more associations found with the Mexican Americans sample.

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1. Introduction

Reviewing human health consequences of DDT (dichlorodiphenyltrichloroethane) use, Eskenazi et al. (2009) concluded DDT and its metabolite DDE (dichlorodiphenyldichloroethylene) may be associated with breast cancer, diabetes, decreased semen quality, spontaneous abortion, and impaired neurodevelopment in children. Since 2001, the majority of the countries in the world have been committed to ending the use of 12 persistent organic pollutants, including DDT, by signing the Stockholm Convention on Persistent Organic Pollutants (United Nations Environment Programme, 2001). However, currently the Stockholm Convention approves DDT for use in 17 countries. These exemptions are primarily for malaria control. The countries exempted are: Botswana, Eritrea, Ethiopia, India, Madagascar, Marshall Islands, Mauritius, Morocco, Mozambique, Namibia, Senegal, South Africa, Swaziland, Uganda, Venezuela, Yemen, and Zambia (Stockholm Convention, 2016). Reports by the news media suggest DDT may also be used to fight the Zika virus (Sanchez, 2016).

DDT was banned in the US in 1972 and banned in Mexico in 2000. Estimates of the half-life of DDT and DDE in humans are 6 and 10 years, respectively (Smith, 1999; Lopez-Carrillo et al., 2001; Eskenazi et al., 2009). DDT in adipose tissue, breast milk of women, and in serum, worldwide have been reported for the years

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1990–2000 (Jaga and Dharmani, 2003). Studies conducted in Mexico before DDT was banned showed high levels of *p,p′*-DDT in serum, 190 ng *p,p′*-DDT/g serum lipids in 1990–1995 (Romieu et al., 2000), 73 ng *p,p′*-DDT/g serum lipids in 1994–1996 (Lopez-Carrillo et al., 1997), and 676 ng *p,p′*-DDT/g serum lipids in 1998 (Koepke et al., 2004). Mexican Americans living in Arizona, California, Colorado, New Mexico, and Texas in 1982–1984 were found to have an association of DDT in serum with self-reported diabetes (Cox et al., 2007). Serum *p,p′*-DDT >3.70 ng/g (8.4% of the sample) had an odds ratio of 2.9 (95% CI 1.2–6.8) for self-reported diabetes in a logistic regression adjusted for age, BMI (body mass index) and alcohol consumption, compared to *p,p′*-DDT <2.00 ng/g. Cox et al. (2007) reported the study included 42% foreign-born subjects, who may have had elevated DDT in their serum when they immigrated to the United States.

Associations of DDT and DDE with Type 2 diabetes have been reported in numerous studies and summarized in a meta-analysis (Evangelou et al., 2016). Estimates were transformed and harmonized to represent top and bottom tertiles in order to calculate summary odds ratios. The third tertile of DDT and *p,p′*-DDT had an odds ratio of 2.06 (95% CI 1.05–4.04) for Type 2 diabetes (specifically Type 2) compared to the first tertile, and the third tertile of DDE and *p,p′*-DDE had an odds ratio of 1.65 (95% CI 1.15–2.37) for Type 2 diabetes (specifically Type 2) compared to the first tertile. Summary odds ratios for diabetes (mainly Type 2, but may include some Type 1) were higher and also significant. Large studies (greater than the median sample size) were found to have a smaller summary effect than small studies (less than the median sample size). A systematic review has also been published on studies of persistent organic pollutants and diabetes in Asia (Jaacks and Staimez, 2015). A Korean case-control study (Son et al., 2010) reviewed, reported an odds ratio of 12.7 (95% CI 1.9–83.7) for the third tertile of *p,p′*-DDT (ng/g serum lipids) compared to the first tertile. Jaacks and Staimez (2015) noted there were "substantial limitations" of the literature they reviewed.

Kidney disease, or nephropathy, can be found in 31.1% of the persons that have diabetes in the United States (Everett and Thompson, 2015). The first level of screening for nephropathy is a measure of urinary albumin excretion based on a spot collection of urine, which is normally <30 mg albumin/g creatinine. Elevated urinary albumin excretion of 30–299 mg albumin/g creatinine is referred to as microalbuminuria, and urinary albumin excretion ≥300 mg albumin/g creatinine is referred to as macroalbuminuria (Molitch et al., 2004). In Everett and Thompson (2015) nephropathy was defined as ≥30 mg albumin/g creatinine (microalbuminuria and macroalbuminuria).

The study by Everett and Thompson (2015) is the only one that has investigated associations of *p,p′*-DDT and *p,p′*-DDE in blood with diabetic nephropathy, and with diabetes without nephropathy. The odds ratio for *p,p′*-DDT ≥0.0860 ng/g (11.4% of the sample) and diabetic nephropathy was 2.08 (95% CI 1.06–4.11) compared to *p,p′*-DDT <0.0860 ng/g, and there was no association of *p,p′*-DDT and diabetes without nephropathy. In contrast, *p,p′*-DDE ≥3.8411 ng/g was not associated with either diabetic nephropathy, or diabetes without nephropathy. These logistic regressions were adjusted for age, gender, race/ethnicity, education, poverty to income ratio, BMI, energy adjusted fruit and vegetable consumption, physical activity, and family history of diabetes.

The purpose of this study is to evaluate associations of DDT and DDE in blood of Mexican Americans with diabetic nephropathy and diabetes without nephropathy. This race/ethnicity group is known to have a high prevalence of diabetes, which may make associations with DDT and DDE easier to detect. As the time period of the study is 1999–2004 and the youngest participants were born in 1992, all immigrants from Mexico would have been exposed to DDT in their lifetime. While the proportion of the sample with *p,p′*-DDT >0.086 ng/g was 11.4% in Everett and Thompson (2015), the proportion with *p,p′*-DDT >0.086 ng/g in this study is 25.4%.

2. Methods

Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 was used to investigate associations of *p,p′*-DDT and *p,p′*-DDE in Mexican Americans with diabetic nephropathy, and with diabetes without nephropathy. Detailed information on the methodology of the NHANES 1999–2004, including laboratory assessment, can be found at the National Center for Health Statistics website (CDC, 2016). Nephropathy was defined as urinary albumin to creatinine ratio >30 mg/g, representing both microalbuminuria and macroalbuminuria (Molitch et al., 2004). Total diabetes was defined as either diagnosed or undiagnosed diabetes. Diagnosed diabetes was determined by self-report answer to the NHANES question: "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" Those who answered "borderline" were considered to not have diabetes. Undiagnosed diabetes was defined as persons who had glycohemoglobin (A1c) ≥6.5% (ADA, 2010). We did not use fasting plasma glucose for determination of undiagnosed diabetes because it was only measured on a fasting subsample of participants and would have reduced by half the number of persons in our analyses.

The organochlorine pesticide *p,p′*-DDT, and its metabolite *p,p′*-DDE, were measured in nonfasting blood samples of a one-third, stratified random, subsample of participants 12 years old and older. We included both teens (12–19 years old) and adults in our sample of Mexican Americans (unweighted N = 1,411, population estimate = 13,760,609, Table 1). High-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry was used to measure *p,p′*-DDT and *p,p′*-DDE in serum. The concentrations were expressed per gram of blood, as recommended by Schisterman et al. (2005), and on a lipid adjusted basis (Akins et al., 1989), to allow for comparisons to recent and older literature. For lipid adjustment, "serum total cholesterol (TC), nonesterified cholesterol (FC), triglycerides (TG), and phospholipids (PL) were assayed by automated, enzymatic methods and total lipids (TL) were calculated from the expression TL = 1.677 * (TC-FC) + FC + TG + PL (Akins et al., 1989)." Each person had a sample-

Table 1
Proportions for Mexican Americans by gender, age, survey year, and country of birth.

	Unweighted N	Population estimate	Proportion (%)
Gender			
Male	665	7,136,968	51.9
Female	746	6,623,641	48.1
Age (years)			
12–19	625	2,718,079	19.8
20–39	310	6,514,391	47.3
40–64	305	3,764,047	27.4
≥65	171	764,092	5.6
Survey Year			
1999–2000	505	3,880,510	28.2
2001–2002	499	4,944,849	35.9
2003–2004	407	4,935,249	35.9
Country of Birth			
US	788	6,664,718	48.4
Mexico	618	7,056,971	51.3
Elsewhere	5	38,920	0.3
Total	1411	13,760,609	100

specific limit of detection. Both *p,p′*-DDT and *p,p′*-DDT lipid adjusted were categorized as being either above or below the maximum limit of detection (MLOD). The MLOD's for *p,p′*-DDT were 0.086 ng/g, and 14.50 ng/g serum lipids. While some concentrations below the MLOD were detectable, most were not. All of the data for *p,p′*-DDE and *p,p′*-DDE lipid adjusted were detectable, however eleven subjects were missing data for these measures (unweighted N = 1400). For the logistic regressions *p,p′*-DDE and *p,p′*-DDE lipid adjusted, for all Mexican Americans, were categorized as below the median for the reference category (*p,p′*-DDE <2.99 ng/g, and *p,p′*-DDE <500.6 ng/g serum lipids), and as the third and fourth quartiles for the elevated categories. We used below the median as the reference because there were so few cases of total diabetes with, and without, nephropathy in the low end of the *p,p′*-DDE concentration range (Table 4).

We compared characteristics of Mexican Americans by country of birth (Table 2). These were mean age, mean poverty to income ratio, mean acculturation score, the proportion of *p,p′*-DDT and *p,p′*-DDT lipid adjusted above the MLOD, mean *p,p′*-DDE, and mean *p,p′*-DDE lipid adjusted. Poverty to income ratio was analyzed as a continuous variable, and was the ratio of a family's income to their appropriate poverty threshold based on family size (US Census Bureau, 2016). If the family's income was equal to the poverty threshold, the poverty to income ratio was equal to one. Poverty to income ratio was top coded at 5, and values below 1.00 were below the official poverty threshold. The acculturation score was determined using the Short Acculturation Scale (Marin et al., 1987), a five-item Spanish language scale with good internal reliability (Cronbach's coefficient alpha ≥0.90). The scale consists of the following five questions:

- "In general, what language do you read and speak?"
- "What was the language(s) you used as a child?"
- "What language(s) do you usually speak at home?"
- "In which language(s) do you usually think?"
- "What language(s) do you usually speak with your friends?"

Each question can be answered as "only Spanish," "more Spanish than English," "both equally," "more English than Spanish," or "only English." These responses were scored from 1 to 5 respectively, so that scores ranged from 5 to 25, with higher scores signifying greater acculturation (Mainous et al., 2006). Sixteen subjects were missing data for the acculturation questions (unweighted N = 1395).

We tested the associations of *p,p′*-DDT, *p,p′*-DDT lipid adjusted, *p,p′*-DDE, and *p,p′*-DDE lipid adjusted in logistic regression models adjusted for participant age, gender, body mass index (BMI) Z-score, poverty to income ratio, energy adjusted fruit and vegetable consumption, and physical activity. BMI Z-score was defined as nine categories ranging from −2 to +2, which varied by sex and age (CDC, 2009), and analyzed as a continuous variable in the logistic regression models. We assumed men and women were fully grown by age 20, and used the tables for 20-year-olds to calculate BMI Z-score for all adults. Adult men with BMI 22.3–23.9 kg/m^2, and adult women with BMI 21.0–22.7 kg/m^2 were assigned a BMI Z-score of 0, and adult men with BMI ≥31.5 kg/m^2, and adult women with BMI ≥33.7 kg/m^2 were assigned BMI Z-score of +2. Number of fruit and vegetable servings consumed per day was determined from questions asked during the NHANES dietary interview and adjusted for energy intake (kcal/day). Physical activity was defined as moderate or vigorous activity over the past 30 days, versus sedentary, from two NHANES questions (CDC, 2016). Of the covariates used in Everett and Thompson (2015), education level of teens was not indicative of socio-economic status, and family history of diabetes was not recorded for teens. Therefore, these two variables were not used in the current study.

We used SAS version 9.3 for all analyses (SAS Institute Inc., 2016). The surveylogistic procedure was used for all logistic regression models as this procedure allows for appropriate population-level estimates from the complex sample design used in the NHANES. The "normal" group with A1c <5.7% (ADA, 2010) and urinary albumin to creatinine ratio <30 mg/g (Molitch et al., 2004) was used as the referent (Table 3) for all logistic regression models. Our analyses incorporated both the stratification and

Table 3
Diabetes categories for Mexican Americans.

Diabetes category	Unweighted N	Population estimate	Proportion (%)
Normal A1c (<5.7%)			
Without Nephropathy	1063	10,657,168	77.4
With Nephropathy	96	843,547	6.1
Pre-diabetes (A1c 5.7–6.4%)			
Without Nephropathy	111	1,097,018	8.0
With Nephropathy	13	106,399	0.8
Total Diabetes (diagnosed or A1c ≥ 6.5%)			
Without Nephropathy	76	673,399	4.9
With Nephropathy	52	383,077	2.8
Total Sample	1411	13,760,609	100

Table 2
Age, poverty to income ratio, acculturation score, proportion of *p,p′*-DDT above the maximum limit of detection, and *p,p′*-DDE concentrations for Mexican Americans by country of birth.

	Born in the US	Born in Mexico
Age (years)	32.6 (30.9–34.4)[a]	35.4 (34.3–36.6)
	IQR = 17.6–42.8[b]	IQR = 24.2–42.7
Poverty to Income Ratio	2.30 (2.09–2.51)	1.52 (1.40–1.64)
	IQR = 1.00–3.46	IQR = 0.82–2.00
Acculturation Score[c]	19.4 (18.5–20.3)	8.0 (7.6–8.3)
	IQR = 15.5–23.5	IQR = 5.0–9.3
p,p′-DDT >0.086 ng/g	13.3% (10.5%–16.0%)[d]	36.9% (32.3%–41.6%)
p,p′-DDT >14.50 ng/g serum lipids	11.6% (8.3%–14.8%)	34.4% (29.4%–39.3%)
p,p′-DDE (ng/g)	4.29 (3.50–5.07)	12.76 (10.96–14.57)
	IQR = 0.97–4.73	IQR = 2.04–11.94
p,p′-DDE (ng/g serum lipids)	662.5 (562.8–762.2)	1978.0 (1688.7–2267.2)
	IQR = 196.1–784.0	IQR = 351.2–2050.1

[a] Mean (95% Confidence Interval).
[b] IQR = Interquartile Range.
[c] 5 = All Spanish, 25 = All English.
[d] Proportion above the Maximum Limit of Detection (95% Confidence Interval).

clustering aspects of the sample design. The proper weighting procedures include adjustments for nonresponse and post-stratification. Moreover, as teens were oversampled and a complex sampling design was employed, sampling weights provided by the NHANES for the organochlorine pesticide subsample were used to compute population estimates based on weighted parameter estimates and standard errors (CDC, 2016).

3. Results

Proportions by gender, age, survey year, and country of birth are shown in Table 1. Teens 12–19 years old were 44.3% of the subjects included (unweighted N = 625), but due to the weighting of the data represented 19.8% of the total analyzed. We included teens to improve our estimates of *p,p′*-DDT and *p,p′*-DDE by increasing the size of our sample, but two subjects in this age range did have diabetes, one with nephropathy and one without.

Characteristics of Mexican Americans born in the US and Mexican Americans born in Mexico are summarized in Table 2. Mean age of the two groups differed by just 2.8 years and had overlapping 95% confidence intervals. Poverty to income ratio was higher (2.30, 95% CI 2.09–2.51) among Mexican Americans born in the US indicating they had greater wealth than those born in Mexico (poverty to income ratio = 1.52, 95% CI 1.40–1.64). Poverty to income ratio less than 1.00 indicates a family is below the official poverty threshold. Similarly, those born in the US were more acculturated than those born in Mexico based on language usage. Mexican Americans born in Mexico had an acculturation score of 8.0 (95% CI 7.6–8.3) whereas those born in the US had an acculturation score of 19.4 (95% CI 18.5–20.3). If a person answered the same to each of the five questions a score of 10.0 would mean the subject used "more Spanish than English," and a score of 20.0 would mean the subject used "more English than Spanish." When we imputed the missing data for the acculturation questions for the 16 subjects missing one or more answer, the acculturation score means by country of birth did not change.

Levels of *p,p′*-DDT and *p,p′*-DDE in blood also differed by country of birth (Table 2). For *p,p′*-DDT >0.086 ng/g (above the maximum limit of detection) there were 13.3% and 36.9% with elevated concentrations among those born in the US, and those born in Mexico, respectively. Similarly, for *p,p′*-DDT >14.50 ng/g serum lipids (above the MLOD) there were 11.6% and 34.4% with elevated concentrations, in those born in the US and in those born in Mexico, respectively. As none of the *p,p′*-DDE data were below the limit of detection, we were able to calculate means by country of birth. Mean *p,p′*-DDE (ng/g) was 4.29 (95% CI 3.50–5.07) for those born in the US and 12.76 (95% CI 10.96–14.57) for those born in Mexico. Lipid adjusted values for *p,p′*-DDE were also higher among those born in Mexico, by a factor of three, compared to those born in the US (Table 2). However, the *p,p′*-DDE data for those born in Mexico were skewed, and better summarized by reference to the interquartile range.

The proportion of Mexican Americans having total diabetes without nephropathy was 4.9%, and the proportion with diabetic nephropathy was 2.8% (Table 3). Of these, 82.2% and 89.9% were in persons 40 years old or older, respectively. For total diabetes without nephropathy, there were 27.3% (unweighted N = 15) that had undiagnosed diabetes, and those with diagnosed diabetes had had the disease for a median of 4.1 years (95% CI 3.0–5.2 years). Similarly, for total diabetes with nephropathy, there were 16.9% (unweighted N = 9) that had undiagnosed diabetes, and those with diagnosed diabetes had had the disease for a median of 8.4 years (95% CI 6.0–10.9 years). While nephropathy is recognized as a complication of diabetes, the fact there are so many with undiagnosed diabetes in the total diabetes with nephropathy group, and that there are persons with pre-diabetes with nephropathy (Table 3, unweighted N = 13) that could progress to incident diabetes with nephropathy very easily, suggests total diabetes with nephropathy can occur without being preceded by total diabetes without nephropathy.

Associations of *p,p′*-DDT and *p,p′*-DDE with total diabetes, without regard to nephropathy status, are shown in Table 4, and associations of *p,p′*-DDT and *p,p′*-DDE with total diabetes, with and without nephropathy, are shown in Table 5. Both *p,p′*-DDT and *p,p′*-DDT lipid adjusted were significantly associated with diabetic nephropathy, and with total diabetes without nephropathy. The odds ratios were higher for total diabetes with nephropathy, but the confidence intervals were also wider. For *p,p′*-DDT >0.086 ng/g the odds ratio was 4.42 (95% CI 2.23–8.76) for diabetic nephropathy, and 2.02 (95% CI 1.19–3.44) for total diabetes without nephropathy.

Table 4
Associations of *p,p′*-DDT and *p,p′*-DDE among Mexican Americans with total diabetes, and unweighted number of subjects in each logistic regression.[a]

	Unweighted N[b]				Total diabetes	
	(1)	(2)	(3)	(4)	Odds ratio	95% CI
p,p′-DDT (ng/g)						
≤0.086	836	30	15	45	1.00	–
>0.086	227	46	37	83	2.61	1.62–4.22
p,p′-DDT (ng/g serum lipids)						
≤14.50	846	32	19	51	1.00	–
>14.50	217	44	33	77	2.46	1.59–3.79
p,p′-DDE (ng/g)						
<2.99	642	6	3	9	1.00	–
2.99–7.67	213	13	11	24	1.38	0.50–3.84
≥7.68	199	56	38	94	3.92	1.43–10.71
p,p′-DDE (ng/g serum lipids)						
<500.6	622	8	3	11	1.00	–
500.6–1195.0	218	16	12	28	1.83	0.73–4.58
≥1195.1	214	51	37	88	3.35	1.40–8.02

[a] Adjusted for age, gender, BMI Z-score, poverty income ratio, energy adjusted fruit and vegetable consumption, and physical activity. Note that C-statistics for the 4 logistic regression models were very good and ranged from 0.918 to 0.920.
[b] Unweighted N for: (1) Reference category. (2) Total diabetes without nephropathy. (3) Total diabetes with nephropathy. (4) Total diabetes without regard to nephropathy status.

Table 5
Associations of *p,p′*-DDT and *p,p′*-DDE among Mexican Americans with total diabetes, with and without nephropathy.[a]

	Total Diabetes Without nephropathy		Total diabetes With nephropathy	
	Odds ratio	95% CI	Odds ratio	95% CI
p,p′-DDT (ng/g)				
≤0.086	1.00	–	1.00	–
>0.086	2.02	1.19–3.44	4.42	2.23–8.76
p,p′-DDT (ng/g serum lipids)				
≤14.50	1.00	–	1.00	–
>14.50	2.14	1.46–3.15	3.18	1.59–6.36
p,p′-DDE (ng/g)				
<2.99	1.00	–	1.00	–
2.99–7.67	0.95	0.29–3.08	5.32	1.05–26.87
≥7.68	2.61	0.88–7.73	14.95	2.96–75.48
p,p′-DDE (ng/g serum lipids)				
<500.6	1.00	–	1.00	–
500.6–1195.0	1.34	0.50–3.61	6.33	1.19–33.57
≥1195.1	2.12	0.81–5.60	14.69	2.94–73.29

[a] Adjusted for age, gender, BMI Z-score, poverty income ratio, energy adjusted fruit and vegetable consumption, and physical activity. Note that C-statistics for the 8 logistic regression models were very good and ranged from 0.913 to 0.929.

The results for *p,p′*-DDE and *p,p′*-DDE lipid adjusted, were very different between the two diabetes categories. Odds ratios for *p,p′*-DDE and *p,p′*-DDE lipid adjusted above the median were significant for diabetic nephropathy, but not significant for total diabetes without nephropathy.

Looking at the severity of diabetic nephropathy, those with macroalbuminuria (≥300 mg/g urinary albumin to creatinine ratio) represented 28.0% of the diabetic nephropathy group (unweighted N = 16). These persons are at greater risk of progressive chronic kidney disease. Comparing total diabetes with microalbuminuria (30–299 mg/g urinary albumin to creatinine ratio) to total diabetes with macroalbuminuria, the associations with *p,p′*-DDT and *p,p′*-DDE for the two groups looked very similar (Supplemental Material Table 1). Hence, the results of this study do not depend on the degree of albuminuria, but rather on its presence.

4. Discussion

High levels of *p,p′*-DDT were found among Mexican Americans included in the 1999–2004 NHANES. In the general adult US population the proportion with *p,p′*-DDT >0.086 ng/g was 11.4% (Everett and Thompson, 2015). In contrast, the proportion of Mexican Americans, born in Mexico, that had elevated levels of *p,p′*-DDT was 36.9%. Concentrations of a metabolite of DDT, *p,p′*-DDE, were also high among those born in Mexico compared to those born in the US. As DDT was not banned in Mexico until 2000, all of the Mexican Americans born in Mexico were exposed to DDT before they came to the United States. Why 13.3% of the Mexican Americans, born in the US, had *p,p′*-DDT >0.086 ng/g is not clear and may be due to the importation of food from Mexico, particularly diary products.

The prevalence of diabetes is known to be higher in Mexican Americans than Non-Hispanic Whites in the United States. In the 1999–2004 NHANES age-standardized prevalence of diabetes among adults ranged from 8.3% to 10.2% in Non-Hispanic Whites, and from 13.2% to 16.6% for Mexican Americans (Menke et al., 2015). The prevalence of total diabetes in our study was 7.7%, which differs from the prevalence for Mexican Americans reported by Menke et al. (2015) due to a difference in the age distribution. We included 625 teens 12–19 years old, which represented 19.8% of our sample, whereas the youngest persons analyzed by Menke et al. (2015) were 20 years old. Genetic predisposition to develop diabetes may interact with high levels of DDT in the body. This could explain why total diabetes without nephropathy was associated with *p,p′*-DDT >0.086 ng/g in the current study when it was not in the general adult US population (Everett and Thompson, 2015). Comparing the odds ratios for the association of *p,p′*-DDT >0.086 ng/g with diabetic nephropathy in the two studies, in the general adult US population the odds ratio was 2.08 (95% CI 1.06–4.11) and in the current study of Mexican Americans the odds ratio was 4.42 (95% CI 2.23–8.76). This also suggests greater susceptibility of Mexican Americans to develop diabetic nephropathy when exposed to elevated DDT levels.

Associations of *p,p′*-DDT and *p,p′*-DDE with total diabetes are reported in Table 4. Comparing the lipid adjusted values to those in Everett and Matheson (2010) shows both similarities and differences. The results for *p,p′*-DDT are similar with *p,p′*-DDT >14.50 ng/g serum lipids having an odds ratio of 2.46 (95% CI 1.59–3.79) in Mexican Americans, and *p,p′*-DDT ≥20.7 ng/g serum lipids having an odds ratio of 1.96 (95% CI 1.29–2.98) in the adult general US population reported in Everett and Matheson (2010). While significant associations were also found for *p,p′*-DDE in both studies, the thresholds described differed with *p,p′*-DDE ≥1195.1 ng/g serum lipids having an odds ratio of 3.35 (95% CI 1.40–8.02) for total diabetes in Mexican Americans, and *p,p′*-DDE ≥168.6 ng/g serum lipids having an odds ratio of 1.90 (95% CI 1.13–3.18) for total diabetes in the adult general US population. In the current study, the *p,p′*-DDE reference category was 50% of the sample (*p,p′*-DDE <500.6 ng/g serum lipids), and in Everett and Matheson (2010) it was 33.3% of the sample (*p,p′*-DDE <168.6 ng/g serum lipids).

In Everett and Thompson (2015) elevated *p,p′*-DDE was defined as the fourth quartile (≥3.8411 ng/g), and neither total diabetes without nephropathy or diabetic nephropathy was associated with elevated *p,p′*-DDE in the general adult US population. In the current study of Mexican Americans *p,p′*-DDE greater than the median (≥2.99 ng/g) was associated with diabetic nephropathy, but not with total diabetes without nephropathy. The odds ratio for the fourth quartile (*p,p′*-DDE ≥7.68 ng/g) and diabetic nephropathy was very high (odds ratio = 14.95, 95% CI 2.96–75.48), which raises questions as to the cause.

The reason for significant associations between *p,p′*-DDE and diabetic nephropathy, and no association between *p,p′*-DDE and total diabetes without nephropathy, is not clear, but some insights can be gained from the literature. Siddarth et al. (2014) studied polymorphism of xenobiotic metabolizing enzyme glutathione S-transferase (GST) genotypes and compared *p,p′*-DDT and *p,p′*-DDE in chronic kidney disease (CKD) patients to age and sex matched healthy controls (N = 540). CKD in this study was defined as deranged renal function for more than 3 months, with or without proteinuria, and estimated glomerular filtration rate <90 ml per min/1.73 m^2 on two different occasions 3 months apart. These CKD patients did not have diabetes. Siddarth et al. (2014) found the GSTM1(−)/GSTT1(−) genotype (absence of both) was associated with CKD having an odds ratio of 1.81 (95% CI 1.08–3.03) for the condition, and that the third tertile of *p,p′*-DDE had an odds ratio of 2.70 (95% CI 1.04–7.02) for CKD compared to the first tertile of *p,p′*-DDE. The third tertile of *p,p′*-DDT was not associated with CKD when compared to the first tertile of *p,p′*-DDT. The DDT and DDE logistic regressions in this study were adjusted for age, sex, BMI and total lipid content. Hence the absence of both GSTM1 and GSTT1 results in less *p,p′*-DDE being metabolized by CKD patients with the genotype.

Datta et al. (2010) looked at GST genotypes in four disease states: 1) healthy controls, 2) diabetes without CKD, 3) diabetes with CKD, and 4) nondiabetic CKD (N = 200). CKD in this study was defined as microalbuminuria or overt proteinuria. The proportion with the GSTM1(−)/GSTT1(−) genotype was 6% for healthy controls, 18% for diabetes without CKD, 32% for diabetes with CKD, and 18% for nondiabetic CKD. Therefore, we can hypothesize that our Mexican Americans having total diabetes with nephropathy had a higher prevalence of the GSTM1(−)/GSTT1(−) genotype, or another xenobiotic metabolizing enzyme genotype, than that of our total diabetes without nephropathy group.

However, we can not rule out reverse causality as a reason for our *p,p′*-DDE findings. Reverse causality in this case is when the disease being investigated precedes the elevated pollutant level in blood. The level of *p,p′*-DDE in blood is not causing the disease, but rather is a result of it. Studying *p,p′*-DDE and incident diabetes, Turyk et al. (2009) tested the plausibility of reverse causality as a reason for an association by comparing serum *p,p′*-DDE in 1994–1995 to that in 2001–2005 by diabetes status (N = 289). Geometric means of annual percent change in *p,p′*-DDE were not significantly different in subjects with or without diabetes in unadjusted analyses or analyses adjusted for age in 1994–1995, sex, BMI in 1994–1995, percent change in BMI, and log *p,p′*-DDE in 1994–1995. Turyk et al. (2009) concluded the reverse causality hypothesis was not supported by their estimates of metabolism using percent change in *p,p′*-DDE. As we report associations, either reverse causality, or a gene × environment interaction, are possible explanations for our *p,p′*-DDE results.

5. Conclusions

Mexican Americans are prone to develop diabetes and have a history of being exposed to DDT in Mexico until the pesticide was banned there in the year 2000. In this study, DDT was associated with both diabetic nephropathy and diabetes without nephropathy among Mexican Americans. In prior work (Everett and Thompson, 2015), the results differed, with *p,p′*-DDT being associated with diabetic nephropathy, but not with diabetes without nephropathy in the general adult US population. Among Mexican Americans, relationships with *p,p′*-DDE may be due to a gene × environment interaction as reported in studies from India (Siddarth et al., 2014; Datta et al., 2010). This hypothesis needs to be tested in future studies involving Mexican American participants.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2016.12.069.

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