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Exposure to organophosphorus insecticides and increased risks of health and cancer in US women

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ABSTRACT

Results of this paper provide evidence that chronic long-term exposure to organophosphorus insecticides poses a significantly higher health risk for US women than for men, based on dialkylphosphate biomarker data from NHANES cycles 2003-2012. The risk of cardiovascular disease for female non-smokers aged 60-85 years in the highest dimethylthiophosphate (DMTP) urinary concentration quartile is 3.0 (odds ratio, OD = 3.0, 95%CI 1.4-6.4) times higher than that in the lowest quartile. Women with higher urinary DMTP concentrations also have significantly higher risk of asthma at the ages 6-39 years and an apparently higher risk of chronic bronchitis at the ages 60-85. Overall cancer risk is significantly higher for female non-smokers aged 60-85 years in the higher urinary DMTP quartiles (OD = 2.7, 95% CI 1.3-5.9). Increasing risks of breast cancer for female smokers and prostate cancer for male smokers aged 60-85 years with higher exposure to organophosphorus insecticides in the US are also significant.

1. Introduction

Organophosphorus (OP) compounds are a group of insecticides widely used for pest control on crops in agriculture and on livestock and for other commercial purposes (EPA, 2017; Ragnarsdottir, 2000). OP insecticides account for about 30% of the global insecticide market (i.e., agricultural, home and garden, industry, commercial, and government) (EPA, 2017). Because of health concerns, household domestic use of most OP insecticides has been phased out, following the implementation of the Food Quality Protection Act of 1996. Exposure to OP insecticides can induce free radical production and consequent lipid peroxidation (Akhgari et al., 2003; Altuntas et al., 2002) which can induce DNA damage (Dizdaroglu et al., 2002; Kang, 2002). For adults, long-term exposure to both small and large doses of OP insecticides can increase the risk for developing respiratory and reproductive problems, diabetes (Montgomery et al., 2008), cardiovascular disease (CVD) (Georgiadis et al., 2018; Hung et al., 2015; Sekhotha et al., 2016), Parkinson's disease (Manthripragada et al., 2010), and Alzheimer's disease (Hayden et al., 2010; Weichenthal et al., 2010). For children, OP exposure has been related to developmental problems, including decreased IQ and ADHD (Bouchard et al., 2010; Bouchard et al., 2011). OP exposure has also been actively studied for the risk for multiple types of cancer for agricultural applicators (Alavanja et al., 2004; Bonner et al., 2010; Mahajan et al., 2006).

However, research on the exposure to OP insecticides for non-agricultural US populations and the health impact on women in the United States has been relatively limited (Burns et al., 1998; Cecchi et al., 2012; Engel et al., 2017). Consequently, knowledge on the potential impact of OP exposure on the broad health of the overall population, especially of US women, are still inadequate (Lerro et al., 2015). The aim of this study was to examine the relation of OP exposure and broad health risk, including cancer risk for the US population with a particular focus on women. Our study uses urinary concentrations of the most commonly detected OP metabolite in the US population as an indicator of OP exposure to examine the relation of this exposure to the frequency of prescription drug usage; the occurrence of general health issues such as asthma, bronchitis, CVD, and the incidence of cancer reported in the US National Health and Nutrition Examination Survey (NHANES). Metabolites of OP insecticides have been used regularly as indicators of OP exposure in US agricultural and related populations studies (Arcury et al., 2016; Barr et al., 2005; Barr et al., 2011; Das et al., 2001).

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2. Material and Methods

2.1. Data

The National Center for Health Statistics of the Centers for Disease Control and Prevention (NCHS/CDC) conducted the NHANES studies. NHANES is designed to measure the health and nutrition status of the civilian, noninstitutionalized U.S. population. NHANES participants were selected based on their age, sex, and racial/ethnic background through a complex statistical process using the most current census information. Urine specimens were collected from participants 6–85 years of age during one of three daily examination periods. Sociodemographic information and medical histories of survey participants and their families were collected during the household interview. Detailed descriptions of the survey design and data collection procedures are available in NHANES documents (CDC, 2020a). NHANES data collection was reviewed and approved by the NCHS ethics review board (CDC, 2020d). All data were approved for public release by the NCHS Research Ethics Review Board, and documented consent was obtained from participants (CDC, 2020d).

Urinary dialkylphosphate (DAP) metabolite concentrations of OP insecticides were measured in a 1/3 subset of participants of each NHANES cycle. For this study, DAP concentrations in 4935 male and 5103 female NHANES participants were obtained from the Organophosphate Insecticides - Diakyl Phosphate Metabolites files of NHANES database and represented four 2-year survey cycles between 2003-2012 (CDC, 2020a). The files contain urinary values of six DAP metabolites of OP insecticides, including: dimethylphosphate, dimethylthiophosphate (DMTP), dimethyldithiophosphate, diethylphosphate, diethylthiophosphate and diethyldithiophosphate (CDC, 2020b). About 75% of registered OP insecticides are metabolized to DAP metabolites in the body (CDC, 2019, 2020b,c,d). Because each of the six urinary DAP metabolites can be produced from the metabolism of more than one OP insecticide or preformed environmental metabolites, the mere presence of one or more DAP metabolites cannot be attributed to a specific OP insecticide (CDC, 2020b). Urinary creatinine data of participants were obtained from the Albumin & Creatinine – Urine files of NHANES database (CDC, 2020a). Urinary samples were collected from participants in the Mobile Examination Center (MEC) by NHANES, and urine samples were measured by the Environmental Health Laboratory at the Centers for Disease Control and Prevention.

Amount and types of prescription drug use of participants corresponding to the four-cycles (2003-2012) of urinary OP metabolites were obtained from Prescription Medications file of the NHANES database (CDC, 2020a). Self-reported medical conditions were obtained from the Medical Conditions file of NHANES database. They include answers to questionnaires on a broad range of health conditions for both children and adults, including inquiry on if participants had been told they had asthma, a heart attack, stroke, coronary diseases, chest pain etc. and if they had ever been told they had cancer, types of cancer, and age when they were first told they had a specific cancer etc. These questions were asked before the physical examination, in the home, using the Computer-Assisted Personal Interviewing-CAPI (interviewer administered) system. Age, sex, race/ethnicity, Interview and Mobile Examination Center (MEC) sample and interview weight data were obtained from the Demographic files in NHANES database. The smoking statuses of participants were obtained from the Smoking-Cigarette Use file in NHANE database. They were part of the interview questions administered during the MEC interview for people aged 20 and above.

2.2. Statistical analyses

Urinary levels of DMTP were selected as the indicator biomarker of exposure to OP insecticides in this study. DMTP is the most frequently detected metabolite of multiple OP insecticides between 2003-2012 (the period data are available) and can be produced from the metabolism of 13 OP insecticides in the US (CDC, 2020b). The 13 OP insecticides are: Azinphos methyl, Chlorpyrifos methyl, Dimethoate, Fenitrothion, Fenthion, Isazaphos-methyl, Malathion, Methidathion, Methyl parathion, Oxydemeton-methyl, Phosmet, Primiphos-methyl and Temephos. Among the six urinary DAP metabolites reported by NHANES, urinary levels of DMTP between 2003-2012 have the highest percentage (80.3%) of values above the limit of detection (LOD). Geometric means of urinary DMTP concentration of each age were calculated for both men and women. Participants were separated into four age groups, 6-19 (No DMTP data for people aged <6 years), 20-39, 40-59, and 60+ following CDC's pooled population study of pesticide DDT (CDC, 2020a). This approach is to ensure sufficient illness/cancer case counts in each age group and still capture the health characteristics of an individual group's response to OP exposure. DMTP values within each of the four-age groups were divided into four exposure quartiles based on their distribution of DMTP concentrations. The 1st quartile has the lowest DMTP levels and is considered to have the least exposure to OP insecticides while the 4th quartile has the highest DMTP levels and is considered to have the highest exposure to OP insecticides. Counts of medical conditions of corresponding age groups were the cumulative counts for each exposure quartile within the respective age group. A count was added when the answer was "yes" to the question "have you ever been told you had" a certain medical condition such as a heart attack or chronic bronchitis. Cancer frequency counts were added for a participant when there is an age in the category for "age when a specific cancer was first diagnosed." The total participant counts of the prescription drug use corresponding to exposure quartile of each age group were the cumulative counts of respective quartile within each of the four-age groups. The counts were added for participants who answered "yes" to the question "Taken prescription medicine, past month." Odds ratios, using the lowest quartile of DMTP concentration as the referent quartile, and 95% test-based confidence intervals were calculated (Kleinbaum et al., 1982) for each sex and age groups with urinary creatinine value, races (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race - Including Multi-Racial) and body mass index (BMI) as independent variables in logistic regression models (Barrr et al., 2005). An odds ratio is considered statistically significant in this paper only when its 95% lower limit is 1 or above. Smokers are defined as the participants who answered "yes" to the question "have you ever smoked 100 or more cigarettes in your life time?" All participants who did not have a "yes" answer to this question were considered non-smokers in this paper. Because this smoking status only involves people aged 20 and above, whenever a discussion involving a smoking status, it is only referring to people aged 20 and above groups. Because of the possible complications of smoking, analyses of counts and odds ratios were done separately for non-smokers and smokers. Conclusions in this paper are primarily for non-smokers, instead of smokers.

Weighted means, standard errors and their 95% confidence levels of urinary DMTP concentrations of 4935 men and 5103 grouped by sex were calculated (excluding 22 zero values for geometric mean calculation). Respective sample weights (interview and MEC from the demographic file) were used to account for differential nonresponse and/or noncoverage, to adjust for planned oversampling of some groups, and to adjust for uneven representation of days of the week. Statistical analyses, including weighted geometric means (using natural log and exponential conversion), standard errors, odds ratios, and their 95% confidence intervals of all NHANES data were calculated in Stata (SE/14) using its Survey Data Analysis tool. Data processes requiring only sorting and simple calculations were conducted in Microsoft Excel.

3. Results

3.1. Sex difference and age trends of urinary DMTP concentrations and health risks

The overall geometric mean (GM) of urinary concentration of DMTP

in women (GM = 2.00 ug/l, 95%CI 1.89-2.11) are 1.01 (95% CI, 0.98-1.03) times of that of men (GM = 1.99 ug/l, 95%CI 1.87-2.11) (Fig. 1). GMs of Urinary DMTP level of three age groups (between 6 and 59 years) of women are higher than that of men while GM of urinary DMTP level of age group 60-85 years of women is smaller than that of men. The ratios of GM of DMTP values are 1.01 (95% CI, 0.98-1.03) and 0.94 (95% CI, 0.91-0.97) between non-smoking women and men, and smoking women and men respectively. Among the four age groups of non-smokers, the GM of urinary DMTP concentration are the lowest for the 20-39 age group (Women: 2.11ug/l, CI95% 1.88-2.38; Men: 1.92 ug/l CI95% 1.67-2.21) and the highest for the 60-85 age group (2.34ug/l, CI95% 1.99-2.74; Men: 3.46 ug/l, CI95% 2.83-4.23) in both women and men. The GMs of urinary DMTP concentration of other nonsmokers are 2.26 ug/L (CI95% 2.03-2.52) for women and 2.23 ug/l (CI95% 2.02-2.45) for men aged 6-19 years and 2.06 ug/l (CI95%1.76-2.41) for women and 1.97 ug/l (CI95% 1.66-2.35) for men aged 40-59 years. 19.7% of women's and men's DMTP values are below the LOD. When the DMTP values were divided into quartiles within each age group, data below the LOD are mostly in the 1 st quartile.

The increased total counts of CVD, including heart failure, coronary heart disease, angina/pectoris, heart attack and stroke, chronic bronchitis and cancers with age are apparent except for asthma (Table 1). There are proportionally fewer asthma cases with increasing age. The illnesses reported in the NHANES medical file that did not reveal a clear relationship with the increased OP concentration during our initial analyses were not listed here. Some of the non-clear relationships are likely due to insufficient illness cases reported for our study period of 2003-2012.

3.2. Increased health risk for woman with higher OP exposure

There is a higher risk of total CVD in the two higher DMTP quartiles than in the two lower DMTP quartiles for both male and female non-smokers aged 40 and above (Table 2). The odds ratios (OD) of CVD counts of the highest DMTP quartile to the lowest DMTP quartile, after adjusted for creatinine, BMI and races in the model are 3.0 with 95%CI 1.4-6.4 for female non-smokers of aged 60-85. Odds ratio of asthma shows a dose-response relationship with the urinary DMTP concentration with the highest at 1.7 (CI95% 1.0-2.9) for women aged 6-19 years (Table 3). Odds ratios of chronic bronchitis of female non-smokers aged 60-85 years of the higher DMTP quartiles to the lowest DMTP quartile also shows are a dose-response relationship and are higher than 1, but not statistically significant.

A dose-dependent relationship of odds ratios between counts of prescription drug usage and OP exposure after adjustment for creatinine, BMI and races in the model was observed as well, but they are not statistically significant for female non-smokers (Tables 2). The total frequency counts of prescription drug usage are slightly higher in the highest DMTP quartile (Table 4). The list of names for the top 20 prescription drugs (based on frequency counts in the highest urinary DMTP quartile) includes drugs for treating breathing difficulties (albuterol), high blood pressure (amlodipine, atenolol, hydrochlorothiazide, lisinopril), high triglyceride levels (atorvastatin), osteoporosis (alendronate) and common pain (ibuprofen) (WebMd.com, 2020) etc. The odds ratios of CVD, chronic bronchitis and asthma are not statistically significant for either male smokers or non-smokers.

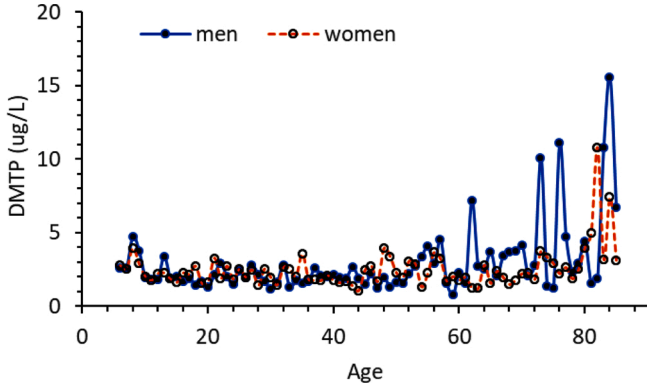

Fig. 1. Geometric means of urinary OP metabolite dimethylthiophosphate (DMTP) concentrations (ug/L) vs. age for 3878 female non-smokers and 3125 male non-smokers. Women's geometric means are apparently higher than men before the age of 60 years.

3.3. Increased cancer risks for both men and women with higher OP exposure

The odds ratios of the higher DMTP quartiles to the lowest DMTP quartile are only significant for total cancer of female non-smokers aged 60-85 years (Table 2). These odds ratios are also larger than 1 for female non-smokers aged 60-85 years, but not statistically significant. For female smokers aged 60-85 years, the odds ratios of the highest DMTP quartile to the lowest DMTP quartile are statistically significant for both breast cancer (Table 2) and total cancer (OD 4.5, 95%CI 1.6-12.4). For male non-smokers, odds ratios of total cancer of the higher DMTP quartiles to the lowest DMTP quartile are not statistically significant for any age groups (Table 2). For male smokers, odds ratios of the highest DMTP to the lowest DMTP quartile are significantly larger than 1 for prostate cancer (OD = 2.8, 95%CI 1-7.9) but not statistically significant for total cancer.

4. Discussion

Sex differences in drug metabolism have been extensively studied (Skett, 1988). Sex differences are found in drug absorption, distribution and excretion. Many cytochrome P450 enzymes show a sex-dependent difference in activity. Experimental studies have found that some drugs were metabolized by certain isoforms of cytochrome P450 at much higher rates in male rats than in female (Kato, 1974). Varied metabolic rates related to hormonal regulation of the production of drug metabolizing enzymes are common in humans (Scandlyn et al., 2008, Yang et al., 2012). High GM of urinary OP metabolite in women than in men before ages 50-60 may indicates a higher urinary clearance of OP metabolite by Cytochromes P450 and paraoxonases in women before menopause. OP may interfere with hormonal functioning by altering estrogen activity and estrogen receptor transactivity (Kjeldsen et al., 2013; Calaf and Echiburu-Chau, 2012). The higher clearance of urinary OP metabolite in women subsided after menopause. Besides sex differences in the OP metabolic rate, sex differences in OP toxicity have also been reported in the hormonally sensitive health outcomes and diseases (Calaf and Roy, 2008; Comfort and Re, 2017; Suarez-Lopez et al., 2020).

4.1. Increased risk and prevalence of CVD with exposure to OP insecticides for women

One of the most significant health risks for female non-smokers corresponding to the high OP exposure category in this study is the increased risk of CVD for women in advanced age group (aged 60-85). CVDs including congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, and stroke are among the most significant causes of mortality in the United States (Benjamin et al., 2019). The dose-response relationship observed between prescription drug use for treating high blood pressure (BP)-hypertension and OP exposure in the advanced age groups of female non-smokers supports this increased risk of CVD observation (Table 2).

Associations between CVD risk and exposure to OP insecticides have been reported in both animal and human epidemiology studies in the past. Early studies of in-vivo experimental models reported dose-dependent, direct cardiotoxic effects from OP exposure, including

Table 1
Counts of reported prescription drug use, asthma, chronic bronchitis, total CVD,breast/prostate cancer, total cancer and total survey participants analyzed in the study

	Age range (yrs)	Prescription drug use	Asthma	Chronic bronchitis	Total CVD	Breast or prostate cancer	Total cancer	Total counts of Participants
Female Non-smokers	6-19	420	287	0	0	0	0	1830
	20-39	248	125	24	6	1	8	789
	40-59	332	72	41	31	6	38	610
	60-85	518	77	43	207	34	96	649
Male Non-smokers	6-19	347	332	0	0	0	0	1794
	20-39	106	75	7	9	0	2	552
	40-59	204	40	13	36	2	16	446
	60-85	264	29	15	142	27	68	333
Female smokers	20-39	158	72	31	8	0	17	392
	40-59	283	78	51	56	7	44	426
	60-85	355	53	57	161	26	69	407
Male smokers	20-39	116	85	13	10	0	3	527
	40-59	280	57	30	98	2	18	558
	60-85	590	72	43	401	51	151	725

Note: Data are from 2003 to 2012 NHANES survey. Total CVD includes counts of heart failure, coronary heart disease, angina/pectoris, heart attack and stroke. Breast cancer counts are only for women and prostate counts are only for men. There were total of 3878 female non-smokers, 1225 female smokers, 3125 male non-smokers and 1810 male smokers.

Table 2
Odds ratios of three higher OP (DMTP) exposure quartiles to the lowest OP exposure quartile for prescription drug use, chronic bronchitis, cardiovascular diseases, breast and prostate cancer, total cancer counts of women and men of aged 40-59 and 60-85 years.

	OP Exposure quartiles	Odds Ratio Ages 40-59	Lower 95% CI	Upper 95% CI	Odds Ratio Ages 60-85	Lower 95% CI	Upper 95% CI
		Female non-smokers' odds ratios					
Prescription Drug use	2	0.7	0.4	1.4	1.3	0.5	3.2
	3	1.2	0.6	2.1	1.4	0.7	3.1
	4	1.7	0.9	3.2	1.8	0.8	4.1
Chronic bronchitis	2	0.3	0.1	1.0	1.3	0.3	5.2
	3	0.7	0.3	2.1	1.4	0.3	6.0
	4	0.5	0.2	1.5	2.5	0.7	9.5
Cardio-vascular disease	2	0.5	0.1	2.1	1.6	0.8	3.5
	3	0.9	0.3	3.4	**2.3**	**1.1**	**4.9**
	4	0.5	0.1	1.7	**3.0**	**1.4**	**6.4**
Total cancer counts	2	1.1	0.3	3.4	1.2	0.5	2.5
	3	1.7	0.6	4.9	**2.7**	**1.3**	**5.9**
	4	1.7	0.5	5.7	1.3	0.6	2.7
		Male non-smokers' odds ratios					
Prescription Drug use	2	1.1	0.6	2.2	2.5	0.9	7.1
	3	1.3	0.7	2.5	1.8	0.6	5.5
	4	1.4	0.7	2.7	3.6	0.9	14.8
Cardio-vascular disease	2	0.7	0.1	4.7	0.9	0.4	2.1
	3	0.6	0.2	2.2	0.7	0.3	1.9
	4	1.1	0.3	3.8	0.7	0.2	2.1
Total cancer counts	2	0.9	0.2	4.1	1.0	0.4	2.7
	3	0.7	0.1	4.2	0.3	0.1	0.9
	4	1.1	0.2	5.7	1.4	0.5	3.6
Smokers		Female breast cancer aged 60-85			Male prostate cancers aged 60-85		
Breast & prostate cancer	2	1.7	0.3	9.4	1.6	0.5	5.1
	3	**4.6**	**1.0**	**20.3**	1.9	0.6	5.8
	4	**4.4**	**1.0**	**19.1**	**2.8**	**1.0**	**7.9**

Note: The 4th quartile has the highest exposure and the 1st quartile has the lowest exposure. "Cardio-vascular disease" includes five categories 1), congestive heart failure, 2) coronary heart disease, 3) angina/angina pectoris, 4) heart attack and 5) stroke. "Total cancer counts" are total counts of people answered yes to the question "Ever told you had cancer or malignancy". Bold numbers indicate values significant with 95% confidence.

Table 3
Odds ratios of asthma of three higher OP (DMTP) exposure quartiles to the lowest OP exposure quartile for asthma in women and men aged 6-19 years and 20-39 years.

		Ages 6-19			Ages 20-39		
	OP Exposure quartiles	Odds Ratio	Lower 95% CI	Upper 95% CI	Odds Ratio	Lower 95% CI	Upper 95% CI
Asthma in women	2	1.2	0.7	2.1	**1.9**	**1.0**	**3.6**
	3	1.5	0.9	2.6	1.2	0.6	2.5
	4	**1.8**	**1.0**	**3.0**	1.1	0.5	2.3
Asthma in men	2	1.0	0.6	1.5	0.9	0.4	2.3
	3	1.2	0.8	1.9	1.8	0.8	4.1
	4	0.8	0.5	1.3	1.6	0.7	3.7

Bold numbers indicate values significant with 95% confidence.

Table 4
Frequency counts of prescription drugs taken by non-smoking women (3878) and men (3125) in the four quartiles of OP (DMTP) insecticide exposure levels.

	Women				men			
Generic Drug Name (illness treated)	1 st	2nd	3rd	4th	1 st	2nd	3rd	4th
Albuterol (breathing problems)	35	22	44	42	20	23	32	28
Atorvastatin (lower cholesterol)	13	7	13	16	5	6	15	12
Levothyroxine (hypothyyroidism)	21	13	11	15	3	1	2	1
Amlodipine (high BP)	9	14	13	14	10	12	8	9
Atenolol (high BP)	6	13	13	14	8	6	7	5
Alendronate (osteoporosis)	9	12	6	12	1	1	0	0
Ethinyl Estradiol; Norgestimate (birth control)	5	4	6	12	0	0	0	0
Acetaminophen; Hydrocodone (pain relief)	9	17	8	10	8	4	6	4
Amoxicillin (antibiotic)	10	14	5	7	6	5	2	8
Cetirizine (allergy)	9	5	7	7	4	9	3	4
Conjugated Estrogens	6	6	5	7	0	0	0	0
Hydrochlorothiazide (high BP)	5	7	6	6	1	6	4	2
Ibuprofen (pain relief)	4	7	6	6	2	1	4	3
Amphetamine; Dextroamphetamine (ADHD)	6	2	2	5	8	2	5	3
Fluoxetine (depression)	3	1	1	5	1	0	3	1
Sertraline (depression, OCD)	3	3	3	5	0	2	1	0
Desogestrel; Ethinyl Estradiol (birth control)	1	2	1	5	0	0	0	0
Lisinopril (High BP)	5	2	8	4	6	5	0	3
Amoxicillin; Clavulanate (antibiotic)	4	3	3	4	1	0	0	1
Diltiazem (chest pain, angina)	3	2	2	4	1	2	0	2
All others	215	199	202	185	143	126	114	163
Total counts	381	355	365	385	228	211	206	249

The list of the prescription drug names was ranked by their frequency counts for women in the 4th quartile of urinary DMTP concentrations. The top 20 list of prescription drug name for men is slightly different. 1st quartile has the lowest amount and the 4th quartile has the highest amount urinary DMTP concentration. Abbreviation: BP, blood pressure; ADHD, attention deficit hyperactivity; OCD, obsessive-compulsive disorder; Only the 1st prescription drug for each participant was counted. Phrases in the parentheses after the drug name are the common health problems that the drug treats and are cited from http://www.wemd.com/drugs.

cardiac failure in rats (Wolthuis and Meeter, 1968). More recent animal studies on the cardiotoxic effects of OP exposure were related to acetylcholinesterase inhibition and parasympathetic over-activity after subchronic-chronic exposure (Roth et al., 1993; Tsatsakis et al., 1996;). In human data from both epidemiology and acute poisoning, there are complex and multifactorial pathways involved in the development of the cardiac toxicity, including disturbed cardiac rhythms and arrhythmias, QT prolongation, ST- and T-abnormalities, histopathological evidence of focal necrosis and regeneration following OP exposure (Bar-Meir et al., 2007; Kiss and Fazekas, 1979; Ludomirsky et al., 1982). Apoptosis, as depicted by Bax/Bcl2 ratio elevation, cytochrome c cytosolic release and caspase-3 activation in cardiac tissue, was also implied in the myocardial damage induced by OP exposure (Razavi et al., 2015).

4.2. Increased prevalence of asthma and chronic bronchitis for women with higher OP exposure

Another two health conditions observed in current studies are the significantly higher risk of asthma for young women (aged 6-39 years) and apparently higher risk of chronic bronchitis for female non-smokers of advanced ages (60-85 years) with higher OP exposure. This result is consistent with results from previous OP exposure studies including non-smoking farm women and plant workers (Kogevinas et al., 1999; Konieczny et al., 1999; Valcin et al., 2007). Exposure to OP insecticides has been associated with a variety of respiratory symptoms, including asthma, bronchitis and chronic obstructive pulmonary disease (Deschamps et al., 1994; Hoppin et al., 2002). OP insecticides are thought to be irritants capable of directly damaging the bronchial mucosa, making the airway sensitive to allergens and thus, increasing the risk of developing asthma and chronic bronchial hyper-activities (Shaffo et al., 2018).

The increasing risk of prescription drugs among female non-smokers in the higher OP exposure quartiles based on their odds ratio also indicates an association of broad health issues with increasing OP exposure. The increasing prescription drug uses linking to higher OP exposure are apparent mainly for breathing difficulty (asthma, COPD and other airway irritation issues) and hypertension (high blood pressure).

4.3. Higher cancer risk with exposure to OP insecticides for US women

There are significantly higher risks of cancer development for female non-smokers with increasing exposure to OP insecticides in the age group of 60-85 years. The breast cancer risk of female non-smokers in higher OP exposure quartiles is also likely higher than that of women in the least OP exposure quartile for this age group, though more data are needed for a conclusive result. Significantly higher risks of prostate cancer for male smokers and breast cancer for female smokers aged 60-85 years with increasing OP exposure also indicate that OP exposure might exacerbate the carcinogenicity of smoking.

This is the first study that provides evidence on the increased risk of total cancer for female non-smokers, breast cancer for female smokers and prostate cancers for male smokers in the general population. Although urinary DMTP concentration is a one-time measurement, it likely reflects the long-term, low-dose, chronic OP exposure of participant groups (Ock et al., 2020). Increased cancer risks associated with several OP insecticides have been reported in previous epidemiologic studies, including case-control studies (De Roos et al., 2003; McDuffie et al., 2001; Miligi et al., 2003). More recently, association of OP exposure and higher cancer risk is also reported among licensed pesticide applicators and their wives in the prospective Agricultural Health Study cohort (Engel et al., 2017; Montgomery et al., 2008). Research suggests that because of the endocrine disrupting properties of OP insecticides and their metabolites, there are higher risks of hormone-related cancer developments such as breast and prostate cancers (Lerro et al., 2015; Mnif et al., 2011). However, the pathology of OP exposure to cancer development is still not clear (Engel et al., 2017; Kitamura et al., 2006).

4.4. Pathways of OP insecticides to people

DMTP was detected in urinary samples of more than 94% of the participants in 2011-2012 participants. There is a higher average DMTP concentration in women than in men between 2003-2012 cycles. Hence,

dietary exposure to OP insecticides is likely one of the major sources of OP exposure for the general population. This conclusion is also supported by a previous study that reported cyclic rising and falling of urinary OP metabolite levels in the same group of children after switching from inorganic to organic food and then from organic to inorganic food in an experimental intervention study (Lu et al. 2006). Though life spans of OP insecticides and their metabolites are generally short, some studies still reported residues of OP insecticides in soil years after its application (Ragnarsdottir, 2000). Residues of pesticides are reported in 78% to 85% of fruits, vegetables and grains (USDA 2015, 2016) and a higher proportion of residues reported in drinking water in agricultural region (Donald et al., 2007; Sun, 2019). Given the significant association of OP exposure with the overall health risk in the general population, particularly for women, reducing the dietary exposure to OP insecticides needs to be prioritized.

It needs to be emphasized that occupational OP exposure for agricultural applicators, manufacturing workers, exterminators, florists and the second-hand exposure for families of OP applicators among other high-level exposures can still pose an elevated risk (Jaga and Dharmani, 2003; Lerro et al., 2015; Montgomery et al., 2008; Weichenthal et al., 2010). Necessary measures for reducing their OP exposure needs to remain mandatory. We suggest that for people with a family history of CVD or breast cancer, reducing OP exposure, including switching to organic foods if possible, in order to lower their OP exposure-associated health risks. We also recommend that CDC continue its urinary OP pesticide monitoring program in future NHANES study so that OP related health risk in the general population can be better understood.

5. Limitations of the study

This study has several limitations. Variations in LOD of DMTP measurement between 2003 and 2012 in NHANES lab affect the accuracy of the result. Though statistics of urinary DMTP measurements of spot data might reflect chronic long-term exposure of population, they are not the actual long-term measurement and can be further complicated as they can be derived from exposure to the preformed environmental metabolite as well as the parent OP insecticide. Possible errors can be introduced during the recall of medical conditions. At the population level, high OP exposure contributes to increasing risk of CVD, overall poor health and increased risk of cancer. But at an individual level, a one-time reading of an individual's DMTP level may not necessarily indicate a greater personal health risk. People with greater exposure to OP insecticide might also have greater exposure to other non-OP pesticides. The health impact of exposure to other pesticides can distort the statistical conclusion with regards to OP exposure in this study. Because of the cross-sectional nature of NHANES data, the temporal causality between OP exposure and health issues cannot be inferred.

6. Conclusions

Urinary DMTP levels, as an indicator of OP exposure, of women in the United States are higher than that of men. Women have a greater health risk of OP toxicity than men between 2003 and 2012. CVD risk, including that of congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack and stroke for female non-smokers of advanced ages (60-85 years) at the two highest OP exposure quartiles are 2.3 and 3.0 times higher than that of women at the lowest OP exposure quartile, respectively. Women with higher OP exposure also have significantly higher risks of asthma at young ages (6-39 years) and apparently higher risk of chronic bronchitis at advanced ages (60-85 years). There are dose-response relationships between risk of prescription drug usage for female non-smokers and increasing exposure to OP insecticides, though not statistically significant. There are significantly higher risks of breast cancer and total cancer incidences for female smokers, and prostate cancer incidences for male smokers aged 60-85 years in higher OP exposure quartiles. Sex differences in activities of cytochrome P450 enzymes and paroxonases and toxicokinetics are suspected to be related to the higher levels of urinary OP metabolite and higher risk of health outcomes in US women. Given the higher burden of OP exposure and their significantly higher overall health risk, including cancer, reducing OP exposure in US women need to be prioritized.

CRediT authorship contribution statement

Hongbing Sun: Conceptualization, Methodology, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Michael Leo Sun:** Data curation, Investigation, Writing - review & editing. **Dana Boyd Barr:** Methodology, Formal analysis, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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