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Prenatal exposures to many classes of commonly used pesticides have been extensively studied and found to have multiple adverse health effects on the developing fetus. While biomonitoring studies have been conducted in several major parts of the world, no such exposure evaluation has been done for the Caribbean region. This paper confirms that neonates in the Caribbean are being exposed to several classes of commonly used pesticides and highlights the need to implement surveillance programs that continuously monitor, intervene, and evaluate the levels of these toxic contaminants to ensure that they are reduced as far as possible.

Environmental Science: Processes & Impacts

PAPER

Evaluation of exposure to organophosphates, carbamates, phenoxy acids, and chlorophenols pesticides in pregnant women from 10 Caribbean countries

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Pesticides are commonly used in tropical regions such as the Caribbean for both household and agricultural purposes. Of particular concern is exposure during pregnancy, as these compounds can cross the placental barrier and interfere with fetal development. The objective of this study was to evaluate exposure of pregnant women residing in 10 Caribbean countries to the following commonly used classes of pesticides in the Caribbean: organophosphates (OPs), carbamates, phenoxy acids, and chlorophenols. Out of 438 urine samples collected, 15 samples were randomly selected from each Caribbean country giving a total of 150 samples. Samples were analyzed for the following metabolites: six OP dialkyl phosphates metabolites [dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP) and diethyldithiophosphate (DEDTP)]; two carbamate metabolites [2-isopropoxyphenol (2-IPP) and carbofuranphenol]; one phenoxy acid 2,4-Dichlorophenoxyacetic acid (2,4-D); and five chlorophenols [2,4-dichlorophenol (DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,5-trichlorophenol (TCP), 2,4,6-trichlorophenol (2,4,6-TCP), and pentachlorophenol (PCP)]. OP metabolites were consistently detected in ≥ 60% of the samples from Antigua and Barbuda, Bermuda, and Jamaica. For the carbamate metabolites, 2-IPP was detected in seven of the 10 Caribbean countries with a detection frequency around 30%, whereas carbofuranphenol was detected in only one sample. The detection frequency for the phenoxy acid 2,4-D ranged from 20% in Grenada to a high of 67% in Belize. Evidence of exposures to chlorophenol pesticides was also established with 2,4-DCP geometric means ranging from 0.52 µg/L in St. Lucia to a high of 1.68 µg/L in Bermuda. Several extreme concentrations of 2,5-DCP were detected in four Caribbean countries—Belize (1100 µg/L), Bermuda (870 µg/L), Jamaica (1300 µg/L), and St-Kitts and Nevis (1400 µg/L). 2,4,5-TCP, 2,4,6-TCP, and pentachlorophenol were rarely detected. This biomonitoring study underscores the need for Caribbean public health authorities to encourage their populations, and in particular pregnant women, to become more aware of the potential routes of exposure to pesticides and to utilize these chemicals more cautiously given the possible adverse effects such exposures can have on their unborn children and infants.

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1. Introduction

In the last decades, more than 50,000 pesticide formulations have been used to get rid of undesirable insects, nematodes, fungi, and

plants. While these products have helped to increase crop yields, lower food costs and reduce deaths from vector-borne diseases, a number of these pesticides have also been responsible for significant human toxicity. Nowadays, the omnipresent low-dose level of these chemicals in the human body occurs essentially as a result of dietary intake and other ubiquitous environmental exposures [1].

1.1 Organophosphates

For a long time, organochlorines (OCs) and other persistent organic pollutants (POPs) were the most used pesticides in agriculture. On account of their long half-lives, however, alternatives were sought and organophosphates (OPs) became attractive substitutes owing to their ability to degrade rapidly. Throughout the Caribbean, OPs are a class of pesticides now used extensively in agriculture and residential settings, in veterinary practices, and in community mosquito spraying control programs. Although OPs degrade faster than OCs, and hence are less persistent in the environment, their main disadvantage is their relatively high acute toxic human health effects [2].

Exposure to OPs may occur in four different ways: occupational exposures, residential use, environmental exposures for communities living in areas with intensive agricultural production or community pest control programs, and dietary exposures of the general population [3]. In particular, the OP malathion is used in many Caribbean countries in fogging programs to control the mosquito population. Once in the body, OP pesticides are rapidly metabolized and excreted in urine [4]. Hydrolysis of ester linkages in the parent compound yields dialkyl phosphate metabolites, which are not considered toxic, such as dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). While direct exposure to dialkyl phosphate metabolites is possible, they are primarily considered to be biomarkers of OP exposure with measurement of these metabolites reflecting recent exposure, predominantly in the previous few days [5].

It is now well established that exposure to OP pesticides can jeopardize neuronal development, specifically due to their high neurotoxicity [6, 7]. These compounds cross the placental barrier and are known to interfere with hormonal and neurological development, the immune system and other physiological functions [8-12].

Several studies have examined the association between prenatal exposure to OPs and a child's health from the time of conception through later on in life. Eskenazi, et al. [13] reported a decrease in gestational age and umbilical cord cholinesterase activity associated with increased levels of maternal urinary dimethyl phosphate metabolites in a cohort of low-income Latina women living in an agricultural area. Other studies have found an increased risk of intrauterine growth retardation [14], gastrointestinal anomalies [15], as well as altered fetal growth and length of gestation [16-18]. Another recent study conducted by Cecchi, et al. [19] suggested an endocrine disruption during pregnancy associated to environmental OP exposure. Studies for monitoring effects of prenatal exposure to OPs showed an association between prenatal levels of OP metabolites and mental development as well as pervasive developmental disorders at 24 months of age [7]. Other studies have found that prenatal exposure to OPs increased reaction time [20], increased the number of abnormal reflexes in newborns [6, 21], and increased mental and emotional symptoms in adolescents [22].

1.2 Carbamates

A metabolite of the carbamate pesticide propoxur (Baygon) is 2-isopropoxyphenol [23]. Propoxur is a non-systemic, N-methylcarbamate insecticide and acaricide. It is used both for agricultural and public health purposes, being applied by spraying or as a dust against insect pests such as chewing and sucking insects, ants, cockroaches, crickets, flies and mosquitoes [24]. Potential exposure to propoxur may occur through the diet, when handling and applying the product, or when entering or contacting treated sites.

In the Philippines, Ostrea, et al. [25] found a significant negative relationship between prenatal propoxur exposure and motor development for children at 2 years of age after controlling for confounders. Prenatal propoxur exposure has been found to be inversely associated with birth weight and/or length [26]. In another study [27], evidence suggests that exposure to propoxur may be a casual factor for the generation of leukemia-associated chromosomal translocations.

Carbofuranphenol is a metabolite of four different carbamate insecticides: benfuracarb, carbofuran, carbosulfan, and furathiocarb [5]. Besides occupational exposures, general population exposures are mainly through the eating of contaminated food with urinary carbofuranphenol levels reflecting recent exposure [5]. The human health effects of low levels of exposures to carbofuranphenol are presently unknown.

1.3 Phenoxy acids

2,4-Dichlorophenoxyacetic acid (2,4-D) is a common phenoxy acid herbicide used in agricultural settings. Human exposures come primarily from contaminated water and food. 2,4-D is directly measured in urine which reflects few days of exposure. Several 2,4-D exposure studies in laboratory animals have found multiple adverse effects ranging from impaired immune system response [28] to urogenital malformations in the fetuses [29] to impaired somite development in rat embryos [30].

Evaluations of the full human health effects of exposure to 2,4-D are still ongoing. In a study of U.S. farmers in Nebraska, after controlling for exposure to other pesticides, researchers found that 2,4-D exposure substantially increased the risk of non-Hodgkin's

lymphoma [31]. While the present combined evidence on 2,4-D does not support a genotoxic mode of action [32], the International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence to classify 2,4-D as a class 2B carcinogen - "possibly carcinogenic to humans" [33].

1.4 Chlorophenols

There are five basic kinds of chlorophenols which give rise to 19 different chlorophenols. Five were analyzed in this study: 2,4-dichlorophenol (2,4-DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,5-trichlorophenol (2,4,5-TCP), 2,4,6-trichlorophenol (2,4,6-TCP), and pentachlorophenol (PCP). It should be noted that 2,4-DCP is used for the production of the phenoxy herbicide 2,4-D. Exposure to chlorophenols can result from direct contact with the parent pesticide, consumption of contaminated food and water, household products, or by exposure to incinerated wastes contaminated by chlorinated compounds (2,4-DCP). In a context of low-level exposure within the general population, Yoshida, et al. [34] found 2,5-DCP, the major metabolite of 1,4-dichlorobenzene (1,4-DCB), to be a useful biological indicator of exposure to this compound.

While presently there is limited information available about risks associated with low exposure to chlorophenols, adverse effects on the liver, immune system, and skin are suspected [35]. Among 440 girls with both reproductive health and laboratory data, Buttke, et al. [36] found that 2,5-DCP and summed environmental phenols (2,5-DCP and 2,4-DCP) were inversely associated with age of menarche [hazard ratios of 1.10; 95% confidence interval (CI): 1.01-1.19 and 1.09; 95% CI: 1.01-1.19, respectively], after accounting for BMI and ethnicity.

There is a paucity of published data on the quantum and type of pesticides currently being used in the English speaking Caribbean islands. In one recent review of pesticide use in Jamaica, it was found that while 87% of the annually imported pesticides into Jamaica are applied within agricultural or household settings, the fate of these locally applied pesticides is presently unknown [37]. In another study that examined the use patterns and residual levels of OP pesticides on vegetables in Trinidad, Yen, et al. [38] found that 10% of examined vegetable produce exceeded internationally acceptable maximum residue limits (MRLs) for OPs. Furthermore, they found that local farming practices related to the application of pesticides and subsequent harvest of treated crops raised concerns over the possibility of excessive residues on crops sold in local markets [38].

While several large biomonitoring studies done in North America and elsewhere have found nearly ubiquitous exposure to many pesticides [5, 39], similar studies in the Caribbean to evaluate human exposures to present-day pesticides have not yet been systematically conducted and published. As part of a Canadian Global Health Research Initiative's (GHRI) Teasdale-Corti grant program funded research initiative, a study was conducted to determine prenatal exposures to persistent organic pollutants (POPs), other commonly used classes of pesticides such as organophosphates, carbamates, phenoxy herbicides, and pyrethroids, two heavy metals mercury and lead, and zoonotic infections [40]. The results of the pyrethroids, heavy metals, and POPs finding have been published elsewhere [41-43]. This paper reports on the findings for six organophosphate (OP) metabolites, the carbamate propoxur, the phenoxy acid 2,4-D, and several chlorophenol metabolites in pregnant women who live in the 10 Caribbean countries where this research study was successfully executed.

2. Materials and methods

2.1 Ethics and sampling

Between August 2008 and April 2011, 438 pregnant or delivering women from 10 Caribbean countries were recruited to participate in this study. From these 438 samples, 15 sub-samples were randomly selected from each Caribbean country giving a grand total of 150 samples analyzed to determine exposure. Applications were made to the institutional review boards or ethics committee (whichever existed) in each participating country to obtain ethical approval for the implementation of the research project. Additionally, governmental approval was then sought and obtained through the Ministry of Health within each country where this study was executed.

2.2 Study protocol

Once governmental and ethical approvals were secured, local nurses and laboratory technicians working in each island were identified and trained to recruit pregnant women to participate in this study, obtain their informed consent, and collect the biological samples in their respective countries. Once collected, urine samples were initially poured into 10 mL vials and stored at -80ºC prior to shipping in International Air Transport Association (IATA) certified boxes packed with dry ice to the Laboratory of Centre de Toxicologie (CTQ) of the Institut national de santé publique du Québec (INSPQ) located in Quebec City, Canada, for analysis.

2.2 Study population and sampling

The recruitment and sampling protocols that were used in this study were comparable to those employed in a similar exposure assessment program, the Arctic Monitoring and Assessment Programme (AMAP, www.amap.no), carried out in circumpolar countries [44]. Following this protocol, pregnant and delivering women ≥ 18 years coming to the main hospital or health clinics during their last prenatal visits or to deliver were invited to participate in this study by the local nurses. In most cases, urine samples were taken before delivery, however, in some cases where this was not possible, the sampling was done within two weeks of delivery. In accordance with the AMAP protocol, a sample size of 50 mothers ≥ 18 years for each country was set.

2.3 Chemical analyses of pesticide metabolites in urine

The concentration of six dialkylphosphate metabolites of the organophosphorus pesticides [diethylphosphate (DEP), diethylthiophosphate (DETP), diethyldithiophosphate (DEDTP), dimethylphosphate (DMP), dimethylthiophosphate (DMTP) and dimethyldithiophosphate (DMDTP)], two carbamate metabolites (2-isoproxyphenol and carbofuranphenol), one phenoxy acid (2,4-D), and five chlorophenols [2,4-dichlorophenol (2,4-DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,5-trichlorophenol (2,4,5-TCP), 2,4,6-trichlorophenol and pentachlorophenol (PCP)] were determined by the Centre de Toxicologie du Québec (CTQ) of the Institut national de santé publique du Québec (INSPQ), from urine samples.

One hundred µL of urine were first enriched with labeled internal standards (DETP-$^{13}C_4$, DEDTP-$^{13}C_4$, DMP-d_6, DMTP-d_6, DMDTP-d_6, carbofuranphenol-$^{13}C_6$, 2,4-D-$^{13}C_6$, 2,4-DCP-$^{13}C_6$, 2,4,5-TCP-$^{13}C_6$, 2,4,6-TCP-$^{13}C_6$, and PCP-$^{13}C_6$). The urinary metabolites were then hydrolyzed with 10 µL of β-glucuronidase enzyme (from Helix Pomatia, type HP-2) in an acetate buffer at pH 5.0 for 3 hours at 37°C. After adding 1 mL of acetonitrile and 200 mg of potassium carbonate, the samples were derivatized with 10 µL of pentafluorobenzyl bromide (PFBBr) at 70°C for 2 hours. The derivatized products were extracted with 7 mL of a mixture dichloromethane:hexane (8:92), mixed for 15 minutes and centrifuged 10 minutes at 3000 rpm. The extraction was repeated a second time before the extracts were analyzed by gas chromatograph-mass spectrometer (GC-MS/MS).

The solvent was then evaporated to dryness, taken up in 2 mL of dichloromethane:hexane (20:80) and analyzed for pesticide analytes on an Agilent 6890 Network gas chromatograph (GC) (Agilent Technologies; Mississauga, Ontario, Canada) coupled to a Waters Quattro Micro GC mass spectrometer in tandem (MS/MS) (Waters; Milford, MA). The GC was fitted with an Agilent 30 m HP-5MS column (0.25 mm i.d., 0.25 µm film thickness) to the MS/MS. The carrier gas was helium, the collision gas was argon and the injections were 1 µL in splitless mode. The oven temperature program was as follows: from initial temperature 70°C (held for 1 min) to 227°C at 10°C/min (held 4 min), to 310°C at 10°C/min (held for 10 min) and then to 70°C at 120°C/min, for a total run time of 45 minutes. The injector temperature was 280°C, the transfer line temperature was 305°C and finally the source temperature was set to 310°C. The mass spectrometer was operated in Multiple Reaction Monitoring (MRM), using negative ion chemical ionization (NCI) with methane (99.97 %) as the reagent gas.

Concentrations were reported in units of micrograms per liter (µg/L) and the limits of detection reported (LOD) for the organophosphates were 1.0 µg/L for DEP and DMP, 0.3 µg/L for DETP, DEDTP, DMDTP, and 0.6 µg/L for DMTP. The LODs for the other pesticide metabolites were as follows: 0.05 µg/L and 0.1 µg/L for the carbamate metabolites 2-isopropoxyphenol and carbofuranphenol respectively; 0.2 for the phenoxy acid 2,4-D; and 0.2 µg/L for the chlorophenols 2,4-DCP and 2,5-DCP, 0.5 µg/L for 2,4,5-TCP, 0.7 µg/L for PCP, and 1 µg/L for the 2,4,6-TCP. LODs were determined by first estimating concentrations of analytes yielding a signal to noise ratio of 3. A synthetic urine sample spiked with analytes in concentrations ranging from 4 to 10 times the estimated LODs was analyzed (10 replicates) and standard deviations were multiplied by three to obtain the LODs. The intra-day precision (repeatability) of the method was between 1.9 to 8.9 % and the inter-day precision (reproducibility) was between 3.1 to 20 % depending on the analyte.

The internal reference materials used to control the quality of the analyses were the non-certified reference material ClinChek (Urine Level 1; RECIPE Chemicals; Munich, Germany) and a homemade reference material from pooled urine samples of exposed people prepared by the Centre de Toxicologie du Québec (CTQ), Institut national de santé publique du Québec (INSPQ). The overall quality and accuracy of the analytical method was monitored by the participation to the inter-laboratory program as the German External Quality Assessment Scheme (G-EQUAS; Erlangen, Germany) for the organophosphate metabolites DEP, DETP, DEDTP, DMP, DMTP and DMDTP, the carbamate metabolite 2-isopropoxyphenol and the chlorophenol PCP.

2.4 Statistical analyses

The results obtained from the 10 Caribbean countries were compared with each other and where available, the overall Caribbean data with comparable data from Canada and the U.S. The U.S. data were extracted from the National Health and Nutrition Examination Survey (NHANES) 2007-2008 survey. From the 2007-2008 survey, a subset of 610 women (age range 20-39 years) analyzed for OP metabolites and 616 women (age range 20-39 years) analyzed for chlorophenols were available for comparison with the Caribbean results obtained in this study. In the case of Canada, data from the 2007-2009 Canadian Health Measures Survey (CHMS) [45] for females in the 20-39 years age range were obtained. It is important to note that the CHMS samples were also analyzed at the Laboratory of Centre de Toxicologie du Québec (CTQ) of the Institut national de santé publique du Québec (INSPQ), the same laboratory used to conduct the analyses for this study.

In order to be comparable with the U.S. and Canadian data, geometric means, lower and upper 95% confidence intervals (CI), the median, the 90th percentile, and the minimum and maximum values recorded were calculated and reported. Additionally, in order to enhance comparability with U.S. and Canadian results, only metabolites or compounds that were detected in ≥ 60% (threshold used in the CHMS) of the cases were reported. A value equal to half the LOD was entered for samples with a result below the detection limit.

Given that the distributions of the selected pesticides in this study were heavily skewed, due for the most part to the presence of extreme values and LOD, and to the small sub-sample size per country (n = 15), the non-parametric Kruskal-Wallis one-way test of variance was conducted to test whether the urinary metabolite concentrations ranked means were different among the 10 studied

countries. Based on Kruskal-Wallis results, Dunn's multiple comparison tests [46] were performed using a SAS macro KW_MC in order to identify significant differences among the Caribbean countries. All analyses were carried out using the SAS 9.4 software.

3. Results

From August 2008 to April 2011, 438 maternal urine samples were collected from pregnant women from 10 Caribbean countries (Table 1). Due to budget reasons, with the exception of Montserrat, 15 samples were randomly selected out of all the samples collected in each island for pesticide exposure analyses. For Montserrat, the very small population size led to only 15 samples being collected, therefore all of this island's samples were selected for pesticide analyses.

3.1 Organophosphate analyses

The urinary concentrations of OP metabolites measured in pregnant women from the Caribbean region, Canada, and the US are given in Table 2. Overall, most of the six dialkyl phosphates metabolites were consistently detected in greater than 60% of the samples from Antigua and Barbuda, Bermuda, and Jamaica. With the exception of Antigua and Barbuda, Jamaica, and St. Kitts and Nevis, DEP geometric mean concentrations in the other seven Caribbean countries were lower than those found in Canadian 20-39 year-old women [39]. Overall, from the Kruskal Wallis test, there is a significant difference in mean scores across the six Caribbean countries that had ≥ 60% detection frequency (p = 0.0386). From the Dunn's test, it appears that only Antigua and Barbuda's mean DEP score was different than Dominica's.

DETP was detected in ≥ 60% of the samples only in Antigua and Barbuda, Jamaica, and St. Vincent and the Grenadines. No significant difference was observed between these three countries (overall test p-value = 0.3518). Several extreme DETP values were recorded in Belize and Jamaica. No significant differences in DETP geometric means were seen between the Caribbean countries.

While the OP metabolite DMP was rarely detected in the U.S. samples, detection frequencies ≥ 60% were observed in Canada and six Caribbean countries—Antigua and Barbuda, Bermuda, Grenada, St. Kitts and Nevis, St. Lucia, and St. Vincent and the Grenadines. The Caribbean women's DMP geometric mean concentrations ranged from a low of 1.28 µg/L measured in St. Lucia to a high of 3.84 µg/L measured in Bermuda. The overall Kruskal-Wallis non-parametric test of variance, examining whether DMP concentrations were different among the 10 Caribbean countries, was significant (p-value = 0.0062), however the Dunn multiple comparison test was inconclusive between Bermuda and St. Lucia. Again, several extreme DMP values were recorded in all of these five Caribbean countries as well as Montserrat.

A similar pattern was also observed for DMTP with the five Caribbean countries Antigua and Barbuda, Bermuda, Jamaica, St. Kitts and Nevis, and St. Vincent and the Grenadines having DMTP detected in ≥ 60% of their samples. No significant differences of DMTP concentration levels were observed (p-value = 0.2584) among these five Caribbean countries.

DMDTP was not commonly detected in Canadian and U.S women with detection frequencies of only 34% and 20% respectively (data not shown). Similarly, this metabolite was not detected in nine of the sampled Caribbean countries with this OP metabolite being detected in 60% of the samples from Bermuda with a geometric mean of 0.42 µg/L. All of the Caribbean samples tested below the LOD for the OP metabolite DEDTP.

Comparing the overall Caribbean Islands geometric means and their non-overlapping confidence intervals results for those Caribbean islands that had a detection frequency ≥ 60% with Canada and the U.S. revealed that DMP concentration levels of were slightly lower in Caribbean Islands compared to Canada. Similarly, DMTP concentration levels were lower in the Caribbean Islands than those in the U.S.

3.2 Carbamate metabolites

The carbamate pesticide propoxur metabolite 2-isopropoxyphenol (2-IPP) was not detected in three Caribbean countries—Belize, Jamaica and St. Kitts and Nevis (Table 3). In the other seven Caribbean countries, the detection frequency was well below 60% averaging around 20%. This metabolite was not detected in 1,324 women from the NHANES U.S. (2001-2002) survey and has not been looked for since 2004. 2-IPP was also not analyzed for in first survey cycle of CHMS. In CHMS Cycle 2, 100% of the samples were found to be below the LOD. For carbofuranphenol, this metabolite was detected in only one sample from Belize (0.3 µg/L).

3.3 Phenoxy acids

For the Caribbean women sampled in this study, the detection frequency for this metabolite ranged from 20% for Grenada to a high of 67% for Belize (Table 4). The geometric mean was higher for Belize as a result of a greater number of extreme values. However, the overall Kruskal-Wallis test did not provide evidence of a significant difference between the three Caribbean countries that had detection frequencies ≥ 60% of this metabolite (p-value=0.9321).

3.4 Chlorophenols

With the exception of Dominica and St. Lucia, the detection frequency for 2,4-DCP was higher in all the Caribbean countries when compared to Canada (Table 5). Caribbean geometric means values range from 0.52 µg/L in St. Vincent and the Grenadines to a high of 1.68 µg/L in Bermuda. While the Kruskal-Wallis test failed to reject the hypothesis that the ranked geometric means were statistically different, the Caribbean Islands' geometric mean was lower when compared to the U.S. mean.

Extreme concentration levels of 2,5-DCP were detected in four Caribbean countries—Belize (1100 µg/L), Bermuda (870 µg/L), Jamaica (1300 µg/L), and St-Kitts and Nevis (1400 µg/L). Similar extreme values were also found in the U.S. 2007-08 cohort (high of 11,300 µg/L). Excluding Montserrat which only had a detection frequency of 53% for this metabolite, the overall Kruskal-Wallis test found a statistically significant difference among the other nine Caribbean Islands (*p*-value = <0.0001). The mean ranked scores were higher in Jamaica, Bermuda, Antigua and St-Kitts and Nevis when compared to St. Lucia and St. Vincent and Grenadines. Overall, concentration levels of 2,5-DCP were lower in the Caribbean Islands compared to the U.S.

2,4,5-TCP was detected in only one sample from St. Vincent and the Grenadines. 2,4,6-TCP was detected in only one sample from Antigua and four samples from Belize. Pentachlorophenol was detected in less than 11% of the entire samples.

4. Discussion

Overall, the results of this study indicate that pregnant women in the English speaking Caribbean islands are exposed to modern pesticides. Many studies have established that these compounds and/or their metabolites can cross the placental barrier and are known to interfere with hormonal and neurological development, the immune system, and other physiological functions.

In general, most of the six measured OP metabolites were consistently detected in greater than 60% of the samples from Antigua and Barbuda, Bermuda, and Jamaica. Where U.S. and Canadian data were available, comparison of the geometric means found that they were more or less similar. Several extreme values, however, were recorded for some OP metabolites in certain Caribbean countries, most commonly Antigua and Barbuda, Bermuda, Jamaica, St. Kitts and Nevis, and St. Vincent and the Grenadines. Since exposure data was not collected from the participants, it is not possible to identify the potential source(s) that gave rise to these high concentrations. Nonetheless, this clearly indicates that high exposures are occurring within this region which warrants further investigation especially given the fact that the primary concern of exposure to OPs is acute toxicity. Furthermore, although we lack full understanding of the health effects of long-term chronic low-dose OP exposure during pregnancy, early evidence points to several adverse health endpoints.

Carbamate exposure, evaluated by looking for the presence of two carbamate metabolites—propoxur metabolite 2-isopropoxyphenol (2-IPP) and carbofuranphenol—was found to be either very low or non-existent throughout the 10 Caribbean countries sampled in this study. This finding is congruent with what was also found in both North American countries where this class of pesticide was not detected in any of the samples.

While exposure to phenoxy acid types of pesticides appear not to be common in the U.S. and Canada, for the Caribbean women sampled in this study, the detection frequency for this metabolite ranged from 20% in Grenada to a high of 67% in Belize. Additionally, several extreme exposures were recorded in Belize. This evidence indicates that this class of pesticide is still commonly used throughout the Caribbean and potential for exposure is high.

The evidence of exposures to chlorophenol pesticides was also established with 2,4-DCP geometric means ranging from 0.52 µg/L in St. Vincent and the Grenadines to a high of 1.68 µg/L in Bermuda. Several extreme concentrations of 2,5-DCP (normal range 5-10 µg/L) were detected in four Caribbean countries—Belize (1100 µg/L), Bermuda (870 µg/L), Jamaica (1300 µg/L), and St-Kitts and Nevis (1400 µg/L). The metabolites 2,4,5-TCP, 2,4,6-TCP, and pentachlorophenol were rarely detected. In a group of 538 pregnant women living in a highly agriculturally active valley in California, the 95th percentile values of the most commonly detected (>50%) chlorophenol pesticides were significantly higher among these women after controlling for age, race, socioeconomic status, and smoking status [47]. In this study, the multiple extreme values may be explained by the frequent use of toilet deodorants which contain paradichlorobenzene [48].

It is well known that levels of chemicals measured during pregnancy can be influenced by physiological (e.g., changes in BMI, plasma volume expansion, and bone mobilization) and behavioral factors [49]. In accordance with other studies, this study's results were compared with those of human biomonitoring for the general population of Canada and the USA [45, 50, 51]. Indeed, a recent study compared levels of chemicals in pregnant and non-pregnant women in the U.S. and found that the levels were comparable between both groups [49]. Furthermore, the study by Castorina, et al. [47] found that the detection frequency of pesticide metabolites in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort was similar to those found in a U.S. reference population of pregnant women.

There are some limitations in how to interpret the results of this regional Caribbean study. The limited sample size restricts the generalization of these results to the entire population of pregnant women in each country. It is possible that selection bias may have occurred in the recruitment of pregnant women in some of the countries, especially in Jamaica and Belize. Jamaica's population is much higher (2.8 million inhabitants) compared to the other Caribbean countries that participated in this study which have populations approximately around 100,000 (Table 1). The Belizean population (327,000 inhabitants) has multiple different subgroups differentiated by culture, language, and ethnicity for which a sample size of 50 pregnant women may not provide a representative snapshot of the entire population. For the other eight countries, however, given that almost all delivering women utilize one or two major healthcare centers in these islands, and given that the populations on these islands are much smaller (<100,000), as well as more homogenous, it is very likely that the

samples collected in this study are representative of the population from which they were drawn.

Since a nonrandomized population based sampling strategy was used, this places some potential limitations on the comparability of this study's results with those from the NHANES and CHMS population based datasets. Given, however, that the dates of conception and delivery are more or less inherently random events, and no evidence was found to suggest that the pregnant women who participated in this study differed in any material way from those who were not sampled, the samples collected in this study could be viewed as very close proxies of randomly population-based samples.

From a statistical standpoint, several extreme OP metabolites were detected in several Caribbean countries. Other studies have shown that postpartum levels of dialkyl phosphates (DAP) are considerably higher than those measured during pregnancy [7]. While the majority of urine samples taken in this study were taken prenatally, a few were taken up to two weeks after delivery. This fact was not noted on the sample form and so it is not possible to determine if these postpartum samples are the same ones that presented with very high DAP concentrations.

Chemical concentrations in this study were not corrected for levels of creatinine which would thus permit adjustment for urine dilution as well as partially account for differences in lean body mass and renal function among persons. A comparison, however, of corrected and uncorrected dialkylphosphate metabolites concentrations published in the Canadian Health Measures Survey report reveals that the mean, median and percentiles values are quite similar for both types of measures[39].

This study's findings were based only on data obtained from English-speaking Caribbean countries. The findings reveal that while some exposure patterns for some pesticides are similar, for others there are notable differences. This variability in exposure profiles may be due in part to several factors such as different pesticides being preferred in each island, differences in dietary choices, or differences in occupational and environmental practices associated with the handling and disposal of pesticides in each Caribbean island. Thus, these results should not be generalized to other English-speaking Caribbean countries or other non-English-speaking Caribbean countries in lieu of determining the pesticide exposure profiles for each individual Caribbean country.

The validity of comparing the findings from these 10 Caribbean countries with each other and with Canadian and U.S. results is strengthened by the fact that this study's entire laboratory analyzes and those for the CHMS study were done by the same laboratory. Thus, the same analytical laboratory techniques and LODs were used validating the comparability of the Caribbean results with those measured in North America, particularly Canada.

5. Conclusion

This initial exploratory biomonitoring study on the concentrations of pesticide chemicals or their metabolites in maternal urine samples taken from 10 Caribbean countries confirm that prenatal exposures to many neurotoxic and developmental toxicants are taking place throughout the Caribbean region. Generally, levels of pesticide metabolites in pregnant Caribbean women were comparable with those found in Canada and the U.S., however, multiple extreme values for some classes of pesticides such as chlorophenols were detected in several Caribbean countries. The significance of both low and high levels of exposure is compounded by the fact that any damage to the fetus' neurological and physiological development will be born out over the child's entire lifetime.

This study's biomonitoring data provides baseline data for future studies monitoring and evaluating changes in pesticide usage and exposure over time in this region of the world. Since pesticides and insecticides are widely used in tropical environments like the Caribbean, and given that the cumulative effect of chronic exposures on pregnant women and their offspring is strongly suggestive of being adverse, it is recommended that public health authorities in the Caribbean region encourage their populations, and in particular pregnant women, to reduce pesticide use, as well as to avoid direct contact with these agents. Finally, this study's data underscores the need for Caribbean public health authorities to encourage their populations, and in particular pregnant women, to become more aware of the potential routes of exposure and to utilize these pesticides more cautiously given the possible adverse effects of exposure to their fetuses and infants.

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Tables

Table 1. Sample size and population characteristics for the 10 Caribbean countries

Country (Country Code)	Total Population[1]	Total No. of Samples Collected	Total No. of Samples Analyzed	Average Age (yrs)	Age range (yrs)
Antigua & Barbuda (**ANU**)	89,018	39	15	N/A[2]	N/A[2]
Belize (**BLZ**)	327,719	50	15	24.4	18 to 36
Bermuda (**BDA**)	69,080	50	15	24.9	18 to 38
Dominica (**DOM**)	73,126	47	15	28.8	19 to 44
Grenada (**GND**)	109,011	50	15	26.5	18 to 44
Jamaica (**JAM**)	2,889,187	47	15	26.1	18 to 42
Montserrat (**MON**)	5,164	15	15	28.8	19 to 31
St. Kitts & Nevis (**SKN**)	50,726	44	15	N/A[2]	N/A[2]
St. Lucia (**SLU**)	162,178	46	15	29.4	19 to 38
St. Vincent & Grenadines (**SVG**)	103,573	50	15	26.7	18 to 42
Total/Average		**438**	**150**	**27**	

[1] Source: Central Intelligence Agency (https://www.cia.gov/library/publications/the-world-factbook/index.html)
[2] Age of participants was not reported by this country's data collection team.

Table 2 Comparison of 10 Caribbean countries organophosphate (OP) metabolites concentrations (µg/L) and 95% CI results with comparable U.S. and Canadian results (Results are **Bold** if detection frequency ≥ 60%)

Diethylphosphate (DEP) (µg/L)	N	Geometric Mean	Lower 95%CI	Upper 95%CI	Median	90th	Min	Max	Mean[¶] Score	DF (%)
Antigua and Barbuda	**15**	**4.47**	**2.80**	**7.13**	**4.30**	**16.00**	**0.50**	**17.00**	**64.2^{A}**	**93**
Belize	15				1.40	19.00	0.50	27.00		53
Bermuda	**15**	**1.95**	**1.21**	**3.11**	**2.30**	**5.40**	**0.50**	**9.10**	**45.2^{AB}**	**73**
Dominica	**15**	**1.31**	**0.81**	**2.10**	**1.10**	**4.50**	**0.50**	**5.40**	**34.2^{B}**	**60**
Grenada	**15**	**1.72**	**1.19**	**2.49**	**1.40**	**3.90**	**0.50**	**9.10**	**39.3^{AB}**	**87**
Jamaica	**15**	**2.07**	**1.10**	**3.90**	**1.50**	**14.00**	**0.50**	**29.00**	**39.3^{AB}**	**73**
Montserrat	15					3.10	0.50	6.60		20
St. Lucia	15				1.30	3.90	0.50	5.40		53
St. Kitts and Nevis	**15**	**2.52**	**1.52**	**4.16**	**2.00**	**6.40**	**0.50**	**41.00**	**47.5^{AB}**	**93**
St. Vincent and the Grenadines	15					6.00	0.50	8.00		47
Caribbean Islands	**150**	**1.65**	**1.39**	**1.97**	**1.50**	**7.20**	**0.50**	**41.00**		**65**
Canada 2007-09 (Women 20-39)	**651**	**2.00**	**1.50**	**2.60**	**2.10**	**NA**	**NA**	**NA**		**77**
United States 2007-08 (Women 20-39)	610					8.49	0.26	106.8		25

Diethylthiophosphate (DETP) (µg/L)	N	Geometric Mean	Lower 95%CI	Upper 95%CI	Median	90th	Min	Max	Mean[¶] Score	DF (%)
Antigua and Barbuda	**15**	**0.43**	**0.28**	**0.66**	**0.48**	**2.00**	**0.15**	**2.50**	**22.5^{A}**	**73**
Belize	14					3.90	0.15	23.00		43
Bermuda	15					0.53	0.15	0.70		40
Dominica	15				0.37	1.50	0.15	1.50		53
Grenada	15					0.61	0.15	1.70		33
Jamaica	**15**	**0.71**	**0.37**	**1.37**	**0.45**	**3.10**	**0.15**	**16.00**	**26.6^{A}**	**80**
Montserrat	15					1.10	0.15	4.00		40
St. Lucia	13					0.70	0.15	1.00		15
St. Kitts and Nevis	15				0.31	0.54	0.15	6.10		53
St. Vincent and the Grenadines	**15**	**0.35**	**0.23**	**0.53**	**0.37**	**1.00**	**0.15**	**2.00**	**19.8^{A}**	**60**
Caribbean Islands	150					1.50	0.15	23.00		50
Canada 2007-09 (Women 20-39)	651					NA	NA	NA		36
United States 2007-08 (Women 20-39)	610					2.40	0.08	51.86		42

Dimethylphosphate (DMP) (µg/L)	N	Geometric Mean	Lower 95%CI	Upper 95%CI	Median	90th	Min	Max	Mean[¶] Score	DF (%)
Antigua and Barbuda	**15**	**3.30**	**1.77**	**6.21**	**3.00**	**14.00**	**0.50**	**20.00**	**54.6^{A}**	**87**
Belize	15					2.20	0.50	2.60		20
Bermuda	**15**	**3.84**	**2.54**	**5.72**	**4.60**	**11.00**	**0.50**	**11.00**	**61.2^{A}**	**93**
Dominica	15				1.00	8.90	0.50	12.00		53
Grenada	**15**	**1.29**	**0.79**	**2.11**	**1.20**	**4.50**	**0.50**	**13.00**	**33.6^{A}**	**60**
Jamaica	15					2.60	0.50	7.50		40
Montserrat	15					14.00	0.50	34.00		47
St. Lucia	**15**	**1.28**	**0.78**	**2.11**	**1.00**	**5.90**	**0.50**	**12.00**	**33.5^{A}**	**60**
St. Kitts and Nevis	**15**	**3.17**	**1.71**	**5.90**	**2.40**	**29.00**	**0.50**	**49.00**	**52.6^{A}**	**93**
St. Vincent and the Grenadines	**15**	**1.51**	**0.91**	**2.50**	**1.40**	**7.70**	**0.50**	**11.00**	**37.5^{A}**	**77**
Caribbean Islands	**150**	**1.60**	**1.33**	**1.94**	**1.40**	**11.00**	**0.50**	**49.00**		**63**

Canada 2007-09 (Women 20-39)	**651**	**2.60**	**2.10**	**3.40**	**3.00**	**NA**	**NA**	**NA**		**77**
United States 2007-08 (Women 20-39)	610					18.0	0.33	136.7		33

Dimethylthiophosphate (DMTP) (µg/L)										
	N	**Geometric Mean**	**Lower 95%CI**	**Upper 95%CI**	**Median**	**90th**	**Min**	**Max**	**Mean¶ Score**	**DF (%)**
Antigua and Barbuda	**15**	**1.85**	**0.85**	**4.02**	**1.60**	**20.00**	**0.30**	**24.00**	**40.8^{A}**	**83**
Belize	15					1.50	0.30	3.40		30
Bermuda	**15**	**2.26**	**1.28**	**3.98**	**3.10**	**6.90**	**0.30**	**19.00**	**47.3^{A}**	**87**
Dominica	15					1.70	0.30	15.00		40
Grenada	15				0.70	2.40	0.30	8.60		53
Jamaica	**15**	**0.96**	**0.54**	**1.71**	**0.90**	**2.80**	**0.30**	**27.00**	**30.9^{A}**	**73**
Montserrat	15					36.00	0.30	37.00		47
St. Lucia	15					3.80	0.30	7.30		47
St. Kitts and Nevis	**15**	**1.39**	**0.55**	**3.50**	**0.90**	**51.00**	**0.30**	**60.00**	**33.8^{A}**	**60**
St. Vincent and the Grenadines	**15**	**1.29**	**0.71**	**2.33**	**1.50**	**6.70**	**0.30**	**19.00**	**37.1^{A}**	**73**
Caribbean Islands	**150**	**1.03**	**0.82**	**1.29**	**0.80**	**7.95**	**0.30**	**60.00**		**60**
Canada 2007-09 (Women 20-39)	**651**	**1.80**	**1.20**	**2.60**		**NA**	**NA**	**NA**		**65**
United States 2007-08 (Women 20-39)	**610**	**2.15**	**1.80**	**2.58**	**1.97**	**16.63**	**0.39**	**195.3**		**74**

CI, Confidence interval. **DF**, detection frequency. **NA,** not available.
¶ Ranked Mean Scores for Kruskal-Wallis test.
^{A,B,AB} Same letter signifies no difference in the mean scores

Table 3 Comparison of 10 Caribbean countries carbamate propoxur metabolite 2-isopropoxyphenol concentrations (μg/L) and 95% CI results with comparable U.S. and Canadian data (Results are **Bold** if detection frequency ≥ 60%)

2-Isopropoxyphenol (μg/L)									
	N	Geometric Mean	Lower 95%CI*	Upper 95%CI*	Median	90th	Min	Max	DF (%)
Antigua and Barbuda	15					0.11	0.025	0.13	20
Belize	15								0
Bermuda	15						0.025	0.08	7
Dominica	15					0.08	0.025	0.11	27
Grenada	15					0.07	0.025	0.71	27
Jamaica	15								0
Montserrat	15					0.10	0.025	0.17	27
St. Lucia	15						0.025	0.18	7
St. Kitts and Nevis	15								0
St. Vincent and the Grenadines	15					0.09	0.025	0.24	13
Caribbean Islands	150					0.07	0.025	0.71	13
Canada 2007-09 (Women 20-39)									none
United States 2007-08 (Women 20-39)									none

CI, Confidence interval. **DF**, detection frequency.

Table 4 Comparison of 10 Caribbean countries phenoxy acid metabolite 2,4-dichlorophenoxyacetic acid (2,4-D) concentrations (µg/L) and 95% CI results with comparable U.S. and Canadian results (Results are **Bold** if detection frequency ≥ 60%)

2,4-Dichlorophenoxyacetic acid (2,4-D) (µg/L)									
	N	Geometric Mean	Lower 95%CI*	Upper 95%CI*	Median	90th	Min	Max	DF (%)
Antigua and Barbuda	15					0.30	0.10	0.30	33
Belize	**15**	**0.33**	**0.17**	**0.63**	**0.21**	**2.70**	**0.10**	**4.00**	**67**
Bermuda	**15**	**0.22**	**0.15**	**0.31**	**0.24**	**0.60**	**0.10**	**0.85**	**60**
Dominica	**15**	**0.24**	**0.15**	**0.36**	**0.23**	**0.80**	**0.10**	**1.40**	**60**
Grenada	15					0.32	0.10	0.80	20
Jamaica	15					0.48	0.10	1.40	47
Montserrat	15					0.31	0.10	0.74	27
St. Lucia	15					0.32	0.10	0.50	33
St. Kitts and Nevis	15					0.31	0.10	0.37	40
St. Vincent and the Grenadines	15					0.45	0.10	0.52	47
Caribbean Islands	150					0.49	0.10	4.00	43
Canada 2007-09 (Women 20-39)	653					NA	NA	NA	35
United States 2007-08 (Women 20-39)	610					0.86	0.28	349.7	35

CI, Confidence interval. **DF**, detection frequency. **NA,** not available

Table 5 Comparison of 10 Caribbean countries' chlorophenol metabolites concentrations (μg/L) and 95% CI results with comparable U.S. and Canadian results (Results are **Bold** if detection frequency ≥ 60%)

2,4-Dichlorophenol (2,4-DCP) (μg/L)	N	Geometric Mean	Lower 95%CI	Upper 95%CI	Median	90th	Min	Max	DF (%)
Antigua and Barbuda	**15**	**0.83**	**0.47**	**1.46**	**1.20**	**3.60**	**0.15**	**3.90**	**80**
Belize	**15**	**0.63**	**0.34**	**1.16**	**0.48**	**3.70**	**0.15**	**15.00**	**80**
Bermuda	**15**	**1.68**	**1.01**	**2.79**	**1.10**	**8.70**	**0.45**	**15.00**	**100**
Dominica	15				0.39	2.90	0.15	3.20	53
Grenada	**15**	**0.80**	**0.45**	**1.42**	**0.62**	**4.40**	**0.15**	**5.70**	**87**
Jamaica	**15**	**0.92**	**0.42**	**2.03**	**0.79**	**7.50**	**0.15**	**26.00**	**73**
Montserrat	**15**	**0.96**	**0.56**	**1.63**	**1.50**	**2.90**	**0.15**	**6.40**	**87**
St. Lucia	14					2.00	0.15	5.10	43
St. Kitts and Nevis	**15**	**1.07**	**0.65**	**1.76**	**0.88**	**2.10**	**0.30**	**19.00**	**100**
St. Vincent and the Grenadines	**15**	**0.52**	**0.29**	**0.93**	**0.47**	**3.00**	**0.15**	**5.00**	**77**
Caribbean Islands	**150**	**0.75**	**0.61**	**0.91**	**0.68**	**3.70**	**0.15**	**26.00**	**78**
Canada 2007-09 (Women 20-39)	**653**	**0.87**	**0.75**	**1.00**	**0.78**	**NA**	**NA**	**NA**	**76**
United States 2007-08 (Women 20-39)	**616**	**1.13**	**0.93**	**1.38**	**0.86**	**7.88**	**0.14**	**161**	**92**

2,5-Dichlorophenol (2,5-DCP) (μg/L)	N	Geometric Mean	Lower 95%CI	Upper 95%CI	Median	90th	Min	Max	DF (%)
Antigua and Barbuda	**15**	**5.14**	**2.63**	**10.02**	**5.80**	**16**	**0.88**	**200**	**100**
Belize	**15**	**3.39**	**0.94**	**12.20**	**1.60**	**110**	**0.15**	**1100**	**100**
Bermuda	**15**	**8.48**	**2.74**	**26.21**	**3.20**	**370**	**0.30**	**870**	**100**
Dominica	**15**	**0.87**	**0.45**	**1.66**	**1.70**	**3.20**	**0.15**	**5.40**	**73**
Grenada	**15**	**1.33**	**0.54**	**3.25**	**1.10**	**20.00**	**0.15**	**100**	**80**
Jamaica	**15**	**9.38**	**2.99**	**29.48**	**4.70**	**340**	**0.40**	**1300**	**100**
Montserrat	15				0.30	3.40	0.15	5.50	53
St. Lucia	**14**	**0.72**	**0.41**	**1.26**	**0.71**	**2.70**	**0.15**	**4.00**	**79**
St. Kitts and Nevis	**15**	**5.01**	**1.88**	**13.35**	**4.80**	**14.00**	**0.15**	**1400**	**100**
St. Vincent and the Grenadines	**15**	**0.67**	**0.40**	**1.11**	**0.71**	**2.70**	**0.15**	**3.70**	**80**
Caribbean Islands	150	2.14	1.53	2.98	1.80	37.00	0.15	1400	87
Canada 2007-09 (Women 20-39)									None
United States 2007-08 (Women 20-39)	**616**	**12.96**	**9.33**	**17.99**	**9.34**	**247.4**	**0.14**	**11300**	**99**

CI, Confidence interval. **DF**, detection frequency. **NA**, not available