# Associations of Urinary Concentrations of Organophosphates and Pyrethroids with Obesity and Diabetes in Canadian Adults

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## List of Acronyms

BMI: Body Mass Index

CHMS: Canadian Health Measures Survey

AChE: Acetylcholinesterase

AlkP: Alkaline phosphatase

AMP: Adenosine monophosphate

CI: Confidence interval

*cis*-CBCA: *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid

CYPM: cytochrome P450-dependent monooxygenases

DAP: Dialkylphosphate

*cis*-DCCA: *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane

DDT: Dichlorodiphenyltrichloroethane

DEP: Diethylphosphate

DEDTP: Diethyldithiophosphate

DETP: Diethylthiophosphate

DMP: Dimethylphosphate

DMDTP: Dimethyldithiophosphate

DMTP: Dimethylthiophosphate

EPA: Environmental Protection Agency

HbA1c: Glycated hemoglobin

NHANES: U.S. National Health and Nutrition Examination Survey

NIH: National Institute of Health

NTE: Neuropathy target esterase

OP: Organophosphate

OPIDP: Organophosphate-induced delayed polyneuropathy

OR: Odds ratio

3-PBA: 3-Phenoxybenzoic acid

PMRA: Pest Management Regulatory Agency

*trans*-DCCA: *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid

VGSC: Voltage-gated sodium channels

WC: Waist circumference

WHO: World Health Organization

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## Preface

Data for this thesis were acquired through the Canadian Health Measures Survey. This survey's conduct and design was reviewed and approved by Health Canada and the Public Health of Canada Research Ethics Board. The survey was created using extensive consultations with recognized experts to ensure all internationally recognized ethical standards for human research were adequately met. Additionally, a full Privacy Impact Assessment was carried out to ensure participants' privacy rights were protected. Participation in the survey was voluntary and respondents had the right to withdraw at any point. Access to the data for this thesis was approved by Statistics Canada (Contract Number: 20-SSH-COOL-6482). No external funding was given for this project except a student bursary given by the Thesis Supervisor Dr. Yue Chen.

**Abstract**

**Background:** The relationships between both obesity and diabetes and the exposure to insecticides, specifically organophosphates and pyrethroids, in the adult Canadian population are not well-understood.

**Methods:** Urinary concentrations of 4 organophosphate metabolites (DEP, DEPT, DMP, and DMPT) and of 4 pyrethroid metabolites (*cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA) were measured for 1,147 adult Canadians aged between 18-79 years old. The geometric means and medians of both creatinine-adjusted and unadjusted urinary insecticide metabolites were estimated. Multiple linear regression and logistic regression analyses were employed to examine the associations between the insecticide metabolite concentrations and obesity and diabetes measures.

**Results:** Both insecticides had detectable levels in over 70% of CHMS respondents. Most metabolites demonstrated a negative significant relationship between their urinary concentrations and BMI as well as waist circumference. No significant relationship was found in regard to HbA1c levels or for diabetes.

**Conclusion:** Organophosphate and pyrethroid metabolites were detected in more than 70% of Canadian adults. Our data showed no evidence that organophosphate and pyrethroid exposures increase the risks of obesity and diabetes in adults. These results should be interpreted with caution as diet may play a large confounding role in the relationships of study.

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# 1. Introduction

Obesity is one of the most prevalent conditions of modern times. Obesity in adults can be defined by the Canadian Guidelines for Body Weight Classification as individuals who have a BMI equal to or greater than 30 $kg/m^2$ (1). Its prevalence has considerably risen across the developed world in the last couple decades (2). Within Canada, 18.6% of the adult population was obese in 2013 and that proportion has been steadily increasing over time (3). Obesity increases the risks of many chronic illnesses, including diabetes, heart disease, and many kinds of cancers (4). Obesity is also correlated with elevated risks of mortality, disability, multimorbidity, and reduced quality of life (3,5,6). As such obesity represents a significant health problem to address in Canada.

Obesity itself can be caused by a myriad of environmental factors (7). One type of potential environmental risk factor is insecticide exposure, although research addressing this association is sparse. Two of the most commonly used insecticides in Canada are organophosphates and pyrethroids. Organophosphates play a major role as a highly efficient insecticide for global agricultural use (8). As such, nearly all individuals have organophosphate residues in their bodies (9). Subpopulations who are heavily exposed to pesticides, such as inner-city populations, those with low socioeconomic status (SES), and agricultural populations, also have high rates of obesity (10,11). As such, insecticide exposure, among other important factors such as the built environment and access to a healthy diet, may contribute to overall obesity within these subpopulations (12).

Organophosphates work by inhibiting cholinesterase, an enzyme which degrades the neurotransmitter acetylcholine (13). They also affect the cyclic adenosine monophosphate

(AMP) pathway by upregulating adenylyl cyclase which can lead to lasting alterations of cyclic AMP regulation (14). This causes the potential to affect adiposity as cyclic AMP plays a role in controlling cardiovascular, metabolic, and hormonal functions. In animal studies, administration of organophosphates can lead to excessive weight gain (15). Also, organophosphate insecticides may contribute to obesity through defective central nervous system functions as the insecticide damages young brains and causes damage to acetylcholine markers that can be repaired through the ingestion of high fat diets (16). This high fat diet may lead to a subconscious behaviour to partake in high fat diets which can persist into adulthood and exacerbate diabetes and obesity (13).

Pyrethroids are the fourth most commonly used group of insecticides globally in both agricultural and urban settings (17). These compounds have generally been reported as having low mammalian toxicity, but they have been shown to act as endocrine disrupting compounds in mammals by blocking, synergizing, and mimicking endogenous hormones (17,18). Different kinds of pyrethroids have been shown to affect different functions including permethrin's effect on adipogenesis/lipogenesis, deltamethrin's effect on fat accumulation, and general pyrethroids' effect on thyroid hormone levels (19–21). Additionally, pyrethroids have been shown in animal studies to affect physiological processes involved in relative weight and appetite control (21–26). These mechanisms may serve as a contributing factor in the development of obesity and diabetes.

Although plausible mechanisms have been studied in animal studies, by which exposure to these insecticides can contribute to obesity and diabetes, there are, to my best knowledge, no human studies that examine these associations. Additionally, the impacts of these insecticides on obesity in Canadians remain unclear, and relevant research is sparse. Earlier cycles of the

Canadian Health Measure Survey (CHMS) have shown that at least 4 of the 6 organophosphate metabolites and 4 of the 5 pyrethroid metabolites have been detected in ≥60% in the Canadian population, suggesting that the majority of the Canadian population has a detectable amount of insecticide metabolites within their bodies (27). The CHMS provides a unique opportunity to examine the associations between insecticides and obesity and diabetes as the survey collects data on both anthropometrical measures and chemical panels of their participants. Having access to these robust measurements addresses the need to examine their relationships.

# 2. Literature Review

## 2.1 Organophosphates

Organophosphates (OPs) are organic compounds that belong to the class of organophosphorus compounds, which have the general structure of a central phosphate molecule with aromatic or alkyl substituents. In nature, the only naturally occurring OPs are one OP produced by cyanobacteria, guanitoxin (formerly called anatoxin-a(S)), and two OPs that were isolated from cultures of the microorganism *Streptomyces antibioticus,* CGA134735 and CGA134736 (28–30). OPs are primarily used as insecticides whose main role is to primarily target acetylcholinesterase (AChE), an enzyme which hydrolyzes the neurotransmitter acetylcholine (31,32). They are also used in medicine, lubricants, flame-retardants, plasticizers, and even in chemical warfare (33). Although use of OPs has diminished due to concerns over their mammalian and environmental toxicity, they are still commonly used in developing countries due to their low cost (34).

Historically, OPs were first discovered in the 1800s by Phillipe de Clermont and Muscovite Wladimir Moschnin when they both independently synthesized tetraethyl phosphate

by reacting ethyl iodide with the silver salt of pyrophosphoric acid (35). In 1932, Willy Lange noted the toxicity of the esters of monofluor phosphoric acids, stating that they caused dizziness and difficulty breathing (36). Following this discovery, German chemist Gerhard Schrader was tasked by the Nazi government to weaponize OP into a nerve gas which resulted in diisopropyl fluorophosphate; however, it was never employed in combat (34,37). The first true synthetic OP (hexaethyl tetra phosphate) was also created by Schrader and demonstrated significant insecticidal properties (37). After World War II, the United States took great interest in hexaethyl tetra phosphate and illuminated its cholinesterase inhibiting abilities as well as its insecticidal properties (37). Using this knowledge, they manufactured the OP called parathion and marketed it as an effective low mammalian toxicity pesticide, despite sizable evidence arguing its high mammalian toxicity (37). Following parathion was malathion, which also was marketed as having low mammalian toxicity, despite what research had shown (37).

OP use gained a lot of popularity in the 1970s after the banning of organochlorine pesticides, such as dichlorodiphenyltrichloroethane (DDT) (34). Up until the 2000s, OP use dominated the insecticide market (constituting 71% of the entire world insect control chemical market in 1987), but has rapidly declined with the introduction of newer and safer insecticides (34,38). In 1999, OPs only accounted for 52% of the world insecticide market (38). The decline was also likely attributable to staggering reports of OP-related death. In 1990s, it was estimated that 200,000 people died annually in part due to pesticide poisoning (39). This number increased to about 350,000 deaths annually in the late 2000s (40,41). OPs were suggested to be associated with about two thirds of these deaths and also contributed to millions of additional nonfatal poisoning cases (40,42). Despite these numbers, OPs' low cost has contributed to their persistent usage in developing countries (34).

OPs' insecticidal activity is centered around the inhibition of AChE. They also have the potential to inhibit plasma butyrylcholinesterase and neuropathy target esterase (NTE) in neural tissue and blood lymphocytes (43). The effects of acute exposure to OP has been well investigated and documented through thousands of case studies and animal studies but long term effects are still subject to a large amount of uncertainty (44).

Routes of exposure and concentrations

The most common routes of exposures to OPs in humans are dermal contact, inhalation, and ingestion. Routes of exposure greatly impact the rapidity of symptoms onset with inhalation representing the quickest route (45). For example, when people are exposed to the nerve gas agent Sarin, they can instantaneously die from respiratory arrest (46). Additionally, farmers can experience rapid acute manifestations within minutes if there is a sudden change in wind direction upon insecticide spraying (47). With respect to OP concentrations in the environment, no generalizations can be made as the physical and chemical characteristics of each OP affect its solubility, environmental persistence, long-range transport, bioaccumulation, and partitioning (43).

With dermal contact, OP toxicity is determined primarily by the degree of intactness of the skin, the volume and duration of exposure, and the solubility characteristics of the OP (45). Dermal contact generally results in symptoms appearing between 30 minutes to more than 24 hours after OP exposure (48–51). Ingestional OP contact's toxicity is dependent on the poison load and absorption characteristics of the OP. Symptom onset with this route of exposure is generally mediated by the liver with the conversion of the organothiophosphates's thions to oxons (45). Humans are most commonly exposed to OPs through the diet, where the consumption of food, mostly fruits and vegetables, may lead to the ingestion of OP insecticide

residue (10,52,53). OPs can be biodegradable as environmental microbes have shown the potential for performing biochemical mechanisms that can breakdown most OPs (54)

In Canada, OP pesticides are mostly used for agricultural purposes through crop dusting or manual spraying over large cultivated areas that usually contain crops (55). A study conducted by Ye et al. using data from Cycle 1 of the CHMS (2007-2009) examined the association between dietary factors and urinary OP concentrations (56). They found that respondents had significantly higher urinary OP concentrations, as measured by the geometric mean, when they had high meat, fruit, vegetable, milk and dairy products, pulses and nuts, or starchy root consumption. Many of these food products involve insecticide use during the manufacturing process which might contribute to the observed higher associated urinary concentrations.

OPs are also used in Canada for pest control, ornamental horticulture, and pest infestation (55). OP's insecticides sales and use is regulated under the Pest Control Products Act in Canada by the Pest Management Regulatory Agency (PMRA) (57). The PMRA's role is to evaluate the OP's toxicity to determine whether the insecticide should be employed for a specific use and to establish a maximum residue limit for of the OP in food for newly registered OPs (58). In addition to monitoring OP's residue levels in food, Health Canada has established several maximum acceptable concentration guidelines for various OPs in Canadian drinking water (59).

As Canada has only recently begun biomonitoring urinary OP metabolites, time trend analysis for their concentrations in humans has yet to be adequately explored (55). Previous cycles of the CHMS demonstrated that at least 4 of the 6 organophosphate metabolites had detection frequencies of ≥60% in the Canadian population (27). There are still many OP formulations that are registered under the PMRA as of May 2021 (Table 2.1). When Cycle 5 of the CHMS was conducted, there were 15 OP insecticides registered for use in Canada (59).

These OPs and their metabolites are summarized in Table 2.2 (59). The geometric means and selected percentiles of urine metabolites concentrations (μg/g creatinine) for all CHMS cycles where these measurements occurred, can be found in Appendices 1a-1f.

**Table 2.1 Organophosphate formulations registered by Health Canada classified by active substances.*** (60)

| Active substance | Domestic | Commercial | Restricted** | Total*** |
|---|---|---|---|---|
| Acephate | 0 | 3 | 0 | 3 |
| Azamethiphos | 0 | 0 | 1 | 1 |
| Bensulide | 0 | 2 | 0 | 2 |
| Chlorpyrifos | 0 | 10 | 6 | 16 |
| Coumaphos | 0 | 1 | 0 | 1 |
| Diazinon | 0 | 7 | 0 | 7 |
| Dichlorvos | 1 | 6 | 0 | 7 |
| Dimethoate | 0 | 8 | 0 | 8 |
| Malathion | 8 | 19 | 2 | 29 |
| Naled | 0 | 1 | 0 | 1 |
| Parathion | 0 | 13 | 0 | 13 |
| Phorate | 0 | 0 | 1 | 1 |
| Phosmet | 0 | 2 | 0 | 2 |
| Tetrachlorvinphos | 24 | 2 | 0 | 26 |
| Trichlorfon | 0 | 1 | 0 | 1 |

*Information collected from Health Canada website on 5/24/2021.
**Restricted indicates only usable in specific circumstances by trained individuals.
*** Multiple pyrethroid active ingredients could be in a single formulation.

**Table 2.2 Parent organophosphate pesticides registered for use in Canada between 2015-2016 and their measured urinary dialkyl phosphate metabolites.** (59)

| | Dialkyl phosphate metabolites | | | | | |
|---|---|---|---|---|---|---|
| **Active substance** | **DMP** | **DMTP** | **DMDTP** | **DEP** | **DETP** | **DEDTP** |
| Acephate | - | - | - | - | - | - |
| Azamethiphos | - | - | - | - | - | - |
| Bensulide | - | - | - | - | - | - |
| Chloropyrifos | - | - | - | Yes | Yes | - |
| Coumaphos | - | - | - | Yes | Yes | - |
| Diazinon | - | - | - | Yes | Yes | - |
| Dichlorvos | Yes | - | - | - | - | - |
| Dimethoate | Yes | Yes | Yes | - | - | - |
| Malathion | Yes | Yes | Yes | - | - | - |
| Naled | Yes | - | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Parathion | - | - | - | - | - | - |
| Phorate | - | - | - | Yes | Yes | Yes |
| Phosmet | Yes | Yes | Yes | - | - | - |
| Propetamphos | - | - | - | - | - | - |
| Tetrachlorvinphos | Yes | - | - | - | - | - |
| Trichlorfon | Yes | - | - | - | - | - |

- Active substance does not metabolize into the organophosphate metabolite

Mechanisms and role as an endocrine disruptor

The primary target of OPs is AChE, a vital enzyme whose role is to hydrolyze the major neurotransmitter acetylcholine (34). Acetylcholine's physiological role is to transmit signals from motor nerves to muscles and is also involved in functions such as movement, memory, and cognition (61). OPs, that have the P = O moiety, can inhibit AChE by phosphorylating the hydroxyl group on serine in the active site of AChE (32,33). The bond between the esteratic site of the AChE and the phosphorus atom is much more stable than the bond between acetylcholine's acetate carbonyl carbon and the same AChE esteratic site (44). Consequently, the breaking of the phosphorus-enzyme bond takes several hours to a few days, depending on the type of OP, as compared to the usual carbon-enzyme bond that is broken in microseconds (44). These phosphorylated AChEs can be hydrolyzed by water at a very slow rate or undergo spontaneous reactivation; however, the phosphorylated AChE irreversibly ages before it can be hydrolyzed or reactivated (44). Once the phosphorylated AChE ages, the enzyme becomes irreversibly inhibited as it loses one of the two alkyl (R) groups, making it unable to hydrolyze acetylcholine for a couple days until new enzymes are synthesized (33,44,62). Consequently, acetylcholine builds up in the cholinergic synapses within autonomic, peripheral, and central nervous system tissues causing overstimulation which potentially results in a myriad of clinical manifestations (63). Figure 2.1 summarizes the AChE active center activity. OPs also target

other enzymes, such as butyrylcholinesterase; however, the mechanisms by which OPs affect these other enzymes and the clinical significance of their inhibition by OP is unclear (9).

**Figure 2.1 Reaction of an OP and AChE's active center compared to the normal reaction of acetylcholine and AChE's active center** (44)***.**

"Figure 2.1 has been removed due to copyright restrictions. It was a diagram detailing organophosphate's metabolic pathways. Original source: Costa LG. Toxic Effects of Pesticides. In: Casarret and Doull's Toxicology, The Basic Science of Poisons [Internet]. Seventh Edition. The McGraw-Hill Companies; 2008 [cited 2020 Oct 23]. p. 883–930. Found at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=958&sectionid=53483747

Acute clinical manifestations, defined as symptoms occurring immediately to hours after exposure, vary depending on which receptor is affected. In general, humans exposed to OPs give off a pungent chemical smell from their clothes and breath (63). The possible symptoms of muscarinic receptor toxidrome caused by OPs are bronchospasms, bronchorrhea, bradycardia, hypotension, alveolar edema, hypersalivation, miosis, nausea, vomiting, abdominal tightness and cramps, and seizures. (33,45,63–65). The possible symptoms of nicotinic receptor toxidrome caused by OPs are muscle weakness, paralysis, and fasciculations, respiratory distress (hypoxia & increased aspiration risk), restlessness, agitation, confusion, convulsions, sweating,

hypertension, and tachycardia (45,63,64). Other factors involved in acute clinical manifestations resulting from OP exposure are the route of exposure, chemical nature, solubility characteristics, and poison load (45).

Intermediate clinical manifestations, delayed onset symptoms, are generally characterized by paralysis lasting 1-4 days after exposure in the neck flexor, motor cranial nerves, respiratory muscles, and the proximal limb muscles (66). Intermediate clinical manifestations generally occur after the resolution of acute cholinergic attacks and there may be overlap between the two phases (67,68). It is hypothesized that the intermediate syndrome is caused by persistent depolarization blockade which results in desensitization due to excessive synaptic acetylcholine in the nicotinic receptors of the neuromuscular junctions (43). Weakness is also common during the intermediate period and can be attributable to neuromuscular junction defects (69). Focal weaknesses, such as laryngeal paralysis, can manifest within 14 days of the exposure (70,71). Most notably, comas can occur as an intermediate clinical manifestation lasting several hours to days (72). Coma occurs in 17-29% of patients exposed to toxic levels of OPs (72). It is hypothesized that the reason for the delayed onset is because of the slow release and re-distribution of OP compounds at CNS receptors over time. As the OP compounds irreversibly binds to AChE, the rate of regeneration of AChE is slower causing symptoms to persist or even worsen over time (45).

The most common late onset clinical manifestation is organophosphate-induced delayed polyneuropathy (OPIDP) (45). OPIDP is caused by the reaction between OPs and NTEs (73). NTEs are essential in maintaining acceptable levels of ER-membrane phosphatidylcholine by catalyzing the deacylation process of phosphatidylcholine into soluble products (74–76). When OPs inhibit NTEs, nervous system tissue accumulates phosphatidylcholine and develops

abnormal membrane structure which eventually leads to cell death (73,77). Consequently, OPIDP is characterized by paresthesia and cramping pain of the extremities following by weaknesses in distal limbs which generally occurs 2-4 weeks following OP exposure (78). Nerve biopsies generally show evidence of axonal degeneration with secondary demyelination of OP exposed individuals (64). Full recovery is common after time, especially in youth; however, mild weakness may persist for 2 years following OP exposure (79).

OPs can produce non-cholinesterase actions that affect other biological processes. One of these processes is the cyclic AMP pathway, where OPs can cause upregulating adenylyl cyclase which can lead to lasting alterations of cyclic AMP regulation (14,80–84). These animal studies found that exposure to OPs, especially during the critical development period, may permanently reprogram the signaling proteins' function and future expression. This potentially affects adiposity as cyclic AMP plays a role in controlling cardiovascular, metabolic, and hormonal functions. Early studies found that prenatal human exposure to OPs resulted in lower cognition; however, more recent studies showed no significant association between OP exposure and cognition regardless of race (55,85–92).

Administration of OPs can lead to excessive weight gain in animal studies. Meggs et al. gave female 6-month-old rats subcutaneous injections of 5mg/kg of chlorpyrifos per day and observed significantly increased weight from increased adipose tissue in the exposed as compared to the controls (mean weight of $374.4 \pm 22.2$g vs $340.2 \pm 25.2$g, $p = 0.006$, at 4 months) (15). Also, Lassiter et al. found that OP pesticides can damage young rat brains by adversely affecting acetylcholine receptors (16). The adverse damage was found to be mitigated when the rats were subject to a high fat diet (16). Consequently, it is possible that consumption of a high fat diet to mitigate the adverse effects of OPs may lead to a subconscious behaviour to

partake in the consumption of highly fatty foods that can persist into adulthood and exacerbate diabetes and obesity (13,16).

OP exposure has also been shown to increase an individual's odds of having diabetes (93). Abdollahi et al. fed adult male rats a diet of malathion mixed in corn oil and found significantly increased plasma glucose concentrations (25%, 17%, and 14% , $p<0.01$, higher than the control for 100ppm, 200ppm and 400ppm of malathion, respectively), significantly higher hepatic phosphoenolpyruvate carboxykinase (25%, 16%, and 21% , $p<0.01$, higher than the control for 100ppm, 200ppm and 400ppm of malathion respectively), and significantly increased hepatic glycogen phosphorylase (22%, 41%, and 32% , $p<0.01$, higher than the control for 100ppm, 200ppm and 400ppm of malathion respectively) as compared to the controls (94). Phosphoenolpyruvate carboxykinase is an important rate-controlling enzyme in gluconeogenesis where high levels of this enzyme results in sustained hyperglycemia that either contributes to or is a byproduct of diabetes (95–97). Hepatic glycogen phosphorylase also contributes to higher levels of plasma glucose, and the development of diabetes, as this enzyme is responsible for phosphorylating liver glycogen into glucose to be released in the blood (98).

The plausible biological mechanism of OP contributing to diabetes can be described as the interaction between pancreatic β cells and OPs. Glucose-dependent production of insulin involves the functioning of muscarinic acetylcholine receptors that are found within the pancreatic β cells (99). Since organophosphates are inhibitors of AChE, they can trigger a potential accumulation of acetylcholine within the pancreatic β cells. Over time, this has the potential to trigger overstimulation of the muscarinic acetylcholine receptors which can down-regulate its receptors to reduce insulin production (100). Also, long-term exposure to elevated

levels of acetylcholine may reduce the sensitivity of pancreatic β cells to glucose, which can further exacerbate diabetes pathology (101).

In summary, OP's AChE effect has the potential to affect adiposity through disrupted cyclic AMP functions and defective central nervous system functions. OPs can also contribute to diabetes pathology by inhibiting AChE receptors in pancreatic β cells which results in reduced insulin production. Both mechanisms suggest biological plausibility between OP exposure and obesity and diabetes.

Metabolism and Toxicokinetics

OPs have the general structure of a central phosphate molecule with aromatic or alkyl substituents. More specifically, they have a pentavalent phosphorus component which is attached with a double bond to either a sulfur or an oxygen atom, attached to two alkoxy groups (could also be isopropyl substitutes), and attached to a leaving group. The leaving group is the most sensitive to hydrolysis and is removed from the OP when it phosphorylates acetylcholinesterase (34). After exposure, OPs rapidly distribute around the body and accumulate rapidly in the liver, kidney, and fat due to its lipophilic nature (102). Contact time with the skin, region of the skin exposed, personal hygiene, whether the OP is a powder form, volatility of the OP involved, lipophilicity of the OP involved, and the presence of an emulsifier or solvent within the formulation can all impact the degree of absorption of the OP into the human body (103).

Most OPs follow a similar metabolic pathway which begins with bioactivation to a toxic oxon form, followed by detoxification into dialkylphosphates (DAPs) (59). Additionally, most OP insecticides have the double bond attached to the sulfur and they need to be bioactivated in vivo to their phosphate analogues oxon, to be able to exert its toxic effects, as only compounds

with a P=O moiety are effective inhibitors of AChE (44,103,104). Consequently, the toxic effects of phosphorothioates (P=S) will be delayed until biotransformation occurs, unless aerial oxidation of the phosphorothioates has already occurred which can create trace amounts of oxon (103). The oxidative desulfuration of phosphothioates to their active phosphate analogues is mediated by cytochrome P450, N-oxidation, S-oxidation, and flavin containing monooxygenase enzymes (44,103,105). In addition to oxidative desulfuration, OPs can undergo thioether oxidation (formation of a sulfoxide following by a sulfone), which is also catalyzed by cytochrome P450 enzymes (44). It is also worth noting that different cytochrome P450 enzymes are responsible for catalyzing different OP insecticides (44,106–108). The cytochrome P450 enzymes will perform hydrolysis on the oxon (or the sulfone), resulting in DAPs that are relatively water soluble and excreted through urine (43,59). Elimination of the OP metabolites varies in length due to OPs lipophilicity which may cause them to persist in fat storages for many days (102,103). Elimination is mostly through urine but can also be eliminated in lesser amounts from expired air and faeces (103).

OP half-life varies depending on the type of OP. A study with 5 human volunteers found chlorpyrifos had a half-life that is was about 15.5 hours for ingestional exposure, and about 30 hours for dermal exposure (109). In this study, about 93% of the oral dose and 1% of the dermal dose was recovered as urinary metabolites (53% of the dermal dose was recovered from the skin surface) (109). Another study with 5 human volunteers (1 had their dermal data omitted) found that propetamphos had a half-life of 1.7 hours for ingestional exposure, and 3.8 hours for dermal exposure (110). Only about 41% of the oral dose and 0.68% of the dermal dose was recovered as the urinary metabolite MEPT (110). It is worth noting that genetic variation greatly affects the

toxicokinetic of OPs as genetically determined variations of the target molecules and enzymes involved in the metabolic pathway can modify its response to OP (111).

OP parent compounds are usually measured in blood by measuring the activity of AChE in erythrocytes as biomarkers of exposure within blood samples (43,64). Additionally, butyrylcholinesterase and NTE can also be used as biomarkers of exposure within the blood plasma and blood lymphocytes, respectively (43). OP concentration levels in humans are usually measured using urinary biomarkers to estimate the dose in humans. Urine sample measuring DAP metabolites of OP is preferred over measuring OP concentrations in blood plasma as pesticide samples tend to be less stable in blood plasma than their urinary metabolite counterparts (112).

In summary, OP concentration levels in humans are generally measured through urinary DAP metabolites concentrations. As their half-life in humans is generally short, urinary DAP metabolite concentrations may better represent recent exposure rather than chronic exposure.

**2.2 Pyrethroids**

Pyrethroids are organic compounds that are structurally similar to natural pyrethrins which originate from the flowers *C. coccineum* and *Chrysanthemum cinerariaefolium*. They consist of one to three asymmetric carbons atoms and have at least 4 stereoisomers with their own biological effects (113). Most pyrethroids also have a cyclopropane carboxylic moiety linked to aromatic alcohols through an central ester or ether bond (113). Pyrethroids are one of the most commonly used groups of insecticides globally in both agricultural and urban settings, accounting for around 25% of the insecticide market (valued about 1.6 billion in 2016),

worldwide (17,114,115). They are among the most used class of synthetic organic insecticides for their high level of effectiveness and low mammalian toxicity (116).

Pyrethrins' use as an insect control agent has been employed since the Middle Ages, serving as one of the few insecticidal agents used before the invention of synthetic insecticides. Pyrethrin in its natural form was underwhelming as an insecticidal agent and was not given much interest until Stäudinger and Ružička chemically analyzed the compound and published reports about its structures. Their research spawned intrigue in the compound which resulted in allethrin, the first synthetic pyrethroid, to be invented in 1949 (117). Early pyrethroids were quickly superseded by superior synthetic pyrethroids created in the 1970s (117). Permethrin, deltamethrin, and cypermethrin were more resistant to environmental degradation which made them more suitable for agricultural use. These compounds were ideal substitutes for DDT and a safer option than the toxic organochlorine and OP pesticides (113). The aforementioned pyrethroids, and their successors (fenvalerate, beta-cyfluthrin, and lambda-cyhalothrin), are still globally employed as cheap and popular agricultural insecticides.

Pyrethroids' insecticidal activity is centered around the disruption of voltage-gated sodium channels (VGSC) functions (118). Neuronal VGSCs are critical in the control of electrical excitability, and its disruption of the initiation and propagation of action potentials gives it insecticidal properties (119). Studies have shown a large variety of adverse health effects associated with pyrethroid exposure. Perinatally, pyrethroid exposure has been shown to affect brain development resulting in abnormal brain maturation as well as improper mental and behaviour development in both rats and humans (120–126). Pyrethroids exposure have also been shown to have reproductive-potential toxicity by adversely affecting sperm parameters and reproductive organ morphology (127–134). Perhaps of most importance, pyrethroids may act as

endocrine disrupting compounds in mammals by blocking, synergizing, and mimicking endogenous hormones (17,18). They are estrogenic compounds that produce estrogen receptor (ER)-specific agonist responses (135). Other adverse health effects suggested through research are neurotoxicity (23,136,137), increased risk of cancer and heart disease (138–140), motor function impairment (141), behavioural problems (142), abnormal blood-brain barrier development (143), and the potential to be an allergen (144).

Routes of exposure and concentrations

Pyrethroids are most often used in agricultural insecticides, commercial insecticides, and household pest control products. They can also be used in personal care products including mosquito-repellant perfume and shampoo (145). Very few studies were found regarding pyrethroid concentrations across any media in Canada. A review conducted by Tang et al. (145) reported estimated pyrethroid concentrations in various environmental media across many other countries. They determined that cypermethrin, followed by permethrin, deltamethrin, fenvalerate, and bifenthrin, were the most used pyrethroids. The pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA) was found to be the main pyrethroid metabolite in human bodies. Pyrethroid residue concentrations have been significantly increasing over the past decades making its potential toxic effects of greater concern (145).

Pyrethroid concentrations in soil are higher in areas with developed agricultural sectors as compared to other regions, though concentrations between regions widely vary (145). Degradation rates also vary in soils depending on factors such as microbial activity of the soil, its phosphorus content, and its pH levels (145). For example, Rafique et al. (146) found farmland soil concentrations in Pakistan ranging from 0.07 ng/g to 1,184 ng/g whereas Mawussi et al.

(147) found farmland soil concentrations in Togo ranging from not-detectable (ND) to 3.73 ng/g. Concentrations within residential soil can also be high. Riederer et al. (148) found pyrethroid residue residential soil concentrations in Atlanta, United States to range from 1.97 ng/g to 724.19 ng/g.

Surface water tends to have the lowest level of pyrethroids residue amongst all environmental media. Pyrethroids accumulate on surface water primarily from downstream transportation from urban areas and agricultural areas through drainage channels and surface runoff (145). High concentrations can also be attributable to improper cleaning of spray equipment, improper disposal of spray waste, and spray drift during insecticide application (149). As such, concentrations greatly vary globally based on the type of surface water and nearby agricultural applications. For example, river water along the Ebro river in Spain had concentrations ranging from 0.73 ng/L to 58.78 ng/L (150) and municipal wastewater in Sacramento, California had concentrations ranging from 200 ng/L to 500 ng/L (151). Pyrethroid concentrations in sediment are on average higher than surface water concentrations, but they follow similar trends (145). In the river water along the Ebro river in Spain, pyrethroid concentration in sediment ranged from 8.27 ng/L to 71.90 ng/L (150) and in Sacramento, California, pyrethroid concentration in sediments ranged from ND to 1211.00 ng/L in runoff from residential neighborhoods (152).

Among all studies reviewed by Tang et al. (145) that measured pyrethroid residue concentrations on crops, at least two pyrethroids were detected in every vegetable sample. Crops and plants generally absorb the pesticides residue from the soils and there is a positive correlation between soils and crops pyrethroid concentration (153). Studies looking at crop concentrations in North America are sparse and only one study was found. In Sonora, Mexico,

pyrethroid residue concentrations on vegetables (onions, lettuce, tomato, peppers, and lettuce) were found to range from 4.00 ng/g to 573.00 ng/g (154).

Indoors, pyrethroids degradation rates are slower than outdoor environments (145). As such, indoor air concentrations are generally higher than concentrations in other medias and poses a great risk to human health as humans likely are in greater contact with them indoors. Levels of pyrethroids tend to be greater in dust samples than in air samples. For example, Leng et al. (155) found pyrethroid concentration in indoor air samples to range from 4.90 ng/$m^3$ to 45.70 ng/$m^3$ whereas pyrethroid concentration in indoor dust samples ranged from 1.00 μg/g to 70.00 μg/g. It has been suggested that this could be due to pyrethroids chemical structure that increases their tendency to adsorb onto household surfaces and their binding affinity towards dust particulates (145,156).

Pyrethroids can also be found amongst land and aquatic organisms and their secretions. Land animals are exposed to pyrethroids usually through residues in their feed whereas aquatic organisms are exposed to sediment and surface water pyrethroid concentrations (145,157). For aquatic organisms, pyrethroids can readily enters the gills and blood of fish directly due to its lipophilic properties (158). Bioaccumulation of the pyrethroids within these fish represents a hazard to humans and other organisms that consume seafood. A Canadian study that looked at fish and shellfish pyrethroid samples purchased from Halifax, Ottawa, and Vancouver had concentrations ranging from 0.30 ng/g to 6.50 ng/g (159). Land organisms pyrethroid levels in organs and tissues are challenging to measure making secretion measurement the better alternative. For example, in honey bee populations in the United States, pyrethroid concentration levels in their honey was on average 19.60 μg/g (160).

For humans, pyrethroid exposure is dependent on many factors, including diet, location, residential insecticide usages, age, and whether their geographic location is agricultural or non-agricultural areas (56,138). Pyrethroids have a very low vapour pressure resulting in high absorption to dust and textiles where they are residually effective for 3-6 months (156,161). Farmworkers are especially at risk due to adherence of pyrethroid residue to clothing. As pyrethroids are lipophilic, they can be absorbed dermally as well as orally (156). High pyrethroid exposure is also attributable to household pesticide usage, especially pyrethroid mosquito repellant (162). Through oral and dermal routes, bioavailability of pyrethroids would be low, but inhalation of dusts containing old pyrethroid powder deposits can be harmful (156). Another common exposure route for humans is through diet. If there are pyrethroid residues on any foods consumed, there is a high chance of oral exposure to pyrethroids. For example, a study measuring urinary 3-PBA conducted in Rome, Italy, found that people who consumed raw and cooked vegetables had high levels of the 3-PBA in their urine (163). They found that high intakes of raw vegetables, cooked vegetables, leafy vegetables, and cruciferous vegetables all contributed to higher urinary 3-PBA levels. Additionally in Canada, a study found that respondents had significantly higher urinary pyrethroid concentrations, as measured by the geometric mean, when they had a high consumption of vegetable, pulses and nuts, or starchy root (56).

The recommendations of the U.S. Environmental Protection Agency (EPA) vary for pyrethroids and acceptable limits on food are from 0.01 to 75 ppm depending on the pyrethroid (164). The World Health Organisation (WHO) recommends that the acceptable daily intake of pyrethroids to be between 0.002 to 0.07 mg/kg body weight per day depending on the pyrethroid molecule (165). Unfortunately, pyrethroids concentrations may not be monitored in drinking

water or food in Canada. For example, Quebec does not regularly test for pyrethroids at water purification plants (166).

In Canada, there are hundreds of pyrethroids formulations that are registered with Health Canada's Pest Management Regulatory Agency (PMRA) with the majority of them being registered for domestic use (Table 2.3). The most used active ingredients were pyrethrin, permethrin, d-phenothrin, tetramethrin, and allethrin. The specific metabolites for each of the pyrethroids is shown in Table 2.4. As with OPs, pyrethroid insecticides sales and use is regulated under the Pest Control Products Act in Canada by the Pest Management Regulatory Agency (PMRA) (57). The PMRA's role is to evaluate the pyrethroid's toxicity to determine whether the insecticide should be used for a specific use and to establish a maximum residue limit for of the pyrethroid in food for newly registered pyrethroids (58).

**Table 2.3 Pyrethroid formulations registered by Health Canada classified by active substances.*** (60)

| **Active substance** | **Domestic** | **Commercial** | **Restricted**** | **Total***** |
|---|---|---|---|---|
| Allethrin | 95 | 5 | 0 | 100 |
| Bifenthrin | 0 | 1 | 0 | 1 |
| Cyfluthrin | 4 | 5 | 0 | 9 |
| Cypermethrin | 0 | 5 | 0 | 5 |
| Deltamethrin | 0 | 13 | 0 | 13 |
| d-Phenothrin (Sumithrin) | 112 | 2 | 0 | 114 |
| Flumethrin | 0 | 1 | 0 | 1 |
| Fluvalinate | 0 | 2 | 0 | 2 |
| Lambda-cyhalothrin | 0 | 13 | 0 | 13 |
| Permethrin | 314 | 45 | 5 | 364 |
| Prallethrin | 12 | 0 | 0 | 12 |
| Pyrethrins | 334 | 107 | 0 | 441 |
| Tefluthrin | 0 | 5 | 0 | 5 |
| Tetramethrin | 104 | 1 | 0 | 105 |

* Information collected from Health Canada website on 05/24/2021.
** Restricted indicates only usable in specific circumstances by trained individuals.
*** Multiple pyrethroid active ingredients could be in a single formulation.

**Table 2.4 Parent pyrethroid pesticides registered for use in Canada between 2015-2016 and their associated measured urinary metabolites.** (59,167,168)

| | Pyrethroid metabolites | | | | |
|---|---|---|---|---|---|
| **Active substance** | ***cis*-DBCA** | ***cis*-DCCA** | **4-F-3-PBA** | **3-PBA** | ***trans*-DCCA** |
| Allethrin | - | - | - | Yes | - |
| Bifenthrin | - | - | - | - | - |
| Cyfluthrin | - | Yes | Yes | - | Yes |
| Cypermethrin | - | Yes | - | Yes | Yes |
| Deltamethrin | Yes | - | - | Yes | - |
| d-Phenothrin (Sumithrin) | - | - | - | Yes | - |
| Flumethrin | - | - | Yes | - | - |
| Fluvalinate | - | - | - | Yes | - |
| Lambda-cyhalothrin | - | - | - | Yes | - |
| Permethrin | - | Yes | - | Yes | Yes |
| Prallethrin | | - | - | Yes | - |
| Pyrethrins | - | - | - | Yes | - |
| Tefluthrin | - | Yes | Yes | - | Yes |
| Tetramethrin | - | - | - | - | - |

- Active substance does not metabolize into the pyrethroid metabolite

Pyrethroid metabolites concentrations have been also measured through the Canadian Health Measures Survey (CHMS), a nationally representative cross-sectional survey. Four of the 5 pyrethroid metabolites were detected in ≥60% of samples (27). The metabolites geometric means and selected percentiles of urine concentrations (μg/g creatinine) per age group for all CHMS cycles, where these measurements occurred, can be found in Appendix 1g-1k (59).

Mechanisms and role as an endocrine disruptor

Pyrethroids' main mechanism of action is through the disruption of VGSC. These compounds interfere with the nerve transmission influx in the axon of neuron by blocking open gates in the sodium channels (169). VGSCs are essential in the control of electrical excitability and the initiation and propagation of action potentials (119). By blocking VGSC gates, repetitive firing, elongated nerve impulses, and depolarization can occur which leads to a plethora of

symptoms (118). Pyrethroid are classified as either type I (permethrin) or type II (cyfluthrin) based on which of these biological responses occur (see Table 2.5).

**Table 2.5 Classification of pyrethroid based on biological response.** (170)

| **Response/action** | **Type I** | **Type II** |
|---|---|---|
| Electrophysiological response in nerve tissue | Rapid onset of symptoms even at sublethal levels.<br><br>Hyperactivity often leading to knockdown.<br><br>Low kill with high recovery.<br><br>Inversely related to changes in temperature. | Slow onset of symptoms<br><br>Convulsion followed by paralysis<br><br>High kill with low recovery<br><br>Little effect of temperature change. |
| Electrophysiological response in nerve tissue | Repetitive discharges in axons | Blockage of conduction at synapses |
| Action on sodium-channel function | Monophasic and rapid decay of tail currents<br><br>Bind preferentially to closed channels | Biphasic and very slow decay of tail currents.<br><br>Bind preferentially to open channels |
| Level of resistance due to resistant houseflies with super-kdr mechanism | Below 100-fold | Over 200-fold |
| Presence of an a-cyano group | Absent | Present |

Type I pyrethroids induce repetitive firings within the axon of sensory nerves and are sometimes accompanied by large bursts of action potentials in the ganglia (169,171). This response also has the potential to cause excess release of diuretic hormones due to stimulation of the neurosecretory system (170). Less than 1% of sodium channels need to be affected by pyrethroids to induce the repetitive firing response (172). Type II pyrethroids cause slow depolarization of the nerve membranes which inhibits nerve conduction. As such, the

concentration needed to kill insects is lower for type II pyrethroids as compared to type I pyrethroids (170).

Type II pyrethroids have been suggested to block $GABA_A$ receptors, but more recent studies found type II pyrethroid toxicological significance on inhibiting $GABA_A$ receptors as questionable (173,174). Chloride channels potentially have a lower opening probability when exposed to pyrethroids (175). Pyrethroids also have the potential to exert non-specific inhibitory effects on nicotinic acetylcholine receptors in neuroblastoma cells (176).

A proposed mechanism between the pyrethroid exposure and BMI involves the hypothalamus' and hippocampus' effects on appetite control. In animal studies, it has been established that pyrethroid molecules tend to highly concentrate in nerve tissue, especially sciatic nerves, the hypothalamus, and the hippocampus (26). One of the roles of the hippocampus involves energy regulation, where high caloric food images elicits neural activation in the hippocampus that increases plasma insulin levels leading to higher BMI (22). Hossain et al. confirmed pyrethroids' ability to affect the hippocampus in producing abnormal signaling through the release of acetylcholine (23).

Within the hypothalamus exists the hypothalamic arcuate nucleus which acts as a major site of leptin resistance and signaling (177). Leptin is an important hormone involved in the negative feedback loop that maintains body fat stores within a normal range (24). Rodriguez et al. demonstrated that cyfluthrin concentrations in mice hypothalamus was the highest among brain and plasma tissues with a high maximal plasma concentration and a large area under the concentration-time curve ($AUC_{(0\text{-}24h)}$) of $1.21 \pm 0.11$ μg/g and $19.36 \pm 2.56$ mg h/L (mean±standard deviation), respectively (26). The cyfluthrin also had a half-life in the hypothalamus of $22.73 \pm 1.60$ h (26). No studies were found where pyrethroids had

hypothalamus-specific estrogenic effects in mammals; however, a study looking at these effects in zebrafish embryos demonstrated a significant disruption of the hypothalamus-pituitary-thyroid axis (21). This resulted in abnormal thyroid hormone levels, which are hormones that play an important role in energy regulation (21). These findings suggest that pyrethroids exposure can result in higher BMI through abnormal energy regulation (a lower metabolism results in less calories burned) and by producing more leptin that results in greater body fat.

Pyrethroids have been suggested to have endocrine disrupting abilities that affect several systems. From a reproductive standpoint, pyrethroids have displayed many signs of reproductive toxicity. Jin et al. found that 100mg/kg permethrin exposure can enantioselectively induce reproductive toxicity in mice by lowering the weight of the testes, serum T concentration, and mRNA levels of HMG CoA synthase (127). Several studies found that human and rat sperm motility was lowered and other sperm parameters were abnormal after pyrethroid exposure (128,129,132–134). Additional, 8-weeks old male mice who were orally given 0, 35, or 70 mg/kg·d for 6 weeks had significantly lower testosterone levels and cytochrome p450 side-chain cleavage enzyme, an essential enzyme for testosterone biosynthesis, and mRNA expression was significant suppressed (131).

Eil et al. found that pyrethroids bind competitively to human genital skin fibroblast androgen receptors as well as sex hormone binding globulin in human plasma (25). All the pyrethroids tested, pyrethrins, bioallethrin, fenvalerate, phenothrin, permethrin, and resmethrin, demonstrated inhibition of the fibroblast binding through competitive binding (25). Additionally, only bioallethrin and pyrethrins were able to displace testosterone for the sex hormone binding globulins in human plasma (25). Adding to this evidence, Garey and Wolff demonstrated the estrogenicity of both fenvalerate and sumithrin using the Ishikawa Var-I human endometrial

cancer cell line, a cell line rich in estrogen receptors (178). Both these pyrethroids elicited the release of alkaline phosphatase (AlkP) in this cell line, which indicated that estrogenic activities as in this specific cancer cell line, AlkP was released in a specific dose-dependent manner to estrogenic activity (178). Conversely, the two other pyrethroids that were tested, d-allethrin and permethrin failed to elicit a significant amount of AlkP and all of the tested pyrethroids failed to show any antiprogestagenic activities (178). As these pyrethroids demonstrate significant estrogenic effects through competitive binding, it is possible that chronic exposure to these compounds may results in abnormal endocrine effects relating to androgen actions. Androgens play an important role in regulation of adipose tissue where they can alter adipose tissue mass in a dose-specific manner (179).

There have been several studies that have explored the relationship between pyrethroid metabolite concentrations and BMI. A Korean study investigated the relationship between the pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA) and obesity using data from a nationally representative survey (116). The investigators found that participants with higher levels of urinary 3-PBA were more likely to be obese or overweight (116). They also observed an inverse U-shape correlation whereby a positive correlation was observed between 3-PBA and BMI to a certain concentration threshold, but after that threshold, there was a negative association (116).

Pyrethroids have been possibly linked to diabetes in several studies. In animal experiments, several studies examined the associations between pyrethroids and glucose levels. A study that exposed rats with 4 mg/kg of cismethrin found that the rats exposed to cismethrin had a higher rate of glucose utilization within the brain (180). These results did not carry to other parts of the body as blood glucose levels were not significantly different between exposed and

non-exposed rats (180). A subsequent study that exposed rats to deltamethrin had similar results where the only significant changes to glucose metabolism were localized to the brain (181).

A cross-sectional study in Bolivia looked at blood glucose levels in male pesticide sprayers and non-exposed individuals during the months before the intensive pesticide spraying season (182). The authors found pyrethroid exposure caused abnormal glucose regulation where those who had elevated HbA1c levels, a sign of prediabetes, also were those who were most exposed to pyrethroids (182). Another study in China sought to evaluate the changes in abnormal glucose regulation of Chinese agricultural workers who were occupationally exposed to the inhalation of pyrethroids (183). They found that there was a significant increase in the prevalence of abnormal glucose regulation among those who were more exposed to pyrethroids (183). All these four studies, however, do not provide strong evidence for an association between pyrethroid exposure and the risk of diabetes.

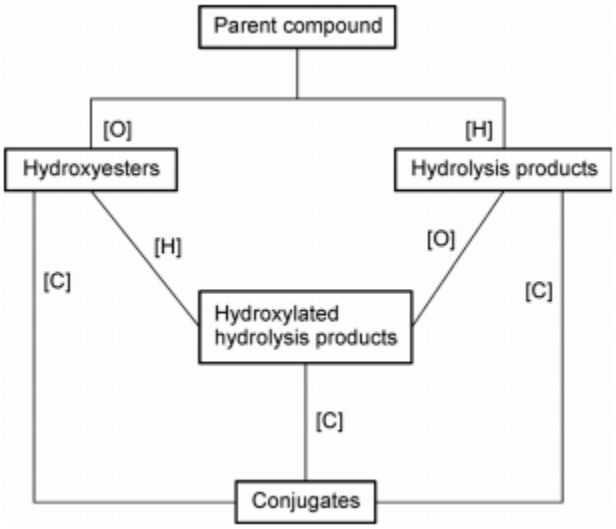
In summary, research regarding pyrethroids' effects on human obesity and diabetes is sparse. A possible biological mechanism for obesity involves abnormal energy regulation caused by their estrogenic effects. This effect can indirectly contribute to diabetes through abnormal glucose regulation.

Metabolism and Toxicokinetics

The metabolic pathway for pyrethroids consists of hydrolysis, conjugation, and oxidative reactions (see Figure 2.2). Initially, the parent compound will be bio-transformed by the actions of a carboxylesterase at the central ester or ether bond, or by the actions of cytochrome P450-dependent monooxygenases (CYPM) at the acid or alcohol moieties (9,184). These actions are dependent on the structure of the pyrethroid and will produce either hydroxyester metabolites or

hydrolysis products. With the ester cleave, the cleaved primary alcohol moieties will undergo additional oxidation to become a carboxylic acid (type II pyrethroids will lose the cyanide and form an aldehyde instead) (169). The products from this ester cleavage can then undergo hydroxylation followed by hydrolyzation to produce hydroxylated hydrolysis products. The initial hydrolysis products can also undergo oxidation and then hydrolyzed to produce hydroxylated hydrolysis products. Through the entire process, conjugation with other substances, including amino acids, sulfates, and sugars, can occur (185).

**Figure 2.2 Generalized pathway of pyrethroid metabolism.** (114)




The metabolic profile differs between all pyrethroids but some of them can be representative for others. For example, *cis*-permethrin has a similar profile to esfenvalerate, cyhalothrin, and cyfluthrin whereas deltamethrin is similar to *trans*-permethrin and cyphenothrin (186). Conversely, some pyrethroids, like bifenthrin, have a unique metabolic profile that is distinct from the others. Metabolically, cis-permethrin is metabolized mainly by carboxylesterase enzymes, bifenthrin is metabolized mainly by CYPMs, and deltamethrin is metabolized by both carboxylesterase enzymes and CYPMs (186).

Pyrethroids are generally excreted quickly, depending on the route of entry. Consequently, hepatic metabolism is usually only limited by the liver blood flow, and hepatic clearance is quicker at a younger age as blood flow and liver weight are both higher per body weight at early ages (186). The main entry routes for pyrethroids into the human body are through ingestion, dermal contact, and the respiration of particles (169). Following absorption, these lipophilic compounds rapidly distribute throughout the body to the liver, kidneys, nervous system, and fatty tissues (165). After being metabolized into hydrophilic products, they are quickly excreted through the urinary system (165,169). This whole process happens relatively quickly with the metabolites having a half-life between 2 hours to a few days (187). With rapid metabolism and excretion, pyrethroids and its metabolites do not bioaccumulate, but continuous exposure may cause a pseudo-steady state concentration that leads to chronic toxicity (165,188). For example, a study looking at flight attendants both pre- and post-flight on planes that performed disinsection of pyrethroids found that these attendants had elevated pre-flight pyrethroids levels, which suggests elevated body burden from long-term exposure abord the disinsected plane (189).

There is large variability in the amount of excretion and absorbance of pyrethroids metabolites in the human body, which could be explained by the vast differences in enzyme abundance in humans (186). A study conducted by Kaneko et al found that at least 96% of orally ingested pyrethroids and 3-17% of dermally absorbed pyrethroids were excreted after 6 days in rats (190). Additionally, 78-85% of the dermally applied doses were not absorbed through the skin (190). Another study using cyfluthrin found that 93% of cyfluthrin metabolites were excreted within 24 hours and that the mean half-lives were 6-9 hours (191). When looking at the variability between subjects with the same exposure, Wielgomas found that there was high

variability among subjects (interclass correlation coefficient = 0.551 – 0.681) when measuring urinary 3-PBA volume-expressed urine concentrations (ng/mL) (112).

Pyrethroids and its metabolites concentrations are usually quantified in urine samples. Urine sampling techniques generate good detection limits which can be as low as 0.08 μg/L in urine (189). In general, the determination of urinary pyrethroid metabolites, such as 3-PBA and *cis*-DCCA, is an appropriate measure for the biological monitoring of pyrethroid exposure (192). Urine samples are generally superior to blood plasma samples in determination of pyrethroid concentration in humans as pyrethroids are less stable in plasma (usually lasts less than a day) as compared to urine samples (can remain stable for 30+ days) (192).

In summary, pyrethroid concentration levels in humans are generally measured through urinary pyrethroid metabolites concentrations. Like OPs, pyrethroids' half-life in humans is generally short meaning that urinary pyrethroid metabolite concentrations may better represent recent exposure rather than chronic exposure.

## 3. Research Objectives and Rationale

Research Objectives

The purpose of this thesis is to determine the relationships between insecticide metabolite concentrations in urine and obesity and diabetes outcomes within the Canadian population. The exposures of interest include the urine metabolite levels (μg/L) of 6 organophosphates metabolites (DMP, DMTP, DMDTP, DEP, DETP, and DEDTP) and 5 pyrethroids metabolites (*cis*-DBCA, *cis*-DCCA, 4-F-3-PBA, 3-PBA, and *trans*-DCCA). The health outcomes of interest include obesity measures (waist circumference (WC) and body mass index (BMI)) and diabetes-related outcomes (glycated hemoglobin HbA1c and self-reported diabetes). Potentially important

covariates include sex, age, race, physical activity, sedentary behaviour, education level, and smoking status.

Rationale

In previous studies, the levels of organophosphate and pyrethroid metabolites in urine in the Canadian population have been measured (27). However, there have been very few studies examining the relationships between human insecticide levels and health-related outcomes such as obesity and diabetes status. The CHMS provides a unique opportunity to examine the association between insecticides and obesity using data from a nationally representative Canadian sample as the survey collects data of both anthropometrical measures and chemical panels of their participants (193). This also allows us to address the need to examine this relationship between insecticide exposure and diabetes, as well as grant us a more robust understanding of how insecticide exposure impacts health.

Research Questions

The study will address two principal research questions:

1. Are those who have elevated urinary insecticide metabolite concentrations at an increased risk of being obese, as defined as having a BMI of $\geq$30 kg/m$^2$?
2. Is there an association between urinary insecticide metabolite concentrations and diabetes?

Hypothesis

The hypotheses of the thesis are:

1. Exposure to organophosphates and pyrethroids, measured by urine metabolite levels, are positively associated with obesity measured by BMI and waist circumference.
2. Exposure to organophosphates and pyrethroids are positively associated with having an increased risk of diabetes (as defined by self-reported diabetes or high HbA1c levels).

Study objectives

The objectives of the thesis are:

1. To determine the levels of each organophosphate and pyrethroid metabolite in urine in the Canadian population;
2. To examine the associations of urinary insecticide metabolite concentrations with the obesity measures; and
3. To examine the associations of urinary insecticide metabolite concentrations with HbA1c levels and self-reported diabetes.

# 4. Methods

## 4.1 Study design

This study used data from the CHMS, a nationally representative survey of Canadian aged 3 to 79 years of age, which was designed to comprehensively collect information on health and habits through an in-person interview in the respondent's home and an in-person visit to one of the mobile examination centers. The CHMS is a repeated cross-sectional survey conducted by Statistics Canada with the help of Health Canada and the Public Health Agency of Canada. It is a complex survey with the features of stratification, unequal selection probability, and cluster sampling. The purpose of this survey is to create a methodologically robust dataset containing

national baseline data pertaining to the extent of major health concerns of many aspects of health, undiagnosed disease and illness burden among Canadians, and to explore relationships between health status and a plethora of risk factors (193). The target population covers Canadians aged 3 to 79 years of age living in the ten provinces. Excluded from this target population are full-time members of the Canadian forces, institutionalized persons, residents of extremely remote regions, persons living on reserves or other Aboriginal settlements, and persons living in the three Canadian territories, which overall represents about 3% of the population.

The CHMS follows a 2-step data collection process. The first step consists of a personal interview at the household of the respondent. Respondents are contacted by mail at the randomly sampled address and an interviewer visits the dwelling to conduct the interview. Through sampling, one or two members within the dwelling are randomly selected to conduct separate health interviews of about 45-60 minutes. Afterwards, an appointment time is scheduled for the second step of the data collection process. The second step is the visit to the CHMS mobile examination centre (MEC), where physical measures of the respondent are collected. The MEC appointment lasts about 2 hours for each respondent depending on suitability for each measure. For respondents under the age of 14 years old, a parent or legal guardian must be present and provide written consent for the child to participate. After the appointment, respondents are provided an activity monitor to measure physical activity patterns for a week and are given the materials to provide a second urine sample for nutritional analysis. The complete household and clinic questionnaires can be found on the Statistics Canada website (194).

The CHMS uses a stratified three-stage sample comprised off a geographical stage, a household stage, and a person stage. The collection site is the sampling unit of the geographical

stage. Collection sites are geographic units that are limited to a radius of about 50km in urban areas and 75km for rural areas and is stratified into 5 Canadian regions [Ontario, Quebec, British Columbia, the Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick), and the Prairies (Alberta, Manitoba, and Saskatchewan)]. The household stage is where dwellings are stratified into 7 hierarchical groups sorted by the household inhabitant demographics to ensure an equal number of respondents from each age stratum would be obtained. The hierarchical groups are defined as:

1) dwellings with 3 to 5 year-olds, else
2) dwellings with 6 to 11 year-olds, else
3) dwellings with 12 to 19 year-olds, else
4) dwellings with 60 to 79 year-olds, else
5) dwellings with 20 to 39 year-olds, else
6) dwellings with 40 to 59 year-olds, else
7) other dwellings without household composition or with all ages outside the ones above (these could include vacant dwellings and dwellings with missing dates of births of the inhabitants)

Dwellings that are not included in the above-mentioned strata are dwelling with missing age stratum information, vacant dwellings at the time of sampling, and dwelling with people who are outside of the CHMS targeted age groups at the time of sampling. Lastly, the person stage is comprised of the residents in the dwelling at the time of the interview stratified into two age groups (3-11 years old and 12-79 years old). If the dwelling has children aged 3-11, two

inhabitants are selected. If no 3 to 11 year olds are living in the dwelling, only one person aged 12-79 is selected (193).

This thesis used data from the 5th Cycle of the CHMS (2015-2016) only. Multiple cycles were not used as this was the first cycle to comprehensively measure urinary metabolites since the 2nd Cycle and there were methodological differences in terms of data collection between the two cycles (195,196). The study population for Cycle 5 was also deemed to be sufficient in size to answer the research questions.

The CHMS has several subsamples in addition to its full sample. The full sample, at the geographical stage, required 16 collection sites allocated to the 5 regions. There were 6 collection sites in Ontario, 4 collection sites in Quebec, and 2 collection sites in each of the remaining regions (Atlantic, British Columbia, and the Prairies). In Cycle 5 of the CHMS, an attempt was made to include a collection site that was located in a census metropolitan area (an area consisting of one or more adjacent municipalities centering on a large urban area) for each region. The urban core of this census metropolitan area had to have a population of at least 100,000 to be considered. As such, the selection process for each region's collection sites (not including the Atlantic region) were changed to target these metropolitan areas. For the household and person stage, the sample size determination and allocation were done together. As the target sample size for Cycle 5 was 5,700 respondents who at least completed the clinical component of the survey, at least 356 respondents were required at each collection site. Within each collection site, the number of dwellings to sample was determined based off many factors, including previous response rates to the CHMS, expected probabilities for many outcomes, and simulations. For the subsamples, sampled dwellings were randomly flagged to instruct the respondent to follow specific instructions to fit the subsample requirements. In regard to the

environment contaminants in urine subsample, the targeted subsample size was 2,500 randomly selected respondents between the ages 3-79 years old. The age-specific targets were 250 for respondents between 3-5 years old, 250 for respondents between 6-11 years old by sex, 250 for respondents between 11-19 years old by sex, and 500 for respondents between 20-79 years old by sex. More details describing the data collection, design, methodology as well as ethical issues of the CHMS can be found on the Statistic Canada website (193).

This survey was unique as it collected data of direct physical measurements including urinary metabolites levels and anthropologic measures. For the 5$^{th}$ Cycle of the CHMS (2015-2016), the survey aimed to achieve an unbiased national estimate with a coefficient of variation of about 16.5% or less across 5 age groups by sex (6-11, 12-19, 20-39, 40-59, and 60-79) and for both sexes of children aged 3-5 years old (193). A total of 8,539 residences were selected to be a part of the survey and 6,361 agreed to participate bringing the household response rate to 74.5%. From these households, 89.8% of selected residents responded to the questionnaire and 72.8% went to the mobile examination center for physical measurements. The overall weighted combined response rate for this cycle was 48.5% at the national level and it was 47.5% for the urine environmental contaminant subsample (193).

**4.2 Data collection**

The methodology describing the procedures used to obtain the measures of interest are detailed in the CHMS Data User Guides, the derived variables documentations, and the data dictionaries that can be provided upon request on the Statistics Canada Website (193,195,197,198). Data collection for the 5$^{th}$ Cycle of the CHMS occurred between January 2016 and December 2017. A brief summary of each measure or covariate is summarized below. In brief, self-reported diabetes status was acquired through the household questionnaire. The

obesity measures were anthropologic measurements taken by a trained research at a mobile examination center. Urine and blood samples were taken at the mobile examination centers (MEC) for environmental contaminant use. A second urine sample had to be provided a week after the visit but only for nutritional analysis purposes.

Computer assisted interviewing was used to record the responses for both the household and MEC components of the CHMS. To reduce data entry error, a data capture system was developed which allowed both one- and two-way communication between the data application and the measurement devices. All recorded data were stored on the MEC's own computer server, where the encrypted data were transmitted via a dedicated out-going phone line to Statistics Canada headquarters.

To minimize non-response, many practices were employed. The first method was to ensure the introductory material that was sent to selected household and to emphasize the importance of the survey by showing examples of how the data would be used. Secondly, interviewers made all reasonable attempts to initiate contact with the chosen households in order to obtain interviews. The interviewers would schedule interviews when the timing of their visits was inconvenient, leave notices at the door if no one were home upon visit, visit the household at different times of the different days until the respondents were home, and phone the household to try and arrange a personal visit.

Thirdly, interviewers emphasized the importance of the survey and tried to convince respondents of the potential benefits of participating in the survey. If they continue to refuse, a letter was sent, and they were contacted by another interviewer who again stressed the importance of the survey. Fourthly, an effort was made to ensure that all material was available in both French and English to circumvent any language barrier. Additionally, the CHMS team

recruited interviews who were competent in a non-official language. When another language was needed to conduct interviews, the specialized interviewer would be contacted to conduct the interview. If there were no available interviews who specialized in the needed language, another member of the household could translate if possible.

Fifthly, for youth and children's respondents, a section of the Consent Booklet was dedicated to parents and guardians and the interviewers ensured that the parents were home for the interview of their child (but not close enough to be in hearing range). These steps were done to ensure parents' worries for their child confidentiality/privacy were mitigated. Lastly, proxy interviews were conducted when the respondent were incapable of soundly completing the interview. In these interviews, another knowledgeable member of the household would answer the questions on the respondent's behalf. This was generally done for children aged under 12 years and for respondents with physical or mental limitations which made them incapable of doing the interview by themselves. In this cycle of the CHMS, 9.3% of interviews were proxy, of which 97.2% were of respondents under the age of 12. Many of these techniques were also employed for the MEC visits, to ensure minimal non-response.

### 4.2.1 Household Questionnaire

The household questionnaire was developed through constructive input from stakeholders and external experts. Selected dwellings were mailed introductory material a week or two prior to their interview to inform them of participation, privacy, consent, and which members of the dwelling would be interviewed. The interviewer then called or visited the dwelling to book an appointment for the meeting, inform them about the survey, and show them an introductory video. Respondents under the age of 11 were required to have an adult/guardian to be present for the interview. Following the interview, the respondents were given an information package

detailing the next steps of the survey, mainly the MEC details. Also following the interview, the interviewer helped the respondents book an appointment at the MEC. At the end of the day, interviewers sent the data from all the completed interviews of that day to Statistics Canada using encrypted software to ensure respondent confidentiality.

Self-Reported Diabetes

Self-reported diabetes was assessed by asking the question "Do you have diabetes?". Before asking the question, the interviewer would emphasize "Remember, we're interested in conditions diagnosed by a health professional".

Race

In Cycle 5 of the CHMS, respondents were asked to select from a list of races whether they belonged to one or more of them. If the respondent responded yes to more than one race, they were classified as multiple racial or cultural origins. If the respondent indicated that they self-identify as Aboriginal in a previous question or if they did not choose any options, they were excluded from the analysis. The list of cultural and racial groups was the following:

- White
- Black
- Korean
- Filipino
- Japanese
- Chinese
- Southeast Asian
- Arab
- West Asian
- Latin America
- Other racial or cultural origin
- Multiple racial or cultural origins

Physical Activity for Adults

Physical activity was measured as the total minutes of physical activity from all domains during the last week for all adult respondents aged 18 to 79 years old. It was calculated by adding together the answers for the following three derived variables.

1) PAADTRVL represents the estimated total time spent (in minutes) using active ways to get to places, during the last 7 days. It is estimated by added together the two household questions associated with the variables PAA_015*60 and PAA_020N. PAA_015 assesses the time spent on active ways to get to places last week (measured in hours so the results of the respondents answer is multiplied by 60 for PAADTRVL) by asking the question, "How much time in total, in the last seven days, did you spend doing these activities? Please only include activities that lasted a minimum of 10 continuous minutes.". PAA_020N assesses the time spent on active ways to get to places last week in minutes by asking the respondents to enter the number of minutes as a follow up to PAA_015. If the respondent did not respond or had a valid skip to PAA_015, PAA_020N, or PAA_005 (this variable asks whether the respondent had used an active way to get to a place during the last week), they would be excluded.

2) PAADREC is defined as the variable which indicates the total time spent (in minutes) participating in recreational physical activity, such as sports, fitness, organized or non-organized, that lasted a minimum of 10 continuous minutes and made them sweat a little and breathe harder, during the last 7 days. It is estimated by added together the two household questions associated with the variables PAA_045*60 and PAA_050N. PAA_045 assesses the time spent on recreational physical activities in the last week (measured in hours so the results of the respondents answer is multiplied by 60 for PAADREC) by asking the question, "(In the last seven days), how much time in total did you spend doing these activities that made you sweat at least a little and breathe harder?". PAA_050N assesses the time spent on recreational physical

activities last week in minutes by asking the respondents to enter the number of minutes as a follow up to PAA_045. If the respondent did not respond or had a valid skip to PAA_045, PAA_050N, they would be excluded. Respondents would also be excluded if they did not respond or had a valid skip to PAA_030 and PAA_035, which were variables that simply asked whether the respondent participated in any recreational physical activities in the last week and if any of these activities made them sweat or breathe harder.

3) PAADOTH is defined as the variable which indicates the total time spent (in minutes) participating in other physical activities while at work, in or around home, or while volunteering, that lasted a minimum of 10 continuous minutes and made them sweat a little and breathe harder, during the last 7 days. It is estimated by added together the two household questions associated with the variables PAA_075*60 and PAA_080N. PAA_075 assesses the time spent on other physical activities in the last week (measured in hours so the results of the respondents answer is multiplied by 60 for PAADREC) by asking the question, (In the last seven days), how much time in total did you spend doing these activities that made you sweat at least a little and breathe harder?". PAA_080N assesses the time spent on other physical activities last week in minutes by asking the respondents to enter the number of minutes as a follow up to PAA_075. If the respondent did not respond or had a valid skip to PAA_075, PAA_080N, they would be excluded. Respondents would also be excluded if they did not respond or had a valid skip to PAA_060 and PAA_065, which were variables that simply asked whether the respondent participated in any other physical activities in the last week and if any of these activities made them sweat or breathe harder.

If any of PAADTRVL, PAADREC, or PAADOTH was missing due to valid skips or no response, the total minutes of physical activity from all domains during the last week were not calculated. The respondents with missing physical activity were not included in the analysis.

Sedentary Behaviour

In the CHMS, the total time spent in sedentary behaviour is defined as the estimated total number of hours per day spent participating in sedentary activities such as playing video games, watching television, texting, browsing social media, among others. For adults, respondents aged 12 years and older, sedentary activities at work or at school were excluded. This variable is calculated by adding the scores of 4 variables (SAC_005, SAC_010, SAC_020, and SAC_025) that were assessed in the household questions. If any of these variables were not answered, the total sedentary behaviour could not be calculated. Each of these variables were assessed by the following questions:

"In the last seven days, how much of your free time did you spend: reading books, magazines, or newspapers, including in electronic formats? Include time spent reading as part of your homework, but do not include time spent reading at work, during class time, while travelling in a vehicle or while exercising."

"In the last seven days, how much of your free time did you spend: watching TV, DVDs, movies or Internet videos? Do not include time spent watching while exercising."

"In the last seven days, how much of your free time did you spend: playing other video or computer games? Include games played on a game console, computer or hand-held electronic device such as a tablet or smart phone."

"In the last seven days, how much of your free time did you spend: In the last seven days, how much of your free time did you spend on a computer, tablet or smart phone, doing activities such as using the Internet, emailing, using Facebook® or doing homework? Do not include time spent at work, during class time or while travelling in a vehicle."

Highest Level of Education

Highest level of education (derived variable EDUDR04) was based on the answers of the variables EDC_01, EDC_02, EDC_03, and EDC_04. These variables were answered in consecutive order depending on the answers given. EDC_01 asked what the highest grade of elementary or high school the respondent has completed. The options were 'grade 8 or lower' (code 1), 'grade 9-10' (code 2), 'grade 11-13' (code 3), or 'don't know' (code 7). If the respondent answered with code 3, they became eligible for EDC_02 which asked if the respondent completed a high school diploma or its equivalent. The options for this variable were 'yes' (code 1), 'no' (code 2), or 'don't know' (code 7). If the respondent answered with code 1, they became eligible for EDC_03 which asked if the respondent had received education that could be counted toward a degree, certificate, or diploma from an educational institution. The options for this variable were 'yes' (code 1), 'no' (code 2), or 'don't know' (code 7). If the respondent answered with code 3, they became eligible for EDC_04 which asked the respondent what their highest degree, certificate, or diploma they had completed. The options for this variable were 'less than high school diploma or its equivalent' (code 1), 'high school diploma or a high school equivalency certificate' (code 2), 'trade certificate or diploma' (code 3), 'college/CEGEP/other non-university certificate or diploma' (code 4), 'university certificate or diploma below the bachelor's level' (code 5), 'bachelor's degree (e.g., B.A., B.Sc., LL.B.)' (code

6); ‘university certificate, diploma, degree above the BA level’ (code 7) or ‘don’t know’ (code 97).

The EDUDR04 variable used the answers from these questions to determine the highest level of education acquired by the respondent. If the respondent answered that they had an education less than grade 10, not achieved a high school diploma or its equivalent, no education that could be counted toward a degree, certificate, or diploma from an educational institution, or achieving less than a high school diploma or its equivalent, they were categorized as having achieved 1) less than secondary school graduation, 2) secondary school graduation, or 3) a post-secondary degree/diploma. If the respondent did not answer any of the questions, they were indicated as having a missing value.

Smoking

In the CHMS, smoking status looked at the type of smoker a respondent was, based on their smoking habits. This variable was only calculated for respondents who were 12 years or older. The variable that determines smoking status (SMKDSTY) is a derived variable based on 5 variables SMK_11, SMK_12, SMK_21A. SMK_23, and SMK_51. SMK_11 asked the respondent if their smoked 100 or more cigarettes in their lifetime. SMK_12 asked the respondent if they are currently smoking cigarettes daily, occasionally, or not at all. SMK_21A asks the respondent if they had smoked at least one cigarette a month. SMK_23 asked the respondent for the number of days in a typical month where they had smoked at least one cigarette. SMK_51 asked the respondent if they had ever smoked cigarettes on a daily basis.

For SMKDSTY, if the respondent answered that he/she was currently smoking cigarettes daily for SMK_12, they were given a code of 1 indicating that he/she was a current daily smoker.

If the respondent answered that he/she was currently occasionally smoking, and either had smoked 31 days in a typical month or had smoked on a daily basis, he/she was given a code of 2 indicating that he/she was an occasional smoker who was a former daily smoker. If the respondent answered that he/she was currently occasionally smoking, and either had not smoked a cigarette once in a typical month or had ever smoked on a daily basis, he/she was given a code of 3 indicating that he/she was an occasional smoker who had never been a daily smoker. If the respondent answered that he/she was not currently smoking, and either had smoked 31 days in a typical month or had smoked on a daily basis, he/she was given a code of 4 indicating that he/she was a non-smoker who was a former daily smoker. If the respondent answered that he/she was not currently smoking, had never smoked on a daily basis, and either had smoked 100 or more cigarettes in their lifetime or had smoked at least one cigarette in a typical month, he/she was given a code of 5 indicating that he/she was a non-smoker who was a former occasional smoker. Lastly, if the respondents answered that he/she was not currently smoking and had not smoked 100 or more cigarettes in their lifetime, he/she was given a code of 6 indicating that he/she had never smoked (at least 100 cigarettes). If the respondent did not answer a question, their smoking status was considered as missing.

### 4.2.2 Mobile Examination Center (MEC)

When respondents arrived at the MEC, MEC staff verified their information using data collected from the household interviews and ensured that pre-testing guidelines were adhered to. Before data collection began, the respondents had to give consent. Before physical measurements were collected, the respondents were asked screening questions. Participants were excluded based upon factors such as age, fasting status, and their answers to the screening questions. Exclusion criteria can be found in Appendix 2.

Respondents provided biospecimens and performed all measures for laboratory tests if eligible. The participants had the right at any time to refuse to participate in a test or measure at any time. Blood and urine samples were processed, analyzed for complete blood counts, and stored in fridges and freezers before being shipped to a reference laboratory for additional analysis. Before leaving the MEC, respondents were given a report containing all processed measurements that were immediately available. In the following months, respondents received a full report of all their measures.

If respondents were either unable or unwilling to visit the MEC, but were willing to have their physical measures taken, they were visited by CHMS staff members for a home visit. During these visits, CHMS staff members did most of the measures that would have been taken at the MEC with minor differences in equipment used. Senior health measures specialist had to verify the data entry to ensure that the data was valid and unbiased.

Standing Height

Standing height measures the maximum vertical size of respondents who were able to stand unassisted. For individuals who were not eligible or refused to have their height measured, had their data from their self-reported height captured. A fixed stadiometer with a vertical backboard and a moveable headboard was used to measured standing height in inches as outlined in the 3rd edition of the Canadian Society for Exercise Physiology-Canadian Physical Training for Health (CSEP-PATH) (199). The measurement was rounded to one decimal place.

Weight

Respondents had their weight measured to the closest 0.1 kg at MECs using a Mettler Toledo digital scale, following the CSEP-PATH 3rd edition protocol (199).

Body Mass Index (BMI)

As BMI is bodyweight relative to the standing height of the respondents, this derived variable was simply calculated by dividing weight in kilograms by height in meters squared. (BMI = Weight (kg) / (Height (m))$^2$). The resulting number was rounded to two decimal places. The excluded population was pregnant women, females who did not answer the pregnancy questions, and respondents who did not obtain a valid measured standing height or weight.

Waist Circumference

Waist circumference (WC) is measured as an indication of abdominal fat distribution and is useful as an indicator of the health risk associated with obesity. The measurements were done in inches and rounded to one decimal place. The waist measurement followed the National Institute of Health (NIH) protocol that an examiner stands to the right of the subject and palpates the upper hip bone to locate the right iliac crest (200). The measuring tape is placed just above the lateral border of this crest and wrapped around the body on this horizontal plane parallel to the floor. The tape is snug around the body but does not compress the skin and the measurement is made at normal minimal respiration (200).

Urine Collection

Urine was collected from consenting respondents using the first catch urine technique, where respondents began by urinating into the specimen container until it was full then continued voiding into the toilet afterwards. The urine samples were stored in the MEC's freezer as quickly as possible to ensure the quality of the sample's viability. This whole process on average took 2 hours from the time of collection with 4 hours being the maximum allowable time for the process. The urine sample was then sent directly to Health Canada's reference laboratory in

Ottawa (for sodium, iodine, and potassium analysis). From there two aliquots were made and shipped for creatinine analysis at the Centre de Toxicologie du Québec and for storage at the National Microbiology Laboratory. Before urine was aliquoted, the specific gravity was measured with two consecutive readings from the same drop of urine. The readings had to be the same or within 0.001 of each other or the measurement was repeated.

Once a week, stored urine aliquots are shipped to reference laboratories on preassigned days. There were 9 reference laboratories, notably the reference laboratory at the Centre de Toxicologie du Québec which evaluated the urine aliquots for environmental biomarkers as well as urine creatinine. All urine specimens were tracked and had their temperatures taken every 30 minutes by preprogramed devices to ensure the urine specimen's integrity during shipping. If there were any faults in the shipping process, the sample's data is removed to ensure the CHMS continues having the highest quality of data.

When the urine was processed and analyzed, the laboratories defined the analytical range of the sample using the U.S. EPA's methodology that low range serves as the limit of detection (LOD), the smallest quantity that is detectable and that is statistically different from zero, and the high range that serves as the limit of quantification (LOQ), the highest standard concentration where the precision of the quantification is no longer measurable. When an analyte has a concentration below the LOD, the concentration is given half the value of the LOD to be put in the CHMS data tables. For analytes that had concentrations above the LOQ, their concentrations were considered outliers and excluded from statistical analysis. For organophosphate metabolites, the LOD for DMP, DMTP, DMDTP, DEP, DETP, and DEDTP were 0.58 μg/L, 0.44 μg/L, 0.093 μg/L, 0.29 μg/L, 0.13 μg/L, and 0.067 μg/L respectively. For pyrethroid

metabolites, the LOD for 3-PBA, 4-F-3-PBA, *cis*-DBCA, *cis*-DCCA, and *trans*-DCCA were 0.012 µg/L, 0.0060 µg/L, 0.0059 µg/L, 0.0045 µg/L, 0.0094 µg/L respectively.

Blood Collection

Blood collection followed very similar collection, processing, and shipping as urine collection. A phlebotomist collected blood using standardized venipuncture technique. The amount of blood taken varied per age group and consent type (consent to having their blood stored):

With consent to storage:

- 3 to 5 years: 24.0 mL
- 6 to 11 years: 40.0 mL
- 12 to 13 years: 59.0 mL
- 14 to 19 years: 77.0 mL
- 20 to 79 years: 83.0 mL

Without consent to storage:

- 3 to 5 years: 22.0 mL
- 6 to 11 years: 34.0 mL
- 12 to 13 years: 39.0 mL
- 14 to 19 years: 49.0 mL
- 20 to 79 years: 57.0 mL

After collection, the whole blood sample was centrifuged at 8°C for 15 minutes at 3,400 revolutions per minute in order to separate the serum and plasma to aliquot the separate samples into smaller tubes. For blood collection, the blood samples had to be processed and stored within four hours of the point of collection to be considered viable. As with the urine aliquots, the temperature was taken every 30 minutes during shipping to ensure sample viability. The blood

aliquots were sent to the reference laboratory at Health Canada in Ottawa to evaluate the plasma HbA1c levels.

### 4.3 Statistical Analysis

There were two steps in the data analysis. The first step was to provide descriptive statistics that described the distributions of insecticide metabolites concentrations in urine, various obesity/diabetes measures, and their covariates. Secondly, regression models were built to determine whether any of the insecticide metabolite concentrations in urine, taking important covariates into account (Table 4.1), increased the probability of being obese or diabetes.

**Table 4.1 Study variables of organophosphate and pyrethroid metabolites in urine as exposures of interest, obesity, and diabetes as outcomes and covariates: CHMS 2015-2016.**

| Variable name | Measurement |
|---|---|
| **Organophosphate Metabolites Urine Levels (Independent Variables)** | |
| LAB_DMP | Dimethylphosphate (DMP) (µg/L) |
| LAB_DMTP | Dimethylthiophosphate (DMTP) (µg/L) |
| LAB_DMDT | Dimethyldithiophosphate (DMDTP) (µg/L) |
| LAB_DEP | Diethylphosphate (DEP) (µg/L) |
| LAB_DETP | Diethylthiophosphate (DETP) (µg/L) |
| LAB_DEDT | Diethyldithiophosphate (DEDTP) (µg/L) |
| **Pyrethroid Metabolites Urine Level (Independent Variables)** | |
| LAB_CDBC | *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*cis*-DBCA) (µg/L) |
| LAB_CDCC | *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*cis*-DCCA) (µg/L) |
| LAB_4F3P | 4-Fluoro-3-phenoxybenzoic acid (4-F-3-PBA) (µg/L) |
| LAB_3PBA | 3-Phenoxybenzoic acid (3-PBA) (µg/L) |
| LAB_TDCC | *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*trans*-DCCA) (µg/L) |
| **Obesity and Diabetes Measures (Dependent Variables)** | |
| HWM_13KG | Weight in kilograms |
| HWM_14CX | Waist circumference in centimeters (NIH protocol) |
| HWMDBMI | Body mass index (BMI) |
| LAB_HBA1 | Glycated hemoglobin A1c (HbA1c) |
| CCC_51 | Self-reported diabetes |
| **Potential Covariates (Independent Variables)** | |
| CLC_AGE | Age at clinical examination |

| | |
|---|---|
| CLC_SEX | Sex |
| WHR_015 | Pregnancy status |
| PGDCGT | Race |
| PAADTOT | Physical activity |
| SACDTOTX | Sedentary behaviour |
| EDUDR04 | Highest level of education - respondent, 4 levels |
| SMKDSTY | Smoking status |

It was determined that the child and youth sample of the CHMS Cycle 5 (<18 years old) to be inadequate for the evaluation of the effects of insecticide exposure on obesity and diabetes outcome in non-adults. The subsample's effective sample size was too small for reliable estimates to be produced. For linear regression models, normality was not present resulting in a violation of the assumptions of linear regression modelling. Additionally, the number of diabetes cases were too low to have an adequate statistical power. As such, the decision to exclude the non-adult subsample was taken.

All analyses were conducted using both creatinine-adjusted concentrations and unadjusted concentrations to reduce any potential biases that might be due to variation in creatinine excretion between sex, age, and ethnicity (112,201). To adjust for creatinine, urine creatinine values were first converted from mmol/L to g/L, then the urinary metabolite concentrations would be divided by the urinary creatinine value. Since creatinine-adjusted concentrations produce the most unbiased estimates, interpretations were only made for results using the creatinine-adjusted estimates. Of the eleven urinary metabolites of interest that were measured in the CHMS Cycle 5, 4-F-3-PBA, DEDTP, and DMDTP were excluded from the analyses as they had over 40% of their sample under the LOD making any estimates generated from this sample possibly biased. For the remaining urinary metabolites, any measurements that were under the LOD were imputed as the LOD/2 to account for non-detectable levels. This is a commonly used technique to deal with missing data that is under the LOD with environmental

contaminants (202–205). Any respondents who did not have a recorded measurement for a specific urinary metabolite was removed from the analysis for the metabolite. All estimates were calculated using standardized weights which was calculated by dividing the regular weight variable by the mean of the weights in the sample. The methodology used to create the sampling weights is described in Appendix 3 (195).

After restricting the population by removing participants that had any missing data for important measures, such as a missing creatinine measurement, the total study population for this thesis project was 1,147. After this restriction, each metabolite would have their own restrictions based on missing concentration measurements and extreme outliers (>3SD away from the median). For DEP, there were 33 with missing measurements, 1 extreme outlier, and 40 respondents with a concentration under the LOD. For DETP, there were 52 with missing measurements, 1 extreme outlier, and 290 respondents with a concentration under the LOD. For DMP, there were 38 with missing measurements, 1 extreme outlier, and 221 respondents with a concentration under the LOD. For DMTP, there were 34 with missing measurements, 1 extreme outlier, and 351 respondents with a concentration under the LOD. For *cis*-DBCA, there was 52 with missing measurements, 0 extreme outlier, and 225 respondents with a concentration under the LOD. For *cis*-DCCA, there was 4 with missing measurements, 2 extreme outliers, and <15 respondents with a concentration under the LOD. For 3-PBA, there was 4 with missing measurements, 4 extreme outliers, and <15 respondents with a concentration under the LOD. For *trans*-DCCA, there was 2 with missing measurements, 4 extreme outliers, and <15 respondents with a concentration under the LOD.

The CHMS was conducted with the use of 12 primary sampling sites. As such, regressions models were limited to 11 degrees of freedom as recommended by the user guide for

Cycle 5 (195). Due to this constraint, each model would have different predictors to create the most parsimonious model. As the goal was to examine the associations of the urinary insecticide exposure with the various obesity and diabetes measures, the different metabolites could have different predictors. The goal of modelling was to illuminate each association of interest using the best possible model. Additionally, all descriptive statistics were calculated using 95% confidence intervals and all the regression models were conducted using 99% confidence intervals as recommended with CHMS survey data use (195).

Re-sampling methods was employed to calculate point and variance estimates. The recommended method for CHMS data analysis is the bootstrap method (195). In this method, bootstrap samples are created from the full sample by randomly selecting "n-1" collection sites with replacement among "n" collection sites in each region. For each respondent in these bootstrap samples, an adjusted weight is calculated. In total, there were 500 bootstrap samples drawn from the environmental urine sample. From each one of these bootstrap samples, a statistic of interest is calculated, and the distribution of that statistic was used to calculate the variance. Bootstrap weights were used to determine the variances of both descriptive and analytic statistics from simple and multiple regression analyses.

### 4.3.1 Descriptive statistics

The baseline characteristics of the study population were described for each urinary metabolite for creatinine-adjusted concentrations (and for unadjusted concentrations in Appendix 4). All characteristics had the number of unweighted participants, the percentage within each level that was weighted to the population using sampling weights. Both the geometric mean and median of the specific urinary metabolite were determined using SAS's Proc Surveymeans.

Although geometric means are more commonly used for descriptive statistics for environmental contaminants concentrations, medians were included as it could be a more accurate central tendency measure when the concentration distribution of a metabolite was skewed. Geometric means were kept in the table to demonstrate both commonly used central tendency measures and due to the Shapiro-Wilk Test of normality demonstrating the distribution of several metabolites to be barely significant (*cis*-DCCA, 3-PBA, and *trans*-DCCA). Lastly, differences in the distributions between the levels of the baseline characteristics were evaluated using the Kolmogorov-Smirnov Test for dichotomous characteristics and the Kruskal-Wallis test for three or more leveled characteristics. All the point estimates and variance estimates were calculated using the bootstrap method.

Age was categorized into 4 groups representing of 18-49 years old, 50-59 years old, 60-69 years old, and 70-79 years old. Race was categorized into 2 groups of white and non-white (all other races). Physical activity and sedentary behavior were categorized based on the Canadian 24-Hour Movement Guidelines for Adults (aged 18-64) and the Canadian 24-Hour Movement Guidelines for Children and Youth (206,207). The adult guidelines indicate that to be healthy, recreational sedentary behaviours should be limited to 3 hours of less a day, and at least 150 minutes of moderate to vigorous aerobic physical activities, at least two muscle strengthening activities, and several hours of light physical activities must be performed in a week. As such, for adults, sedentary behaviours were categorized into 3 groups of healthy (less than 3 hours a day), moderately healthy (between 3 to 6 hours in a day), and unhealthy (more than 6 hours a day). As the CHMS only asks for how much of the respondent's free time is spent doing sedentary behaviours, the respondent's actual time being sedentary may be different if their job consists of sedentary activities. For physical activeness, respondents were classified as

active if they had 150 minutes or more active minutes per week, or inactive, if they had less than 150 active minutes per week.

BMI was categorized based on the Canadian Guidelines for Body Weight Classification in adults (1). Briefly, it was categorized as underweight and healthy (BMI<25.0), overweight (25.0≤BMI<30.0), and obese (BMI≥30). For WC, male respondents who were ≥94 cm and <102 cm were categorized as overweight, and those who were ≥102 cm were categorized as obese based on the findings from Lean et al. (208). Women respondents' WC, also based on the findings from Lean et al., were categorized as overweight when they were between ≥80 cm and <88cm, and obese when they were ≥88 cm (208). Education and smoking status were categorized based on the methodology used in data collection (see 4.2.1). Age, race, BMI, and physical activeness were categorized in a condensed manner to allow for inclusion in logistic regression modelling (at least 10 counts per cell).

### 4.3.2 Regression models

Multiple linear regression was conducted (using SAS's Proc Surveyreg) using the log-transformed urinary concentration of a metabolite as the independent variable and the obesity measures and diabetes measures as the dependent variables in unadjusted models and creatinine-adjusted models. Three models were created for both unadjusted and creatinine-adjusted log-transformed urinary concentrations. The first model was a crude model, the second model was adjusted for sex and age, and the third model was adjusted by all significant covariates representing the best fitting model. When an interaction between the log-transformed urinary concentration and sex was present, within each model, a general model was created that included the interaction term, as well as sex-specific models. For model 3, the significant covariates that

the model was adjusted for are detailed in the footnotes of tables. If there was effect modification, the models would be stratified by the effect modifying variable to create stratum-specific models. As the weights were created to be representative of the Canadian population, influential data points with a large weight can bias the estimates in a manner that may hide the true association between the obesity measures and the urinary metabolite concentrations (195). As such, influential data points with Cook d value of higher than 0.20 were removed from the model. An eye-test examining the Cook d value by the obesity measures was also conducted to further remove any remaining influential data points. The number of participants removed from each model is detailed in the table's footnotes. A sensitivity analysis was performed with the influential data points and there were no significant changes in the resulting regression coefficients.

Multiple logistic regression was performed (using SAS's Proc Surveylogistic) using the concentration quartiles of the log-transformed urinary metabolites concentrations to predict the odds of having diabetes. A general model was also performed using just the concentration of the log-transformed urinary metabolite concentration, and covariates, to predict the odds of having diabetes. As the prevalence of diabetes is above 5%, odds ratios may be a biased measure of association (209). Relative risk was calculated using the SAS macro NLMeans and the steps used in the macro can be found on the SAS website (210). The results were found to be comparable to the odds ratio and presented in Appendix 5. Influential data points were not removed for the logistic regression models to ensure that there were no violations of the assumptions of logistic regression modelling (<10 count per cell). All of the regression analyses were done using the bootstrap technique with 500 re-samples as recommended by the CHMS to

control for its sampling structure and to achieve a proper variance. All analyses were conducted with SAS 9.4 (SAS Institute Inc, Cary, NC).

## 5. Organophosphates

### 5.1. Results

#### 5.1.1. Baseline Characteristics

Tables 5.1 to 5.4 depicts the baseline characteristic of the study population for each urinary metabolite. The total population for DEP, DETP, DMP, and DETP were 1,113, 1,094, 1,108, and 1,112, respectively. Among these population, the crude weighted prevalence of diabetes was about 8.1%. The geometric means of DEP, DETP, DMP, and DETP were 1.900 µg/g (95% CI: 1.706, 2.117), 0.317 µg/g (95% CI: 0.257, 0.353), 1.478 µg/L (95% CI: 1.253, 1.743), and 1.087 µg/g (95% CI: 0.937, 1.263), respectively. The medians of DEP, DETP, DMP, and DETP were 1.982 µg/g (95% CI: 1.727, 2.237), 0.305 µg/g (95% CI: 0.257, 0.353), 1.457 µg/g (95% CI: 1.246, 1.668), and 0.924 µg/g (95% CI: 0.785, 1.063), respectively.

The geometric mean was consistently higher across all OPs for individuals who were female, 70 years old or older, white, active, or those who had a post-secondary degree/diploma. There was also high sampling variability among OP metabolites' geometric means for the 60-69 and 70+ age groups, those with a BMI of 30 or higher, those who had diabetes, those who did not have a post-secondary degree/diploma, or those who smoked daily.

For DEP, females had a geometric mean of 2.167 µg/g (95% CI: 1.587, 2.959) as compared to males who had a geometric mean of 1.670 µg/g (95% CI: 1.200, 2.324). For DETP, females had a geometric mean of 0.361 µg/g (95% CI: 0.252, 0.516) as compared to males who had a geometric mean of 0.279 µg/g (95% CI: 0.192, 0.405). For DMP, females had a geometric

mean of 1.791 µg/g (95% CI: 1.138, 2.816) as compared to males who had a geometric mean of 1.233 µg/g (95% CI: 0.752, 1.991). For DMTP, females had a geometric mean of 1.235 µg/g (95% CI: 0.829, 1.839) as compared to males who had a geometric mean of 0.961 µg/g (95% CI: 0.646, 1.428). DEP, DETP, DMP, and DMTP geometric means were 29.7%, 29.3%, 45.0%, and 28.5% higher in females than in males, respectively.

The median was consistently higher across all OPs for individuals who were female, 70 years old or older, white, or physically active, those who had a BMI less than 25, or those who had a post-secondary degree/diploma. There was also high sampling variability among OP metabolites' medians for those who had diabetes. There was a significant difference in urinary OP metabolite concentrations among sex, age, BMI, or smoking groups.

For DEP, females had a median of 2.292 µg/g (95% CI: 1.999, 2.585) as compared to males who had a median of 1.609 µg/g (95% CI: 1.195, 2.024). For DETP, females had a median of 0.348 µg/g (95% CI: 0.288, 0.408) as compared to males who had a median of 0.249 µg/g (95% CI: 0.170, 0.329). For DMP, females had a median of 1.690 µg/g (95% CI: 1.447, 1.933) as compared to males who had a median of 1.221 µg/g (95% CI: 0.958, 1.485). For DMTP, females had a median of 0.994 µg/g (95% CI: 0.784, 1.204) as compared to males who had a median of 0.810 µg/g (95% CI: 0.568, 1.052). DEP, DETP, DMP, and DMTP medians were 42.4%, 39.8%, 38.4%, and 22.7% higher in females than in males, respectively.

**Table 5.1 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary diethylphosphate (DEP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1113 (100.0) | 1.900 (1.706, 2.117) | 1.982 (1.727, 2.237) | |
| **Sex** | | | | <0.001 |
| Male | 561 (50.5) | 1.670 (1.200, 2.324) | 1.609 (1.195, 2.024) | |
| Female | 552 (49.5) | 2.167 (1.587, 2.959) | 2.292 (1.999, 2.585) | |
| **Age (yrs)** | | | | <0.001 |
| 18-49 | 660 (56.7) | 1.779 (1.432, 2.210) | 1.752 (1.370, 2.133) | |
| 50-59 | 122 (18.4) | 1.732 (1.214, 2.471) | 1.828 (1.225, 2.431) | |
| 60-69 | 219 (17.7) | 2.289 (1.480, 3.541)[E] | 2.255 (1.734, 2.777) | |
| 70-79 | 112 (7.2) | 2.562 (1.333, 4.924)[E] | 2.576 (2.016, 3.135) | |
| **Body mass index** | | | | <0.001 |
| Underweight and healthy | 402 (42.0) | 1.985 (1.651, 2.385) | 2.219 (1.879, 2.560) | |
| Overweight | 381 (29.9) | 2.028 (1.644, 2.502) | 2.094 (1.837, 2.351) | |
| Obese class | 329 (28.1) | 1.662 (1.152, 2.398)[E] | 1.619 (1.328, 1.910) | |
| **Waist circumference** | | | | 0.454 |
| Underweight and healthy | 406 (41.5) | 1.848 (1.542, 2.214) | 2.058 (1.601, 2.515) | |
| Overweight | 226 (17.9) | 1.851 (1.625, 2.109) | 1.861 (1.506, 2.217) | |
| Obese class | 481 (40.6) | 1.978 (1.723, 2.271) | 1.932 (1.647, 2.217) | |
| **Diabetes** | | | | 0.069 |
| No | 1044 (91.9) | 1.854 (1.646, 2.087) | 1.950 (1.704, 2.195) | |
| Yes | 69 (8.1) | 2.515 (1.324, 4.778)[E] | 2.152 (0.944, 3.360)[E] | |
| **Race** | | | | 0.100 |
| White | 856 (70.5) | 1.953 (1.721, 2.216) | 2.011 (1.739, 2.284) | |
| Non-White | 257 (29.5) | 1.780 (1.358, 2.334) | 1.757 (1.236, 2.279) | |
| **Physical activity** | | | | 0.074 |
| Active | 609 (52.2) | 2.175 (1.622, 2.916) | 2.298 (2.080, 2.516) | |
| Inactive | 504 (47.8) | 1.640 (1.153, 2.333) | 1.651 (1.299, 2.002) | |
| **Sedentary behaviour** | | | | 0.186 |
| Healthy | 497 (47.8) | 2.025 (1.608, 2.549) | 2.142 (1.650, 2.635) | |
| Moderately sedentary | 467 (39.1) | 1.716 (1.277, 2.304) | 1.727 (1.331, 2.122) | |
| Sedentary | 149 (13.1) | 2.044 (1.487, 2.810) | 2.226 (1.769, 2.684) | |
| **Highest level of education** | | | | 0.003 |

| | | | | |
|---|---|---|---|---|
| Less than secondary school | 105 (6.6) | 1.720 (1.340, 2.208) | 1.731 (1.285, 2.178) | |
| Secondary school | 294 (27.7) | 1.532 (0.893, 2.631)[E] | 1.609 (1.102, 2.116) | |
| Post-secondary degree/diploma | 714 (65.7) | 2.102 (1.683, 2.626) | 2.076 (1.749, 2.403) | |
| **Smoking status** | | | | <0.001 |
| Non-smoker | 579 (50.5) | 1.980 (1.600, 2.450) | 2.206 (1.855, 2.557) | |
| Former smoker | 331 (30.7) | 2.024 (1.634, 2.507) | 1.933 (1.523, 2.342) | |
| Daily smoker | 203 (18.8) | 1.537 (0.913, 2.589)[E] | 1.241 (0.954, 1.528) | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

**Table 5.2 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary diethylthiophosphate (DETP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1094 (100.0) | 0.317 (0.278, 0.362) | 0.305 (0.257, 0.353) | |
| **Sex** | | | | 0.005 |
| Male | 547 (50.1) | 0.279 (0.192, 0.405)[E] | 0.249 (0.170, 0.329) | |
| Female | 547 (49.9) | 0.361 (0.252, 0.516) | 0.348 (0.288, 0.408) | |
| **Age (yrs)** | | | | <0.001 |
| 18-49 | 646 (56.3) | 0.289 (0.217, 0.383) | 0.273 (0.217, 0.329) | |
| 50-59 | 122 (18.6) | 0.280 (0.182, 0.431)[E] | 0.418 (0.299, 0.537) | |
| 60-69 | 215 (17.8) | 0.405 (0.225, 0.727)[E] | 0.357 (0.207, 0.507)[E] | |
| 70-79 | 111 (7.3) | 0.498 (0.205, 1.210)[F] | 0.484 (0.250, 0.719)[E] | |
| **Body mass index** | | | | <0.001 |
| Underweight and healthy | 397 (42.0) | 0.414 (0.233, 0.737)[E] | 0.370 (0.285, 0.455) | |
| Overweight | 372 (29.8) | 0.284 (0.201, 0.403) | 0.308 (0.224, 0.392) | |
| Obese class | 325 (28.2) | 0.240 (0.122, 0.472)[E] | 0.236 (0.144, 0.327)[E] | |
| **Waist circumference** | | | | 0.018 |
| Underweight and healthy | 399 (41.4) | 0.401 (0.233, 0.689)[E] | 0.359 (0.271, 0.447) | |
| Overweight | 222 (17.9) | 0.255 (0.140, 0.463)[E] | 0.273 (0.193, 0.353) | |
| Obese class | 473 (40.7) | 0.275 (0.192, 0.394) | 0.286 (0.222, 0.350) | |
| **Diabetes** | | | | 0.837 |
| No | 1027 (92.0) | 0.323 (0.278, 0.374) | 0.309 (0.260, 0.359) | |
| Yes | 67 (8.0) | 0.259 (0.132, 0.508)[E] | 0.256 (0.121, 0.391)[E] | |
| **Race** | | | | <0.001 |
| White | 842 (70.2) | 0.322 (0.267, 0.388) | 0.307 (0.236, 0.379) | |
| Non-White | 252 (29.8) | 0.307 (0.233, 0.405) | 0.295 (0.224, 0.367) | |
| **Physical activity** | | | | 0.003 |
| Active | 600 (52.2) | 0.346 (0.278, 0.430) | 0.374 (0.309, 0.438) | |
| Inactive | 494 (47.8) | 0.289 (0.220, 0.378) | 0.274 (0.216, 0.333) | |
| **Sedentary behaviour** | | | | 0.483 |
| Healthy | 489 (47.8) | 0.373 (0.253, 0.550)[E] | 0.355 (0.284, 0.426) | |
| Moderately sedentary | 464 (39.2) | 0.260 (0.168, 0.402)[E] | 0.273 (0.198, 0.349) | |
| Sedentary | 141 (13.0) | 0.318 (0.242, 0.416) | 0.319 (0.222, 0.416) | |
| **Highest level of education** | | | | 0.027 |

| | | | | |
|---|---|---|---|---|
| Less than secondary school | 106 (6.8) | 0.283 (0.200, 0.400) | 0.202 (0.088, 0.316)[E] | |
| Secondary school | 288 (27.5) | 0.231 (0.103, 0.518)[F] | 0.221 (0.134, 0.308)[E] | |
| Post-secondary degree/diploma | 700 (65.7) | 0.367 (0.264, 0.509) | 0.358 (0.291, 0.424) | |
| **Smoking status** | | | | <0.001 |
| Non-smoker | 565 (49.8) | 0.369 (0.257, 0.529) | 0.349 (0.297, 0.402) | |
| Former smoker | 328 (31.0) | 0.350 (0.255, 0.479) | 0.382 (0.261, 0.503) | |
| Daily smoker | 201 (19.2) | 0.183 (0.038, 0.874)[E] | 0.167 (0.106, 0.227) | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Table 5.3 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary dimethylphosphate (DMP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1108 (100.0) | 1.478 (1.253, 1.743) | 1.457 (1.246, 1.668) | |
| **Sex** | | | | <0.001 |
| Male | 558 (50.4) | 1.233 (0.752, 1.991)[E] | 1.221 (0.958, 1.485) | |
| Female | 550 (49.6) | 1.791 (1.138, 2.816)[E] | 1.690 (1.447, 1.933) | |
| **Age (yrs)** | | | | <0.001 |
| 18-49 | 657 (56.6) | 1.343 (1.004, 1.798) | 1.349 (1.108, 1.590) | |
| 50-59 | 122 (18.6) | 1.420 (0.948, 2.129)[E] | 1.251 (0.766, 1.735)[E] | |
| 60-69 | 216 (17.5) | 1.704 (1.074, 2.705)[E] | 1.598 (1.003, 2.193)[E] | |
| 70-79 | 113 (7.3) | 2.423 (0.972, 6.040)[F] | 2.059 (1.201, 2.916)[E] | |
| **Body mass index** | | | | <0.001 |
| Underweight and healthy | 402 (42.2) | 1.793 (1.099, 2.923)[E] | 1.767 (1.440, 2.095) | |
| Overweight | 378 (29.8) | 1.507 (1.178, 1.928) | 1.444 (1.161, 1.727) | |
| Obese class | 328 (28.0) | 1.082 (0.474, 2.468)[F] | 1.130 (0.814, 1.445) | |
| **Waist circumference** | | | | 0.032 |
| Underweight and healthy | 405 (41.6) | 1.524 (1.252, 1.856) | 1.508 (1.270, 1.746) | |
| Overweight | 227 (18.1) | 1.656 (1.082, 2.534)[E] | 1.622 (1.184, 2.060) | |
| Obese class | 476 (40.3) | 1.360 (0.976, 1.894) | 1.307 (0.993, 1.621) | |
| **Diabetes** | | | | 0.183 |
| No | 1040 (91.9) | 1.476 (1.230, 1.770) | 1.422 (1.200, 1.644) | |
| Yes | 68 (8.1) | 1.501 (1.031, 2.186)[E] | 1.644 (0.930, 2.358)[E] | |
| **Race** | | | | 0.153 |
| White | 851 (70.4) | 1.571 (1.243, 1.985) | 1.466 (1.148, 1.785) | |
| Non-White | 257 (29.6) | 1.278 (0.885, 1.844) | 1.375 (1.194, 1.557) | |
| **Physical activity** | | | | 0.486 |
| Active | 606 (52.3) | 1.566 (1.233, 1.990) | 1.494 (1.164, 1.823) | |
| Inactive | 502 (47.7) | 1.386 (1.140, 1.685) | 1.397 (1.234, 1.560) | |
| **Sedentary behaviour** | | | | |
| Healthy | 497 (48.1) | 1.491 (1.213, 1.832) | 1.513 (1.270, 1.757) | 0.633 |
| Moderately sedentary | 464 (38.8) | 1.390 (1.017, 1.900) | 1.400 (1.004, 1.796) | |
| Sedentary | 147 (13.1) | 1.714 (1.123, 2.617)[E] | 1.553 (0.964, 2.143)[E] | |
| **Highest level of education** | | | | 0.012 |

| | | | | |
|---|---|---|---|---|
| Less than secondary school | 106 (6.7) | 1.349 (1.026, 1.776) | 1.375 (0.976, 1.774) | |
| Secondary school | 292 (27.8) | 1.062 (0.446, 2.528)[F] | 1.143 (0.960, 1.326) | |
| Post-secondary degree/diploma | 710 (65.5) | 1.716 (1.194, 2.466) | 1.671 (1.389, 1.953) | |
| **Smoking status** | | | | <0.001 |
| Non-smoker | 576 (50.5) | 1.608 (1.254, 2.062) | 1.614 (1.408, 1.821) | |
| Former smoker | 331 (30.8) | 1.651 (1.111, 2.452)[E] | 1.459 (0.977, 1.941) | |
| Daily smoker | 201 (18.7) | 0.978 (0.307, 3.117)[F] | 1.027 (0.728, 1.325) | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Table 5.4 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary dimethylthiophosphate (DMTP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1112 (100.0) | 1.087 (0.937, 1.263) | 0.924 (0.785, 1.063) | |
| **Sex** | | | | 0.004 |
| Male | 561 (50.6) | 0.961 (0.646, 1.428)[E] | 0.810 (0.568, 1.052) | |
| Female | 551 (49.4) | 1.235 (0.829, 1.839)[E] | 0.994 (0.784, 1.204) | |
| **Age (yrs)** | | | | <0.001 |
| 18-49 | 660 (56.8) | 0.981 (0.716, 1.346) | 0.793 (0.602, 0.985) | |
| 50-59 | 121 (18.4) | 0.931 (0.572, 1.517)[E] | 0.913 (0.464, 1.363)[E] | |
| 60-69 | 218 (17.5) | 1.428 (0.803, 2.540)[E] | 1.343 (0.895, 1.790) | |
| 70-79 | 113 (7.3) | 1.860 (0.644, 5.376)[F] | 1.658 (0.605, 2.710)[E] | |
| **Body mass index** | | | | <0.001 |
| Underweight and healthy | 401 (41.8) | 1.429 (0.748, 2.731)[E] | 1.026 (0.414, 1.638)[E] | |
| Overweight | 381 (29.9) | 1.081 (0.810, 1.443) | 0.969 (0.570, 1.369)[E] | |
| Obese class | 330 (28.3) | 0.730 (0.253, 2.105)[F] | 0.732 (0.544, 0.920) | |
| **Waist circumference** | | | | 0.006 |
| Underweight and healthy | 405 (41.3) | 1.237 (0.803, 1.903)[E] | 0.940 (0.424, 1.457)[E] | |
| Overweight | 227 (18.1) | 1.212 (0.879, 1.671) | 0.994 (0.634, 1.355) | |
| Obese class | 480 (40.6) | 0.909 (0.560, 1.476)[E] | 0.870 (0.665, 1.074) | |
| **Diabetes** | | | | 0.590 |
| No | 1043 (91.9) | 1.116 (0.957, 1.301) | 0.937 (0.793, 1.080) | |
| Yes | 69 (8.1) | 0.814 (0.366, 1.812)[F] | 0.705 (0.147, 1.262)[F] | |
| **Race** | | | | <0.001 |
| White | 856 (70.6) | 1.261 (0.871, 1.828) | 1.077 (0.739, 1.415) | |
| Non-White | 256 (29.4) | 0.762 (0.292, 1.988)[F] | 0.529 (0.333, 0.725)[E] | |
| **Physical activity** | | | | 0.449 |
| Active | 608 (52.1) | 1.160 (0.921, 1.462) | 1.109 (0.778, 1.440) | |
| Inactive | 504 (47.9) | 1.013 (0.823, 1.247) | 0.833 (0.716, 0.950) | |
| **Sedentary behaviour** | | | | 0.859 |
| Healthy | 496 (47.8) | 1.162 (0.815, 1.657) | 0.983 (0.557, 1.409)[E] | |
| Moderately sedentary | 468 (39.1) | 0.998 (0.709, 1.405) | 0.917 (0.613, 1.220) | |
| Sedentary | 148 (13.1) | 1.104 (0.760, 1.603)[E] | 0.904 (0.517, 1.291)[E] | |
| **Highest level of education** | | | | <0.001 |

| | | | | |
|---|---|---|---|---|
| Less than secondary school | 106 (6.7) | 0.841 (0.371, 1.907)[F] | 0.807 (0.345, 1.269)[E] | |
| Secondary school | 294 (27.8) | 0.803 (0.343, 1.876)[F] | 0.701 (0.439, 0.964)[E] | |
| Post-secondary degree/diploma | 712 (65.5) | 1.270 (0.876, 1.842)[E] | 1.151 (0.817, 1.486) | |
| **Smoking status** | | | | <0.001 |
| Non-smoker | 578 (50.6) | 1.237 (0.872, 1.755) | 1.142 (0.816, 1.467) | |
| Former smoker | 332 (30.6) | 1.376 (0.818, 2.315)[E] | 1.021 (0.566, 1.476)[E] | |
| Daily smoker | 202 (18.8) | 0.526 (0.051, 5.385)[F] | 0.498 (0.300, 0.695)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

### 5.1.2 Organophosphate Obesity Measures

#### Body Mass Index

For unadjusted log-transformed urinary OP metabolites, there was no significant association observed with BMI (Table 5.5). With creatinine-adjustment, all 4 log-transformed urinary OP metabolites were significantly negatively associated with BMI. All metabolites also demonstrated significant negative associations across all models. A significant interaction was present between sex and DEP as well as between sex and DMP. For both interactions, the coefficient for males were insignificant and the coefficient for females were significant. For every 1 unit increase in log-transformed DETP and log-transformed DMTP, the BMI increased by -0.94 (99% CI: -1.72, -0.17) and -0.81 (99% CI: -1.38, -0.25), respectively. For every 1 unit increase in log-transformed DEP, the BMI increased by -0.32 (99% CI: -1,14, 0.49) for males and -1.64 (99% CI: -2.42, -0.87) for females. For every 1 unit increase in log-transformed DMP, the BMI increased by -0.46 (99% CI: -1.24, 0.32) for males and -1.97 (99% CI: -3.44, -0.50) for females. Age and race were significantly associated with BMI in all the OP models. Physical activeness was also significant for 3 of the 4 OPs and was adjusted for in their respective models.

**Table 5.5 Linear regression models predicting BMI from log-transformed urinary organophosphates levels in Canadians 18 years or older in the CHMS 2015-2016.**

| Metabolite | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| | ß (99% CI) | p-value | ß (99% CI) | p-value |
| **DEP[a]** | | | | |
| **Model 1** | | | | |
| General | 0.31 (-0.56, 1.18) | 0.30 | -0.65 (-1.15, -0.15)* | <0.01 |
| Male | 0.10 (-1.18, 1.37) | 0.82 | -0.10 (-0.99, 0.78) | 0.26 |
| Female | 0.52 (-0.44, 1.48) | 0.12 | -1.49 (-2.17, -0.82)* | <0.01 |
| **Model 2** | | | | |
| General | | | | |
| DEP | 0.06 (-1.11, 1.23)* | 0.87 | -0.31 (-1.14, 0.53)* | 0.28 |
| DEP x sex | 0.49 (-0.93, 1.91)* | 0.30 | -1.42 (-2.27, -0.57)* | <0.01 |
| Male | 0.05 (-1.10, 1.21)* | 0.89 | -0.34 (-1.19, 0.50)* | 0.23 |
| Female | 0.55 (-0.35, 1.45)* | 0.09 | -1.69 (-2.27, -1.11)* | <0.01 |
| **Model 3** | | | | |
| General | | | | |
| DEP | 0.15 (-1.11, 1.40)* | 0.72 | -0.22 (-1.14, 0.71)* | 0.48 |
| DEP x sex | 0.39 (-0.99, 1.77)* | 0.40 | -1.51 (-2.43, -0.60)* | <0.01 |
| Male | 0.07 (-1.05, 1.20)* | 0.85 | -0.32 (-1.14, 0.49)* | 0.24 |
| Female | 0.52 (-0.34, 1.39)* | 0.09 | -1.64 (-2.42, -0.87)* | <0.01 |
| **DETP[b]** | | | | |
| Model 1 | -0.34 (-1.19, 0.50) | 0.24 | -0.82 (-1.58, -0.06)* | 0.01 |
| Model 2 | -0.35 (-1.12, 0.42)* | 0.18 | -0.97 (-1.74, -0.19)* | <0.01 |
| Model 3 | -0.35 (-1.14, 0.44)* | 0.20 | -0.94 (-1.72, -0.17)* | <0.01 |
| **DMP[c]** | | | | |
| **Model 1** | | | | |
| General | -0.22 (-1.24, 0.81) | 0.53 | -0.93 (-1.97, 0.10) | 0.02 |
| Male | -0.25 (-1.18, 0.69) | 0.43 | -0.33 (-1.19, 0.53) | 0.26 |
| Female | -0.19 (-1.80, 1.43) | 0.73 | -1.65 (-3.14, -0.16)* | 0.01 |
| **Model 2** | | | | |
| General | | | | |
| DEP | -0.24 (-1.17, 0.69)* | 0.44 | -0.46 (-1.23, 0.30)* | 0.09 |
| DEP x sex | 0.02 (-1.53, 1.57)* | 0.97 | -1.44 (-2.79, -0.09)* | 0.01 |
| Male | -0.24 (-1.18, 0.70)* | 0.44 | -0.47 (-1.28, 0.33)* | 0.10 |
| Female | -0.22 (-1.67, 1.24)* | 0.65 | -1.88 (-3.24, -0.52)* | <0.01 |
| **Model 3** | | | | |
| General | | | | |
| DEP | -0.26 (-1.18, 0.65)* | 0.39 | -0.45 (-1.17, 0.28)* | 0.08 |

| | | | | |
|---|---|---|---|---|
| DEP x sex | -0.01 (-1.59, 1.57)* | 0.98 | -1.52 (-2.96, -0.08)* | 0.01 |
| Male | -0.26 (-1.18, 0.66)* | 0.40 | -0.46 (-1.24, 0.32)* | 0.09 |
| Female | -0.28 (-1.79, 1.23)* | 0.58 | -1.97 (-3.44, -0.50)* | <0.01 |
| **DMTP[d]** | | | | |
| Model 1 | -0.25 (-0.88, 0.38) | 0.25 | -0.60 (-1.09, -0.10)* | <0.01 |
| Model 2 | -0.30 (-0.90, 0.30)* | 0.14 | -0.74 (-1.29, -0.19)* | <0.01 |
| Model 3 | -0.38 (-1.01, 0.25)* | 0.09 | -0.81 (-1.38, -0.25)* | <0.01 |

**Abbreviations:** BMI, Body Mass Index; DEP, diethylphosphate; DETP, diethylthiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; logdep, log-transformed diethylphosphate; logdmp, log-transformed dimethylphosphate; ß, regression coefficient; CI, confidence interval

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, and the interaction between log-transformed DEP and sex, Model 3 is adjusted for age, sex, race, education, and the interaction between log-transformed DEP and sex. N=1110, males=561, females=550; 3 participants were removed for being highly influential data points.

[b] Model 3 is adjusted for age, sex, race, and physical activeness. n=1089; 5 participants were removed for being highly influential data points.

[c] Model 3 is adjusted for age, sex, race, and physical activeness. n=1103, males=555, females= 548; 5 participants were removed for being highly influential data points.

[d] Model 3 is adjusted for age, sex, race, and physical activeness. n=1108; 4 participants were removed for being highly influential data points.

* Model is significant (<0.01)

**Waist Circumference**

For unadjusted log-transformed urinary OP metabolites, there was no significant association observed with WC (Table 5.6). With creatinine-adjustment, all 4 log-transformed urinary OP metabolites were significantly negatively associated with WC (Table 5.6). A significant interaction was present between sex and DEP where the coefficients for males were insignificant and the coefficients for females were significant. For every 1 unit increase in log-transformed DETP and log-transformed DMTP, the WC increased by -2.90cm (99% CI: -5.17, -0.62) and -2.18cm (99% CI: -3.69, -0.66) respectively. DETP also demonstrated a significant negative association across all models. For every 1 unit increase in log-transformed DEP, the

WC increased by -0.74cm (99% CI: -2.89, 1.41) for males and -4.97cm (99% CI: -8.04, -1.89) for females. The negative association remained significant for females across all models. Sex, age, race, and physical activeness were the covariates that were significant for all the models. Education and smoking status were also significant for 3 of the 4 OPs and were adjusted for in their respective models.

**Table 5.6 Linear regression models predicting waist circumference (cm) from log-transformed urinary organophosphate levels.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **ß (99% CI)** | **p-value** | **ß (99% CI)** | **p-value** |
| **DEP[a]** | | | | |
| **Model 1** | | | | |
| General | 0.15 (-2.47, 2.77) | 0.86 | -2.48 (-4.41, -0.55)* | <0.01 |
| Male | -0.50 (-4.02, 3.02) | 0.67 | -0.41 (-3.02, 2.20) | 0.63 |
| Female | 0.70 (-1.99, 3.39) | 0.43 | -4.22 (-7.52 -0.92)* | <0.01 |
| **Model 2** | | | | |
| General | | | | |
| DEP | -0.52 (-3.55, 2.51)* | 0.60 | -1.13 (-3.46, 1.20)* | 0.16 |
| DEP x sex | 1.31 (-2.17, 4.79)* | 0.27 | -3.98 (-6.96, -0.99)* | <0.01 |
| Male | -0.52 (-3.49, 2.44)* | 0.59 | -1.25 (-3.61, 1.11)* | 0.13 |
| Female | 0.78 (-1.43, 2.99)* | 0.30 | -4.97 (-8.04, -1.89)* | <0.01 |
| **Model 3** | | | | |
| General | | | | |
| DEP | -0.25 (-3.09, 2.60)* | 0.79 | -0.62 (-2.95, 1.71)* | 0.43 |
| DEP x sex | 1.15 (-1.95, 4.25)* | 0.27 | -4.31 (-7.32, -1.30)* | <0.01 |
| Male | -0.31 (-3.01, 2.39)* | 0.73 | -0.74 (-2.89, 1.41)* | 0.31 |
| Female | 0.89 (-1.03, 2.82)* | 0.18 | -4.81 (-7.85, -1.77)* | <0.01 |
| **DETP[b]** | | | | |
| Model 1 | -1.32 (-3.98, 1.35) | 0.15 | -2.74 (-5.08, -0.39)* | <0.01 |
| Model 2 | -1.33 (-3.57, 0.90)* | 0.09 | -2.96 (-5.14, -0.78)* | <0.01 |
| Model 3 | -1.23 (-3.57, 1.11)* | 0.13 | -2.90 (-5.17, -0.62)* | <0.01 |
| **DMP[c]** | | | | |
| Model 1 | -0.40 (-3.38, 2.59) | 0.69 | -2.21 (-5.13, 0.71) | 0.04 |
| Model 2 | -0.28 (-2.95, 2.40)* | 0.76 | -2.39 (-5.13, 0.35)* | 0.02 |

| | | | | |
|---|---|---|---|---|
| Model 3 | -0.52 (-3.43, 2.40) | 0.59 | -2.75 (-5.78, 0.28) | 0.02 |
| **DMTP[d]** | | | | |
| Model 1 | -0.47 (-2.52, 1.59) | 0.49 | -1.44 (-3.05, 0.17) | 0.02 |
| Model 2 | -0.69 (-2.42, 1.03)* | 0.24 | -1.78 (-3.26, -0.30)* | <0.01 |
| Model 3 | -0.99 (-2.81, 0.84)* | 0.12 | -2.18 (-3.69, -0.66)* | <0.01 |

**Abbreviations:** DEP, diethylphosphate; DETP, diethylthiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; logdep, log-transformed diethylphosphate; logdmp, log-transformed dimethylphosphate; ß, regression coefficient; CI, confidence interval

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, and the interaction between log-transformed DEP and sex, Model 3 is adjusted for age, sex, race, physical activeness, education, and the interaction between log-transformed DEP and sex. n=1105, males=556, females=549; 2 participants were removed for missing waist circumference and 6 participants were removed for being highly influential data points.

[b] Model 3 is adjusted for age, sex, race, physical activeness, sedentary behaviour, education, and smoking status. n=1086; 2 participants were removed for missing waist circumference measurements and 6 participants were removed for being highly influential data points.

[c] Model 3 is adjusted for age, sex, race, physical activeness, sedentary behaviour, and smoking status. n=1099; 2 participants were removed for missing waist circumference measurements and 7 participants were removed for being highly influential data points.

[d] Model 3 is adjusted for age, sex, race, physical activeness, education, and smoking status. n=1105; 2 participants were removed for missing waist circumference measurements and 5 participants were removed for being highly influential data points.

* Model is significant (<0.01)

### 5.1.3 Organophosphate Diabetes Measures

#### Glycated Hemoglobin (HbA1c)

Both unadjusted and creatinine-adjusted log-transformed urinary OP metabolites had insignificant associations with HbA1c (Table 5.7). Sex, age, and race were the only covariates that were significant for every OP in predicting BMI. Education was also significant for 3 of the 4 OPs and were adjusted for in their respective models.

**Table 5.7 Linear regression models predicting HbA1c levels from log-transformed urinary organophosphates levels.**

| Metabolite | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| | ß (99% CI) | p-value | ß (99% CI) | p-value |
| **DEP[a]** | | | | |
| Model 1 | 0.04 (-0.05, 0.12) | 0.22 | 0.07 (-0.04, 0.17) | 0.07 |
| Model 2 | 0.03 (-0.03, 0.09)* | 0.12 | 0.05 (-0.05, 0.15)* | 0.17 |
| Model 3 | 0.04 (-0.02, 0.10)* | 0.09 | 0.05 (-0.05, 0.15)* | 0.15 |
| **DETP[b]** | | | | |
| Model 1 | 0.00 (-0.06, 0.07) | 0.96 | 0.00 (-0.05, 0.06) | 0.82 |
| Model 2 | 0.00 (-0.05, 0.05)* | 0.90 | -0.01 (-0.05, 0.04)* | 0.68 |
| Model 3 | 0.00 (-0.04, 0.05)* | 0.80 | 0.00 (-0.05, 0.04)* | 0.90 |
| **DMP[c]** | | | | |
| Model 1 | -0.01 (-0.06, 0.04) | 0.59 | -0.01 (-0.08, 0.06) | 0.74 |
| Model 2 | -0.01 (-0.06, 0.04)* | 0.43 | -0.02 (-0.10, 0.06)* | 0.44 |
| Model 3 | 0.00 (-0.05, 0.05)* | 0.97 | -0.01 (-0.10, 0.08)* | 0.81 |
| **DMTP[d]** | | | | |
| Model 1 | 0.00 (-0.04, 0.04) | 0.98 | 0.00 (-0.03, 0.04) | 0.90 |
| Model 2 | -0.01 (-0.04, 0.02)* | 0.37 | -0.02 (-0.05, 0.02)* | 0.22 |
| Model 3 | 0.00 (-0.03, 0.03)* | 0.76 | 0.00 (-0.04, 0.03)* | 0.80 |

**Abbreviations:** HbA1c, glycated hemoglobin; DEP, diethylphosphate; DETP, diethylthiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; ß, regression coefficient; CI, confidence interval

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, and race. n=1091; 19 participants were removed for HbA1c measurements, and 3 participants were removed for being highly influential data points.

[b] Model 3 is adjusted for age, sex, race, and education. n=1069; 19 participants were removed for HbA1c measurements, and 6 participants were removed for being highly influential data points.

[c] Model 3 is adjusted for age, sex, race, and education. n=1082; 19 participants were removed for HbA1c measurements, and 7 participants were removed for being highly influential data points.

[d] Model 3 is adjusted for age, sex, race, and education. n=1087; 19 participants were removed for HbA1c measurements, and 6 participants were removed for being highly influential data points.

* Model is significant (<0.01)

**Self-Reported Diabetes**

Tables 5.8 and 5.9 present the results from logistic regression analysis for the associations of both unadjusted and creatinine-adjusted log-transformed urinary OP concentrations with the prevalence of diabetes. For the unadjusted models, there was a dose-response tendency for the association between DEP and prevalent diabetes and each 1 unit increase in log-transformed DEP was associated with an odds ratio of 1.68 (99% CI: 0.99, 2.89) for diabetes after adjustment for covariates (Table 5.9). Other urinary concentrations of OPs were not significantly associated with the prevalence of diabetes.

For creatinine-adjusted log-transformed urinary OP concentration quartiles, DEP was the only OP to show a significant odds ratio (OR: 4.57, 99% CI: 1.09, 19.24) for diabetes when comparing the $4^{th}$ quartile with the $1^{st}$ quartile (Table 5.8). For each 1 unit increase in creatinine-adjusted log-transformed DEP, the odds ratio was 1.80 (99% CI: 0.99, 3.26) for having diabetes (Table 5.9). Higher concentrations of DEP and DMP tended to be associated with a higher risk of having diabetes whereas higher concentrations of DETP and DMTP tended to be associated with a lower risk of having diabetes (Table 5.9).

**Table 5.8 Odds ratios (ORs) and 99% confidence intervals (CIs) for the 4th, 3rd, and 2nd quartiles compared to the 1st quartile for urinary concentrations of organophosphates in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **OR (99% CI)** | **p-value** | **OR (99% CI)** | **p-value** |
| **DEP[a]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.79 (0.29, 10.82) | 0.42 | 3.04 (1.01, 9.21) | <0.01 |
| Quartile 3 | 1.98 (0.31, 12.77) | 0.35 | 1.05 (0.36, 3.09) | 0.91 |
| Quartile 2 | 1.04 (0.09, 11.38) | 0.97 | 2.01 (0.55, 7.44) | 0.17 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 1.95 (0.42, 9.09) | 0.27 | 2.96 (0.87, 10.10) | 0.02 |
| Quartile 3 | 1.78 (0.34, 9.38) | 0.38 | 0.90 (0.27, 3.02) | 0.83 |
| Quartile 2 | 1.08 (0.07, 15.70) | 0.95 | 1.74 (0.52, 5.86) | 0.24 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 2.85 (0.48, 16.78) | 0.13 | 4.57 (1.09, 19.24) | <0.01 |
| Quartile 3 | 2.58 (0.48, 13.75) | 0.15 | 1.29 (0.28, 6.07) | 0.68 |
| Quartile 2 | 1.94 (0.12, 31.41) | 0.55 | 1.69 (0.55, 5.16) | 0.23 |
| Quartile 1 | Reference | | Reference | |
| **DETP[b]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 0.88 (0.12, 6.57) | 0.88 | 0.61 (0.10, 3.75) | 0.54 |
| Quartile 3 | 1.18 (0.17, 8.41) | 0.84 | 0.96 (0.18, 5.21) | 0.95 |
| Quartile 2 | 0.90 (0.07, 11.83) | 0.92 | 0.68 (0.14, 3.27) | 0.92 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 0.94 (0.15, 5.92) | 0.94 | 0.54 (0.08, 3.70) | 0.42 |
| Quartile 3 | 1.18 (0.17, 8.10) | 0.84 | 0.88 (0.12, 6.65) | 0.88 |
| Quartile 2 | 1.13 (0.07, 19.32) | 0.92 | 0.78 (0.16, 3.84) | 0.70 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 1.01 (0.12, 8.45) | 0.99 | 0.53 (0.05, 5.24) | 0.49 |
| Quartile 3 | 1.34 (0.17, 10.43) | 0.73 | 1.02 (0.14, 7.28) | 0.98 |
| Quartile 2 | 1.21 (0.06, 23.54) | 0.88 | 0.83 (0.19, 3.59) | 0.76 |
| Quartile 1 | Reference | | Reference | |
| **DMP[c]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 2.08 (0.75, 5.75) | 0.07 | 0.74 (0.07, 8.24) | 0.76 |
| Quartile 3 | 1.33 (0.26, 6.78) | 0.67 | 1.76 (0.32, 9.60) | 0.40 |
| Quartile 2 | 3.07 (0.45, 20.70) | 0.13 | 0.79 (0.10, 6.40) | 0.78 |

| | | | | |
|---|---|---|---|---|
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 2** | | | | |
| Quartile 4 | 2.29 (0.73, 7.18) | 0.06 | 0.68 (0.04, 11.22) | 0.74 |
| Quartile 3 | 1.36 (0.26, 7.17) | 0.64 | 1.61 (0.19, 13.83) | 0.58 |
| Quartile 2 | 3.50 (0.39, 31.61) | 0.14 | 0.70 (0.07, 6.96) | 0.70 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 3.18 (0.57, 17.71) | 0.09 | 1.06 (0.08, 14.47) | 0.96 |
| Quartile 3 | 1.38 (0.19, 10.17) | 0.69 | 1.88 (0.25, 14.05) | 0.42 |
| Quartile 2 | 3.56 (0.32, 40.00) | 0.18 | 0.57 (0.07, 4.77) | 0.50 |
| Quartile 1 | Reference | | Reference | |
| **DMTP[d]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 0.67 (0.19, 2.36) | 0.42 | 0.74 (0.11, 4.85) | 0.70 |
| Quartile 3 | 0.71 (0.09, 5.68) | 0.68 | 0.77 (0.05, 10.72) | 0.81 |
| Quartile 2 | 0.82 (0.07, 8.97) | 0.84 | 1.17 (0.18, 7.78) | 0.84 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 2** | | | | |
| Quartile 4 | 0.69 (0.16, 3.04) | 0.53 | 0.68 (0.08, 5.75) | 0.98 |
| Quartile 3 | 0.58 (0.08, 4.21) | 0.49 | 0.63 (0.03, 12.18) | 0.71 |
| Quartile 2 | 0.75 (0.05, 11.51) | 0.80 | 1.02 (0.13, 8.31) | 0.70 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 0.85 (0.13, 5.40) | 0.83 | 0.85 (0.10, 7.32) | 0.86 |
| Quartile 3 | 0.55 (0.07, 4.35) | 0.47 | 0.64 (0.03, 13.79) | 0.72 |
| Quartile 2 | 0.85 (0.04, 19.91) | 0.90 | 0.95 (0.09, 10.52) | 0.96 |
| Quartile 1 | Reference | | Reference | |

**Abbreviations:** DEP, diethylphosphate; DETP, diethylthiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, body mass index and education. n=1113.

[b] Model 3 is adjusted for age, sex, body mass index and sedentary behaviour. n=1094.

[c] Model 3 is adjusted for age, sex, body mass index and education. n=1108.

[d] Model 3 is adjusted for age, sex, body mass index and sedentary behaviour. n=1087.

**Table 5.9 Odds ratios (ORs) and 99% confidence intervals (CIs) for urinary concentrations (µg/L) of organophosphates as continuous variables in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **OR (99% CI)** | **p-value** | **OR (99% CI)** | **p-value** |
| **DEP[a]** | | | | |
| Model 1 | 1.40 (0.88, 2.23) | 0.06 | 1.46 (0.85, 2.52) | 0.07 |
| Model 2 | 1.50 (0.94, 2.39) | 0.03 | 1.46 (0.85, 3.92) | 0.07 |
| Model 3 | 1.68 (0.98, 2.89) | 0.01 | 1.80 (0.99, 3.26) | 0.01 |
| **DETP[b]** | | | | |
| Model 1 | 0.93 (0.60, 1.44) | 0.68 | 0.88 (0.51, 1.49) | 0.55 |
| Model 2 | 0.93 (0.62, 1.39) | 0.66 | 0.85 (0.46, 1.55) | 0.50 |
| Model 3 | 0.98 (0.62, 1.55) | 0.91 | 0.91 (0.47, 1.76) | 0.72 |
| **DMP[c]** | | | | |
| Model 1 | 1.09 (0.77, 1.54) | 0.53 | 1.02 (0.60, 1.73) | 0.93 |
| Model 2 | 1.10 (0.74, 1.63) | 0.54 | 0.98 (0.47, 2.04) | 0.95 |
| Model 3 | 1.24 (0.75, 2.04) | 0.27 | 1.17 (0.58, 2.37) | 0.58 |
| **DMTP[d]** | | | | |
| Model 1 | 0.90 (0.65, 1.25) | 0.42 | 0.85 (0.58, 1.24) | 0.27 |
| Model 2 | 0.89 (0.61, 1.31) | 0.44 | 0.80 (0.46, 1.39) | 0.30 |
| Model 3 | 0.95 (0.60, 1.50) | 0.79 | 0.87 (0.52, 1.44) | 0.49 |

**Abbreviations:** DEP, diethylphosphate; DETP, diethylthiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1113.

[b] Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1094.

[c] Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1108.

[d] Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1087.

## 6. Pyrethroids

### 6.1 Results

#### 6.1.1 Baseline Characteristics

Tables 6.1 to 6.4 depicts the baseline characteristic of the study population for each urinary pyrethroid metabolite. The total population for *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA were 1,095, 1,141, 1,139, and 1,141, respectively. Among these study populations, the crude weighted prevalence of diabetes varied between 7.7% to 8.3%. The geometric means of *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA were 0.016 µg/g (95% CI: 0.014, 0.021), 0.179 µg/g (95% CI: 0.126, 0.254), 0.515 µg/g (95% CI: 0.411, 0.647), and 0.260 µg/g (95% CI: 0.185, 0.364), respectively. The medians of *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA were 0.016 µg/g (95% CI: 0.013, 0.020), 0.147 µg/g (95% CI: 0.102, 0.192), 0.388 µg/g (95% CI: 0.299, 0.476), and 0.212 µg/g (95% CI: 0.146, 0.278).

The geometric mean for each of the urinary pyrethroids tended to be higher for individuals who were female, non-white, active, sedentary, had a post-secondary degree/diploma, had a BMI of 25 or higher, had diabetes, or did not smoke. There was also a higher sampling variability for males, the 50-59, 60-69 and 70+ age groups, those with a BMI of less than 25, daily smokers, those who were non-white, or those who were inactive.

For *cis*-DBCA, females had a geometric mean of 0.019 µg/g (95% CI: 0.013, 0.029) as compared to males who had a geometric mean of 0.014 µg/g (95% CI: 0.009, 0.021). For *cis*-DCCA, females had a geometric mean of 0.231 µg/g (95% CI: 0.122, 0.438) as compared to males who had a geometric mean of 0.138 µg/g (95% CI: 0.065, 0.296). For 3-PBA, females had a geometric mean of 0.726 µg/g (95% CI: 0.360, 1.464) as compared to males who had a

geometric mean of 0.369 µg/g (95% CI: 0.147, 0.924). For *trans*-DCCA, females had a geometric mean of 0.355 µg/g (95% CI: 0.175, 0.641) as compared to males who had a geometric mean of 0.202 µg/g (95% CI: 0.097, 0.420). *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA geometric means were 35.7%, 67.4%, 96.7%, and 75.7% higher in females than in males, respectively.

The median tended to be higher across all pyrethroids for individuals who were female, non-white, physically active, had a post-secondary degree/diploma, or were non-smokers. There was also a higher sampling variability of medians for those who had a waist circumference classified as overweight, had diabetes, had no post-secondary degree/diploma, were inactive or sedentary, or smoked daily. There was a significant difference in pyrethroid metabolite concentrations between males and females, and between active and inactive respondents.

For *cis*-DBCA, females had a median of 0.020 µg/g (95% CI: 0.015, 0.025) as compared to males who had a median of 0.012 µg/g (95% CI: 0.010, 0.015). For *cis*-DCCA, females had a median of 0.183 µg/g (95% CI: 0.136, 0.230) as compared to males who had a median of 0.109 µg/g (95% CI: 0.053, 0.164). For 3-PBA, females had a median of 0.519 µg/g (95% CI: 0.377, 0.660) as compared to males who had a median of 0.277 µg/g (95% CI: 0.194, 0.360). For *trans*-DCCA, females had a median of 0.264 µg/g (95% CI: 0.183, 0.344) as compared to males who had a median of 0.146 µg/g (95% CI: 0.076, 0.216. *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA medians were 66.6%, 67.9%, 87.4%, and 80.8% higher in females than in males, respectively.

**Table 6.1 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*cis*-DBCA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)[*] | Geometric Mean (µg/g) | Median (µg/g) | p-value[**] |
|---|---|---|---|---|
| **Total** | 1095 (100.0) | 0.016 (0.014, 0.021) | 0.016 (0.013, 0.020) | |
| **Sex** | | | | <0.001 |
| Male | 550 (49.4) | 0.014 (0.009, 0.021)[E] | 0.012 (0.010, 0.015) | |
| Female | 545 (50.6) | 0.019 (0.013, 0.029) | 0.020 (0.015, 0.025) | |
| **Age (yrs)** | | | | 0.622 |
| 18-49 | 656 (57.0) | 0.017 (0.014, 0.021) | 0.015 (0.012, 0.019) | |
| 50-59 | 120 (18.4) | 0.011 (0.004, 0.031)[F] | 0.011 (0.005, 0.017)[E] | |
| 60-69 | 214 (17.5) | 0.020 (0.012, 0.033)[E] | 0.019 (0.012, 0.025) | |
| 70-79 | 105 (7.1) | 0.023 (0.011, 0.051)[F] | 0.023 (0.016, 0.031) | |
| **Body mass index** | | | | 0.114 |
| Underweight and healthy | 391 (41.9) | 0.018 (0.013, 0.025)[E] | 0.015 (0.009, 0.021)[E] | |
| Overweight | 380 (29.8) | 0.015 (0.010, 0.025)[E] | 0.016 (0.011, 0.021) | |
| Obese class | 324 (28.3) | 0.016 (0.012, 0.022) | 0.017 (0.011, 0.022)[E] | |
| **Waist circumference** | | | | 0.265 |
| Underweight and healthy | 396 (40.6) | 0.017 (0.014, 0.021) | 0.014 (0.009, 0.019) | |
| Overweight | 230 (18.0) | 0.013 (0.007, 0.025)[E] | 0.012 (0.007, 0.017)[E] | |
| Obese class | 469 (41.4) | 0.017 (0.014, 0.022) | 0.019 (0.016, 0.022) | |
| **Diabetes** | | | | 0.173 |
| No | 1023 (91.7) | 0.016 (0.013, 0.020) | 0.016 (0.013, 0.020) | |
| Yes | 72 (8.3) | 0.018 (0.009, 0.033)[E] | 0.013 (0.003, 0.024)[F] | |
| **Race** | | | | 0.341 |
| White | 837 (70.2) | 0.016 (0.013, 0.019) | 0.015 (0.012, 0.019) | |
| Non-White | 258 (29.8) | 0.018 (0.013, 0.027)[E] | 0.019 (0.014, 0.025) | |
| **Physical activity** | | | | 0.043 |
| Active | 595 (51.7) | 0.017 (0.014, 0.022) | 0.017 (0.014, 0.021) | |
| Inactive | 500 (48.3) | 0.015 (0.011, 0.022)[E] | 0.015 (0.007, 0.023)[E] | |
| **Sedentary behaviour** | | | | 0.612 |
| Healthy | 484 (46.5) | 0.017 (0.013, 0.023) | 0.017 (0.012, 0.022) | |
| Moderately sedentary | 459 (39.9) | 0.015 (0.011, 0.020) | 0.014 (0.011, 0.018) | |
| Sedentary | 152 (13.6) | 0.019 (0.012, 0.030)[E] | 0.020 (0.014, 0.026)[E] | |
| **Highest level of education** | | | | 0.463 |
| Less than secondary school | 101 (6.4) | 0.015 (0.011, 0.020) | 0.016 (0.009, 0.023)[E] | |
| Secondary school | 287 (27.7) | 0.015 (0.010, 0.021) | 0.013 (0.006, 0.021)[E] | |
| Post-secondary degree/diploma | 707 (65.8) | 0.017 (0.014, 0.021) | 0.017 (0.013, 0.020) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | <0.001 |
| Non-smoker | 570 (50.6) | 0.019 (0.013, 0.029)[E] | 0.020 (0.014, 0.026) | |
| Former smoker | 322 (30.2) | 0.016 (0.012, 0.020) | 0.016 (0.011 0.020) | |
| Daily smoker | 203 (19.2) | 0.012 (0.005, 0.029)[F] | 0.012 (0.007, 0.017)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Table 6.2 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane (*cis*-DCCA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1141 (100.0) | 0.179 (0.126, 0.254) | 0.147 (0.102, 0.192) | |
| **Sex** | | | | <0.001 |
| Male | 577 (50.4) | 0.138 (0.065, 0.296)[F] | 0.109 (0.053, 0.164)[E] | |
| Female | 564 (49.6) | 0.231 (0.122, 0.438)[E] | 0.183 (0.136, 0.230) | |
| **Age (yrs)** | | | | 0.074 |
| 18-49 | 681 (57.2) | 0.171 (0.106, 0.276)[E] | 0.142 (0.072, 0.213)[E] | |
| 50-59 | 126 (18.3) | 0.177 (0.114, 0.275)[E] | 0.145 (0.089, 0.202)[E] | |
| 60-69 | 219 (17.0) | 0.195 (0.130, 0.292)[E] | 0.154 (0.091, 0.217)[E] | |
| 70-79 | 115 (7.5) | 0.206 (0.116, 0.367)[E] | 0.162 (0.099, 0.225)[E] | |
| **Body mass index** | | | | 0.599 |
| Underweight and healthy | 410 (41.6) | 0.215 (0.119, 0.390)[E] | 0.175 (0.106, 0.245)[E] | |
| Overweight | 393 (30.5) | 0.171 (0.119, 0.245) | 0.143 (0.084, 0.202)[E] | |
| Obese class | 338 (27.9) | 0.142 (0.074, 0.272)[E] | 0.122 (0.081, 0.162) | |
| **Waist circumference** | | | | 0.091 |
| Underweight and healthy | 413 (41.1) | 0.195 (0.114, 0.333)[E] | 0.174 (0.102, 0.245)[E] | |
| Overweight | 236 (18.3) | 0.192 (0.138, 0.266) | 0.181 (0.106, 0.257)[E] | |
| Obese class | 492 (40.6) | 0.158 (0.103, 0.242)[E] | 0.135 (0.101, 0.170) | |
| **Diabetes** | | | | 0.383 |
| No | 1066 (91.7) | 0.178 (0.121, 0.261)[E] | 0.146 (0.097, 0.189) | |
| Yes | 75 (8.3) | 0.189 (0.139, 0.257) | 0.166 (0.049, 0.284)[E] | |
| **Race** | | | | <0.001 |
| White | 875 (70.7) | 0.167 (0.114, 0.243)[E] | 0.143 (0.097, 0.189) | |
| Non-White | 266 (29.3) | 0.211 (0.132, 0.339)[E] | 0.178 (0.123, 0.233) | |
| **Physical activity** | | | | 0.032 |
| Active | 627 (52.6) | 0.197 (0.140, 0.279) | 0.173 (0.125, 0.221) | |
| Inactive | 514 (47.4) | 0.160 (0.090, 0.283)[E] | 0.128 (0.068, 0.188)[E] | |
| **Sedentary behaviour** | | | | 0.872 |
| Healthy | 510 (47.4) | 0.192 (0.130, 0.283)[E] | 0.160 (0.089, 0.232)[E] | |
| Moderately sedentary | 478 (39.6) | 0.153 (0.094, 0.249) | 0.137 (0.088, 0.186) | |
| Sedentary | 153 (13.0) | 0.220 (0.099, 0.491) | 0.130 (0.067, 0.192)[E] | |
| **Highest level of education** | | | | <0.001 |
| Less than secondary school | 106 (6.5) | 0.131 (0.059, 0.288)[F] | 0.103 (0.049, 0.157)[E] | |
| Secondary school | 300 (27.2) | 0.152 (0.070, 0.329)[F] | 0.126 (0.064, 0.187)[E] | |
| Post-secondary degree/diploma | 735 (66.3) | 0.197 (0.139, 0.279) | 0.169 (0.122, 0.216) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.011 |
| Non-smoker | 591 (50.3) | 0.203 (0.137, 0.302)[E] | 0.173 (0.141, 0.205) | |
| Former smoker | 340 (30.3) | 0.179 (0.121, 0.264)[E] | 0.142 (0.071, 0.213) [E] | |
| Daily smoker | 210 (19.4) | 0.128 (0.050, 0.325)[F] | 0.100 (0.031, 0.169)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Table 6.3 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary 3-phenoxybenzoic acid (3-PBA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1139 (100.0) | 0.515 (0.411, 0.647) | 0.388 (0.299, 0.476) | |
| **Sex** | | | | <0.001 |
| Male | 574 (50.5) | 0.369 (0.147, 0.924)[F] | 0.277 (0.194, 0.360) | |
| Female | 565 (49.5) | 0.726 (0.360, 1.464)[E] | 0.519 (0.377, 0.660) | |
| **Age (yrs)** | | | | 0.323 |
| 18-49 | 678 (56.9) | 0.514 (0.375, 0.705) | 0.370 (0.239, 0.501) | |
| 50-59 | 126 (18.4) | 0.476 (0.318, 0.712)[E] | 0.321 (0.139, 0.503)[E] | |
| 60-69 | 220 (17.2) | 0.545 (0.366, 0.812)[E] | 0.454 (0.194, 0.713)[E] | |
| 70-79 | 115 (7.5) | 0.562 (0.361, 0.874)[E] | 0.415 (0.247, 0.583)[E] | |
| **Body mass index** | | | | 0.008 |
| Underweight and healthy | 409 (41.8) | 0.700 (0.363, 1.349)[E] | 0.578 (0.404, 0.752) | |
| Overweight | 393 (30.6) | 0.428 (0.261, 0.701)[E] | 0.351 (0.264, 0.438) | |
| Obese class | 337 (27.6) | 0.398 (0.190, 0.834)[F] | 0.282 (0.203, 0.360) | |
| **Waist circumference** | | | | 0.682 |
| Underweight and healthy | 414 (41.4) | 0.587 (0.382, 0.900)[E] | 0.469 (0.355, 0.583) | |
| Overweight | 235 (18.2) | 0.529 (0.401, 0.699) | 0.390 (0.211, 0.568)[E] | |
| Obese class | 490 (40.4) | 0.446 (0.296, 0.673)[E] | 0.309 (0.227, 0.392) | |
| **Diabetes** | | | | 0.858 |
| No | 1066 (92.3) | 0.507 (0.390, 0.658) | 0.381 (0.285, 0.477) | |
| Yes | 73 (7.7) | 0.632 (0.333, 1.200)[E] | 0.550 (0.000, 1.159)[F] | |
| **Race** | | | | 0.111 |
| White | 874 (70.6) | 0.474 (0.357, 0.630) | 0.360 (0.274, 0.446) | |
| Non-White | 265 (29.4) | 0.630 (0.409, 0.970)[E] | 0.543 (0.426, 0.659)[E] | |
| **Physical activity** | | | | 0.037 |
| Active | 627 (53.1) | 0.562 (0.428, 0.739) | 0.410 (0.313, 0.508) | |
| Inactive | 512 (46.9) | 0.467 (0.299, 0.731)[E] | 0.371 (0.231, 0.510)[E] | |
| **Sedentary behaviour** | | | | 0.641 |
| Healthy | 508 (47.6) | 0.543 (0.414, 0.712) | 0.459 (0.346, 0.572) | |
| Moderately sedentary | 478 (39.4) | 0.458 (0.338, 0.620) | 0.360 (0.276, 0.444) | |
| Sedentary | 153 (13.0) | 0.610 (0.302, 1.231)[E] | 0.356 (0.186, 0.527)[E] | |
| **Highest level of education** | | | | <0.001 |
| Less than secondary school | 107 (6.6) | 0.396 (0.196, 0.799)[E] | 0.255 (0.105, 0.404)[E] | |
| Secondary school | 298 (27.3) | 0.446 (0.235, 0.846)[E] | 0.287 (0.157, 0.418)[E] | |
| Post-secondary degree/diploma | 734 (66.1) | 0.562 (0.434, 0.726) | 0.431 (0.353, 0.508) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.048 |
| Non-smoker | 592 (50.0) | 0.550 (0.409, 0.740) | 0.414 (0.320, 0.507) | |
| Former smoker | 338 (30.4) | 0.527 (0.423, 0.657) | 0.412 (0.322, 0.503) | |
| Daily smoker | 209 (19.6) | 0.421 (0.218, 0.812)[E] | 0.339 (0.116, 0.562)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Table 6.4 Geometric means and medians (95% confidence intervals) of creatinine-adjusted urinary *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*trans*-DCCA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)* | Geometric Mean (µg/g) | Median (µg/g) | p-value** |
|---|---|---|---|---|
| **Total** | 1141 (100.0) | 0.260 (0.185, 0.364) | 0.212 (0.146, 0.278) | |
| **Sex** | | | | <0.001 |
| Male | 575 (50.2) | 0.202 (0.097, 0.420)[E] | 0.146 (0.076, 0.216)[E] | |
| Female | 566 (49.8) | 0.335 (0.175, 0.641)[E] | 0.264 (0.183, 0.344) | |
| **Age (yrs)** | | | | 0.604 |
| 18-49 | 679 (57.0) | 0.260 (0.164, 0.410)[E] | 0.217 (0.126, 0.308)[E] | |
| 50-59 | 126 (18.3) | 0.237 (0.138, 0.408)[E] | 0.240 (0.157, 0.322) | |
| 60-69 | 220 (17.2) | 0.285 (0.192, 0.425)[E] | 0.212 (0.100, 0.324)[E] | |
| 70-79 | 116 (7.5) | 0.261 (0.164, 0.417)[E] | 0.182 (0.057, 0.306)[E] | |
| **Body mass index** | | | | 0.043 |
| Underweight and healthy | 410 (41.6) | 0.351 (0.170, 0.727)[E] | 0.267 (0.144, 0.390)[E] | |
| Overweight | 393 (30.5) | 0.228 (0.145, 0.359)[E] | 0.191 (0.130, 0.252) | |
| Obese class | 338 (27.9) | 0.190 (0.080, 0.451)[F] | 0.152 (0.078, 0.226)[E] | |
| **Waist circumference** | | | | 0.802 |
| Underweight and healthy | 414 (41.1) | 0.316 (0.172, 0.580)[E] | 0.174 (0.102, 0.245)[E] | |
| Overweight | 235 (18.1) | 0.265 (0.205, 0.344) | 0.181 (0.106, 0.257)[E] | |
| Obese class | 492 (40.8) | 0.211 (0.117, 0.381)[E] | 0.135 (0.101, 0.170)[E] | |
| **Diabetes** | | | | 0.834 |
| No | 1066 (91.7) | 0.260 (0.181, 0.374) | 0.146 (0.097, 0.189)[E] | |
| Yes | 75 (8.3) | 0.252 (0.169, 0.374)[E] | 0.166 (0.049, 0.284)[E] | |
| **Race** | | | | 0.984 |
| White | 875 (70.7) | 0.243 (0.170, 0.348) | 0.210 (0.137, 0.283) | |
| Non-White | 266 (29.3) | 0.303 (0.192, 0.478)[E] | 0.237 (0.185, 0.289) | |
| **Physical activity** | | | | 0.037 |
| Active | 627 (52.7) | 0.291 (0.206, 0.413) | 0.261 (0.195, 0.328) | |
| Inactive | 514 (47.3) | 0.228 (0.125, 0.417)[E] | 0.163 (0.084, 0.243)[E] | |
| **Sedentary behaviour** | | | | 0.818 |
| Healthy | 509 (47.3) | 0.278 (0.191, 0.404)[E] | 0.244 (0.177, 0.312) | |
| Moderately sedentary | 479 (39.7) | 0.227 (0.144, 0.357)[E] | 0.173 (0.098, 0.249)[E] | |
| Sedentary | 153 (13.0) | 0.306 (0.136, 0.687)[F] | 0.184 (0.080, 0.287)[E] | |
| **Highest level of education** | | | | <0.001 |
| Less than secondary school | 106 (6.5) | 0.203 (0.109, 0.380)[E] | 0.147 (0.053, 0.241)[E] | |
| Secondary school | 300 (27.2) | 0.219 (0.099, 0.483)[F] | 0.188 (0.104, 0.272)[E] | |
| Post-secondary degree/diploma | 735 (66.3) | 0.285 (0.205, 0.397) | 0.241 (0.173, 0.310) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.382 |
| Non-smoker | 591 (50.3) | 0.292 (0.201, 0.425)[E] | 0.241 (0.183, 0.299) | |
| Former smoker | 340 (30.3) | 0.255 (0.176, 0.370)[E] | 0.213 (0.126, 0.300) [E] | |
| Daily smoker | 210 (19.4) | 0.196 (0.090, 0.428)[F] | 0.150 (0.062, 0.238)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

### 6.1.*2* Pyrethroid Obesity Measures

#### Body Mass Index

For unadjusted log-transformed urinary pyrethroid concentrations, there was no significant association found with BMI (Table 6.5). For creatinine-adjusted log-transformed urinary pyrethroid concentrations, 3-PBA and *trans*-DCCA were the two pyrethroids metabolites that were significantly negatively associated with BMI. *cis*-DBCA and *cis*-DCCA did not have a significant association between their concentrations and BMI. For every 1 unit increase in log-transformed 3-PBA and log-transformed *trans*-DCCA, the BMI increased by -0.68 (99% CI: -1.24, -0.13) and -0.70 (99% CI: -1.36, -0.03) respectively. Age and race were the only covariates that was significant for every pyrethroid in predicting BMI.

**Table 6.5 Linear regression models predicting BMI from log-transformed urinary pyrethroids levels.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **ß (99% CI)** | **p-value** | **ß (99% CI)** | **p-value** |
| ***cis*-DBCA[a]** | | | | |
| Model 1 | 0.41 (-0.23, 1.05) | 0.07 | -0.08 (-0.70, 0.54) | 0.70 |
| Model 2 | 0.46 (-0.16, 1.07)* | 0.04 | -0.14 (-0.84, 0.57)* | 0.56 |
| Model 3 | 0.51 (-0.09, 1.11)* | 0.02 | -0.08 (-0.79, 0.63)* | 0.74 |
| ***cis*-DCCA[b]** | | | | |
| Model 1 | -0.10 (-0.84, 0.64) | 0.68 | -0.51 (-1.14, 0.12) | 0.03 |
| Model 2 | -0.07 (-0.72, 0.58)* | 0.74 | -0.56 (-1.18, 0.06)* | 0.02 |
| Model 3 | 0.00 (-0.68, 0.67)* | 0.99 | -0.48 (-1.09, 0.13)* | 0.03 |
| **3-PBA[c]** | | | | |
| Model 1 | -0.30 (-0.80, 0.21) | 0.10 | -0.67 (-1.14, -0.21)* | <0.01 |
| Model 2 | -0.28 (-0.75, 0.20)* | 0.10 | -0.75 (-1.28, -0.22)* | <0.01 |
| Model 3 | -0.22 (-0.75, 0.32)* | 0.23 | -0.68 (-1.24, -0.13)* | <0.01 |
| ***trans*-DCCA[d]** | | | | |
| Model 1 | -0.43 (-1.20, 0.33) | 0.11 | -0.77 (-1.51, -0.02)* | 0.01 |
| Model 2 | -0.35 (-1.00, 0.29)* | 0.12 | -0.75 (-1.44, -0.05)* | 0.01 |
| Model 3 | -0.31 (-0.93, 0.31)* | 0.99 | -0.70 (-1.36, -0.03)* | 0.01 |

**Abbreviations:** BMI, Body Mass Index; *cis*-DBCA, *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; 3-PBA, 3-Phenoxybenzoic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; ß, regression coefficient; CI, confidence interval

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, race, and smoking status. n=1091; 4 participants were removed for being highly influential data points.

[b] Model 3 is adjusted for age, sex, race, and education. n=1139; 2 participants were removed for being highly influential data points.

[c] Model 3 is adjusted for age, sex, race, physical activeness, and smoking status. n=1132; 7 participants were removed for being highly influential data points.

[d] Model 3 is adjusted for age, sex, race, and education. n=1137; 4 participants were removed for being highly influential data points.

* Model is significant (<0.01)

**Waist Circumference**

For unadjusted log-transformed urinary pyrethroid concentrations, there was no significant association found with WC (Table 6.6). For creatinine-adjusted log-transformed urinary pyrethroid concentrations, 3 of the 4 pyrethroids metabolites were significantly negatively associated with WC. For every 1 unit increase in log-transformed *cis*-DCCA, log-transformed 3-PBA, and log-transformed *trans*-DCCA, the WC increased by -1.60cm (99% CI: -3.14, -0.07), -2.40cm (99% CI: -3.82, -0.99), and -1.95 (99% CI: -3.33, -0.56), respectively. Age, race, and smoking status were the covariates that were significant for every pyrethroid in predicting WC.

**Table 6.6 Linear regression models predicting waist circumference (cm) from log-transformed urinary pyrethroids levels.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **ß (99% CI)** | **p-value** | **ß (99% CI)** | **p-value** |
| ***cis*-DBCA[a]** | | | | |
| Model 1 | 1.00 (-1.13, 3.12) | 0.17 | -0.48 (-2.05, 1.10)* | 0.37 |
| Model 2 | 1.24 (-0.69, 3.16)* | 0.07 | -0.33 (-2.03, 1.36)* | 0.55 |
| Model 3 | 1.50 (-0.44, 3.45)* | 0.04 | -0.04 (-1.73, 1.65)* | 0.94 |
| ***cis*-DCCA[b]** | | | | |
| Model 1 | -0.71 (-3.01, 1.58) | 0.36 | -1.94 (-3.83, -0.04)* | 0.01 |
| Model 2 | -0.46 (-2.27, 1.34)* | 0.44 | -1.77 (-3.40, -0.14)* | 0.01 |
| Model 3 | -0.31 (-2.12, 1.50)* | 0.61 | -1.60 (-3.14, -0.07)* | 0.01 |
| **3-PBA[c]** | | | | |
| Model 1 | -1.77 (-3.73, 0.18) | 0.02 | -2.91 (-4.47, -1.35)* | <0.01 |
| Model 2 | -1.38 (-2.86, 0.09)* | 0.01 | -2.60 (-4.03, -1.16)* | <0.01 |
| Model 3 | -1.18 (-2.63, 0.28)* | 0.03 | -2.40 (-3.82, -0.99)* | <0.01 |
| ***trans*-DCCA[d]** | | | | |
| Model 1 | -1.54 (-3.63, 0.56) | 0.04 | -2.52 (-4.31, -0.74)* | <0.01 |

| | | | | |
|---|---|---|---|---|
| Model 2 | -1.15 (-2.65, 0.34)* | 0.04 | -2.17 (-3.60, -0.74)* | <0.01 |
| Model 3 | -0.95 (-2.41, 0.52)* | 0.07 | -1.95 (-3.33, -0.56)* | <0.01 |

**Abbreviations:** *cis*-DBCA, *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; 3-PBA, 3-Phenoxybenzoic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; ß, regression coefficient, CI, confidence interval

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, race, and smoking status. n=1089; 2 participants were removed for missing waist circumference measurements, and 4 participants were removed for being highly influential data points.

[b] Model 3 is adjusted for age, sex, race, and smoking status. n=1136; 2 participants were removed for missing waist circumference measurements, and 3 participants were removed for being highly influential data points.

[c] Model 3 is adjusted for age, sex, race, education, and smoking status. n=1134; 2 participants were removed for missing waist circumference measurements, and 3 participants were removed for being highly influential data points.

[d] Model 3 is adjusted for age, sex, race, physical activeness, education, and smoking status. n=1134; 2 participants were removed for missing waist circumference measurements, and 5 participants were removed for being highly influential data points.

* Model is significant (<0.01)

### 6.1.3 Pyrethroid and Diabetes Measures

#### Glycated Hemoglobin (HbA1c)

All 4 log-transformed unadjusted and creatinine-adjusted log-transformed urinary pyrethroid metabolites had insignificant associations with HbA1c (Table 6.7). Age and race were the only covariates that were significant for every pyrethroid in predicting BMI. Education was also significant for 3 of the 4 pyrethroids and were adjusted for in their respective models.

**Table 6.7 Linear regression models predicting HbA1c levels from log-transformed urinary pyrethroids levels.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **ß (99% CI)** | **p-value** | **ß (99% CI)** | **p-value** |
| ***cis*-DBCA[a]** | | | | |
| Model 1 | 0.00 (-0.10, 0.10) | 0.99 | 0.00 (-0.10, 0.10) | 0.91 |
| Model 2 | 0.01 (-0.08, 0.10)* | 0.71 | 0.00 (-0.09, 0.10)* | 0.95 |
| Model 3 | 0.01 (-0.08, 0.10)* | 0.74 | 0.00 (-0.10, 0.09)* | 0.95 |
| ***cis*-DCCA[b]** | | | | |
| Model 1 | -0.04 (-0.12, 0.04) | 0.19 | -0.04 (-0.12, 0.04) | 0.13 |
| Model 2 | -0.03 (-0.09, 0.03)* | 0.19 | -0.04 (-0.10, 0.02)* | 0.08 |
| Model 3 | -0.03 (-0.08, 0.02)* | 0.10 | -0.04 (-0.09, 0.01)* | 0.03 |
| **3-PBA[c]** | | | | |
| Model 1 | -0.02 (-0.12, 0.07) | 0.43 | -0.02 (-0.11, 0.07) | 0.43 |
| Model 2 | -0.01 (-0.09, 0.06)* | 0.56 | -0.02 (-0.09, 0.05)* | 0.41 |
| Model 3 | -0.02 (-0.10, 0.06)* | 0.52 | -0.02 (-0.11, 0.06)* | 0.38 |
| ***trans*-DCCA[d]** | | | | |
| Model 1 | -0.04 (-0.11, 0.03) | 0.13 | -0.04 (-0.11, 0.03) | 0.08 |
| Model 2 | -0.02 (-0.08, 0.03)* | 0.19 | -0.03 (-0.09, 0.02)* | 0.08 |
| Model 3 | -0.02 (-0.08, 0.03)* | 0.18 | -0.03 (-0.09, 0.02)* | 0.07 |

**Abbreviations:** HbA1c, glycated hemoglobin; *cis*-DBCA, *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; 3-PBA, 3-Phenoxybenzoic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; ß, regression coefficient; CI, confidence interval

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, race, and education. n=1070; 21 participants were removed for HbA1c measurements, and 4 participants were removed for being highly influential data points.

[b] Model 3 is adjusted for age, sex, and race. n=1114; 21 participants were removed for HbA1c measurements, and 6 participants were removed for being highly influential data points.

[c] Model 3 is adjusted for age, sex, race, and education. n=1116; 21 participants were removed for HbA1c measurements, and 2 participants were removed for being highly influential data points

[d] Model 3 is adjusted for age, sex, race, and education. n=1116; 21 participants were removed for HbA1c measurements, and 4 participants were removed for being highly influential data points.

* Model is significant (<0.01)

**Self-Reported Diabetes**

Logistic regression modelling demonstrated no significant association of both unadjusted and creatinine-adjusted log-transformed urinary pyrethroid concentration quartiles with having diabetes (Table 6.8). For unadjusted concentrations, when modelling the pyrethroid's total concentration for having diabetes, no significant associations were observed (Table 6.9). This model showed that for each 1 unit increase in log-transformed *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA, the respondents had odds ratios of 1.19 (99% CI: 0.76, 1.86), 1.14 (99% CI: 0.82, 1.58), 1.35 (99% CI: 0.67, 2.74), and 1.11 (99% CI: 0.83, 1.48), respectively. All the associations tended to be positive, but they were not statistically significant.

For creatinine-adjusted concentrations, when modelling the pyrethroid's total concentration for having diabetes, no significant associations were observed. The models showed that for each 1 unit increase in log-transformed *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA, the respondents had odds ratios of 1.11 (99% CI: 0.56, 2.20), 1.09 (99% CI: 0.78, 1.53), 1.35 (99% CI: 0.66, 2.80), and 1.06 (99% CI: 0.80, 1.41), respectively. All the associations tended to be positive, but they were not statistically significant.

**Table 6.8 Odds ratios (OR) and 99% confidence intervals (CIs) for the 4th, 3rd, and 2nd quartiles compared to the 1st urinary concentrations of pyrethroids in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Variable** | **OR (99% CI)** | **p-value** | **OR (99% CI)** | **p-value** |
| ***cis*-DBCA[a]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.61 (0.30, 8.69) | 0.48 | 1.00 (0.21, 4.84) | 0.99 |
| Quartile 3 | 0.86 (0.13, 5.83) | 0.85 | 1.03 (0.12, 9.06) | 0.97 |
| Quartile 2 | 1.48 (0.26, 8.52) | 0.58 | 0.95 (0.17, 5.40) | 0.94 |
| Quartile 1 | Reference | | Reference | |

| | | | | |
|---|---|---|---|---|
| **Model 2** | | | | |
| Quartile 4 | 2.04 (0.36, 11.55) | 0.29 | 1.23 (0.16, 9.18) | 0.80 |
| Quartile 3 | 1.04 (0.14, 7.82) | 0.96 | 1.02 (0.10, 10.51) | 0.98 |
| Quartile 2 | 1.72 (0.32, 9.22) | 0.41 | 1.00 (0.15, 6.55) | 0.99 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 1.90 (0.35, 10.30) | 0.33 | 1.17 (0.15, 8.84) | 0.85 |
| Quartile 3 | 1.05 (0.15, 7.60) | 0.95 | 1.15 (0.08, 17.34) | 0.90 |
| Quartile 2 | 1.94 (0.35, 10.82) | 0.33 | 0.98 (0.11, 8.39) | 0.98 |
| Quartile 1 | Reference | | Reference | |
| ***cis*-DCCA[b]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.63 (0.17, 15.7) | 0.59 | 1.38 (0.37, 5.13) | 0.54 |
| Quartile 3 | 1.49 (0.26, 8.56) | 0.57 | 1.09 (0.14, 8.42) | 0.92 |
| Quartile 2 | 1.65 (0.27, 9.89) | 0.48 | 1.15 (0.29, 4.57) | 0.81 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 2** | | | | |
| Quartile 4 | 1.65 (0.16, 17.62) | 0.60 | 1.28 (0.30, 5.50) | 0.68 |
| Quartile 3 | 1.53 (0.27, 8.79) | 0.54 | 0.99 (0.10, 10.21) | 0.99 |
| Quartile 2 | 1.49 (0.23, 9.77) | 0.60 | 0.93 (0.21, 4.11) | 0.91 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 1.80 (0.22, 14.42) | 0.47 | 1.35 (0.35, 5.12) | 0.58 |
| Quartile 3 | 1.90 (0.26, 13.89) | 0.41 | 0.98 (0.08, 12.16) | 0.99 |
| Quartile 2 | 1.80 (0.26, 12.42) | 0.44 | 0.68 (0.14, 3.36) | 0.54 |
| Quartile 1 | Reference | | Reference | |
| **3-PBA[c]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.38 (0.17, 11.13) | 0.83 | 1.55 (0.51, 4.76) | 0.32 |
| Quartile 3 | 0.64 (0.06, 7.05) | 0.64 | 0.39 (0.07, 2.11) | 0.16 |
| Quartile 2 | 1.21 (0.21, 7.14) | 0.65 | 0.93 (0.18, 4.78) | 0.92 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 2** | | | | |
| Quartile 4 | 1.51 (0.18, 12.51) | 0.63 | 1.64 (0.59, 4.55) | 0.22 |
| Quartile 3 | 0.70 (0.07, 7.36) | 0.71 | 0.40 (0.06, 2.76) | 0.22 |
| Quartile 2 | 1.12 (0.15, 8.12) | 0.89 | 0.78 (0.17, 3.53) | 0.69 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 1.91 (0.13, 27.54) | 0.55 | 2.02 (0.44, 9.34) | 0.24 |
| Quartile 3 | 0.87 (0.07, 10.59) | 0.90 | 0.44 (0.05, 3.87) | 0.34 |
| Quartile 2 | 1.35 (0.10, 17.67) | 0.78 | 0.81 (0.19, 3.53) | 0.72 |
| Quartile 1 | Reference | | Reference | |
| **trans-DCCA[d]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.57 (0.38, 6.46) | 0.42 | 1.23 (0.26, 5.87) | 0.75 |

| | | | | |
|---|---|---|---|---|
| Quartile 3 | 0.79 (0.14, 4.54) | 0.74 | 1.23 (0.15, 11.62) | 0.82 |
| Quartile 2 | 0.81 (0.27, 2.48) | 0.64 | 0.77 (0.18, 3.33) | 0.66 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 1.71 (0.46, 6.35) | 0.30 | 1.23 (0.31, 4.88) | 0.71 |
| Quartile 3 | 0.92 (0.16, 5.19) | 0.91 | 1.47 (0.20, 10.93) | 0.63 |
| Quartile 2 | 0.83 (0.32, 2.12) | 0.63 | 0.77 (0.18, 3.37) | 0.51 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 2.23 (0.53, 9.38) | 0.15 | 1.76 (0.41, 7.46) | 0.32 |
| Quartile 3 | 1.21 (0.27, 5.55) | 0.76 | 1.77 (0.23, 13.76) | 0.48 |
| Quartile 2 | 0.98 (0.29, 3.33) | 0.97 | 1.05 (0.21, 5.24) | 0.94 |
| Quartile 1 | Reference | | Reference | |

**Abbreviations:** *cis*-DBCA, *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; 3-PBA, 3-Phenoxybenzoic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, body mass index, and education. n=1095.

[b] Model 3 is adjusted for age, sex, body mass index and sedentary behaviour. n=1141.

[c] Model 3 is adjusted for age, sex, body mass index and education. n=1139.

[d] Model 3 is adjusted for age, sex, body mass index and education. n=1141.

**Table 6.9 Odds ratios (ORs) and 99% confidence intervals (CIs) for urinary concentrations (µg/L) of pyrethroids as continuous variables in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Variable** | **OR (99% CI)** | **p-value** | **OR (99% CI)** | **p-value** |
| ***cis*-DBCA[a]** | | | | |
| Model 1 | 1.12 (0.67, 1.87) | 0.58 | 1.05 (0.58, 1.89) | 0.84 |
| Model 2 | 1.20 (0.73, 1.98) | 0.35 | 1.11 (0.58, 2.11) | 0.69 |
| Model 3 | 1.19 (0.76, 1.86) | 0.32 | 1.11 (0.56, 2.20) | 0.71 |
| ***cis*-DCCA[b]** | | | | |
| Model 1 | 1.07 (0.78, 1.48) | 0.60 | 1.03 (0.72, 1.46) | 0.84 |
| Model 2 | 1.10 (0.81, 1.48) | 0.42 | 1.03 (0.72, 1.48) | 0.84 |
| Model 3 | 1.14 (0.82, 1.58) | 0.31 | 1.09 (0.78, 1.53) | 0.52 |
| **3-PBA[c]** | | | | |

| | | | | |
|---|---|---|---|---|
| Model 1 | 1.15 (0.66, 1.99) | 0.53 | 1.11 (0.66, 1.87) | 0.62 |
| Model 2 | 1.24 (0.66, 2.32) | 0.39 | 1.18 (0.69, 2.02) | 0.44 |
| Model 3 | 1.35 (0.67, 2.74) | 0.28 | 1.35 (0.66, 2.80) | 0.29 |
| **trans-DCCA[d]** | | | | |
| Model 1 | 1.03 (0.78, 1.37) | 0.80 | 0.99 (0.73, 1.34) | 0.94 |
| Model 2 | 1.06 (0.85, 1.33) | 0.51 | 1.00 (0.76, 1.30) | 0.99 |
| Model 3 | 1.11 (0.83, 1.48) | 0.36 | 1.06 (0.80, 1.41) | 0.61 |

**Abbreviations:** *cis*-DBCA, *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; 3-PBA, 3-Phenoxybenzoic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1095.

[b] Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1141.

[c] Model 3 is adjusted for age, sex, body mass index, education, and smoking status. n=1139.

[d] Model 3 is adjusted for age, sex, body mass index, sedentary behaviour, and education. n=1141.

## 7. Discussion

In this study, the urinary concentrations of OP and pyrethroids metabolites were measured for a representative sample of adult Canadian population. The relationships of OP and pyrethroid exposures with obesity outcomes were explored using multiple linear regression models. The relationships of OP and pyrethroid exposures with diabetes outcomes were explored using both multiple linear regression models and multiple logistic regression models. All the estimates that were calculated were generated from a representative survey to reflect the adult Canadian population.

**Urinary Concentrations of Organophosphates and Pyrethroids in Canada**

The urinary concentrations of OP metabolites were lower and the urinary concentrations of pyrethroid metabolites were higher in in 2015-16 than in 2009-10. Health Canada released both the geometric means and medians for urinary OP and pyrethroid concentrations for Cycle 2 of the CHMS, which was conducted between 2009 and 2011, and Cycle 5, which was conducted between 2015 and 2016 (Appendix 1a-1k) (59). The report from Health Canada provided the estimates for the combined children and adults populations (59).

For DEP, the urinary concentration was higher in adults than in children. The concentrations dropped over time as the unadjusted geometric mean and median were 2.8 μg/L (95% CI: 2.6, 3.1) and 2.8 μg/L (95% CI: 2.5, 3.1) for Cycle 2 and were 2.0 μg/L (95% CI: 1.7, 2.3) and 1.9 μg/L (95% CI: 1.5, 2.3) in adults for Cycle 5, respectively (Appendix 4a.). This trend was similar for creatinine-adjusted DEP concentration, the geometric mean and median decreased from 2.7 μg/L (95% CI: 2.5, 2.9) and 2.6 μg/L (95% CI: 2.3, 2.9) to 1.9 μg/L (95% CI: 1.7, 2.1) and 2.0 μg/L (95% CI: 1.7, 2.2) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of DETP was lower in adults than in children. The concentrations dropped over time as the unadjusted geometric mean and median were 0.66 μg/L (95% CI: 0.60, 0.72) and 0.60 μg/L (95% CI: 0.51, 0.70) for Cycle 2 and were 0.34 μg/L (95% CI: 0.28, 0.40) and 0.30 μg/L (95% CI: 0.24, 0.36) in adults for Cycle 5, respectively (Appendix 4b.). This trend was similar for creatinine-adjusted DETP, the geometric mean and median decreased from 0.60 μg/L (95% CI: 0.54, 0.66) and 0.59 μg/L (95% CI: 0.50, 0.68) to 0.32 μg/L (95% CI: 0.28, 0.36) and 0.31 μg/L (95% CI: 0.26, 0.35) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of DMP was higher in adults than in children. The concentration dropped over time as the geometric mean and median were 3.3 μg/L (95% CI: 2.9,

3.7) and 3.5 µg/L (95% CI: 3.0, 4.0) for Cycle 2 and were 1.5 µg/L (95% CI: 1.3, 1.8) and 1.5 µg/L (95% CI: 1.2, 1.7) in adults for Cycle 5, respectively (Appendix 4c.). This trend was similar for creatinine-adjusted DMP, the geometric mean and median decreased from 3.2 µg/L (95% CI: 2.9, 3.6) and 3.0 µg/L (95% CI: 2.7, 3.3) to 1.5 µg/L (95% CI: 1.3, 1.7) and 1.5 µg/L (95% CI: 1.2, 1.7) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of DMTP was higher in adults than in children. The concentration dropped over time as the geometric mean and median were 2.7 µg/L (95% CI: 2.3, 3.2) and 2.8 µg/L (95% CI: 2.2, 3.5) for Cycle 2 and were 1.1 µg/L (95% CI: 0.98, 1.3) and 1.0 µg/L (95% CI: 0.78, 1.2) in adults for Cycle 5, respectively (Appendix 4d.). This trend was similar for creatinine-adjusted DMP, the geometric mean and median decreased from 2.7 µg/L (95% CI: 2.3, 3.1) and 2.5 µg/L (95% CI: 1.8, 3.1) to 1.1 µg/L (95% CI: 0.94, 1.3) and 0.92 µg/L (95% CI: 0.79, 1.0) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of *cis*-DBCA was lower in adults than in children. The concentrations increased over time as the geometric mean and median were 0.012 µg/L (95% CI: 0.010, 0.014) and 0.009 µg/L (95% CI: 0.008, 0.010) for Cycle 2 and were 0.017 µg/L (95% CI: 0.014, 0.021) and 0.017 µg/L (95% CI: 0.014, 0.020) in adults for Cycle 5, respectively (Appendix 4e.). This trend was similar for creatinine-adjusted *cis*-DBCA, the geometric mean and median increased from 0.011 µg/L (95% CI: 0.010, 0.013) and 0.010 µg/L (95% CI: 0.009, 0.011) to 0.016 µg/L (95% CI: 0.014, 0.021) and 0.016 µg/L (95% CI: 0.013, 0.020) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of *cis*-DCCA was higher in adults than in children. The concentrations increased over time as the geometric mean and median were 0.12 µg/L (95% CI:

0.10, 0.15) and 0.09 µg/L (95% CI: 0.08, 0.11) for Cycle 2 and were 0.19 µg/L (95% CI: 0.13, 0.28) and 0.16 µg/L (95% CI: 0.11, 0.22) in adults for Cycle 5, respectively (Appendix 4f.). This trend was similar for creatinine-adjusted *cis*-DCCA, the geometric mean and median increased from 0.12 µg/L (95% CI: 0.10, 0.15) and 0.09 µg/L (95% CI: 0.07, 0.10) to 0.18 µg/L (95% CI: 0.13, 0.25) and 0.15 µg/L (95% CI: 0.10, 0.19) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of 3-PBA was similar in adults and in children. The concentrations increased over time as the geometric mean and median were 0.43 µg/L (95% CI: 0.35, 0.53) and 0.36 µg/L (95% CI: 0.29, 0.43) in Cycle 2 and were 0.54 µg/L (95% CI: 0.40, 0.72) and 0.47 µg/L (95% CI: 0.35, 0.59) in adults for Cycle 5, respectively (Appendix 4g.). This trend was similar for creatinine-adjusted 3-PBA, the geometric mean and median increased from 0.42 µg/L (95% CI: 0.34, 0.51) and 0.33 µg/L (95% CI: 0.26, 0.39) to 0.52 µg/L (95% CI: 0.41, 0.65) and 0.39 µg/L (95% CI: 0.30, 0.48) from Cycle 2 to Cycle 5, respectively.

The urinary concentration of *trans*-DCCA was similar in adults and in children. The concentrations increased over time as the geometric mean and median were 0.29 µg/L (95% CI: 0.23, 0.36) and 0.22 µg/L (95% CI: 0.17, 0.26) in Cycle 2 and were 0.27 µg/L (95% CI: 0.18, 0.40) and 0.23 µg/L (95% CI: 0.17, 0.30) in adults for Cycle 5, respectively (Appendix 4h.). This trend was similar for creatinine-adjusted *trans*-DCCA, the geometric mean and median increased from 0.28 µg/L (95% CI: 0.23, 0.35) and 0.19 µg/L (95% CI: 0.15, 0.24) to 0.26 µg/L (95% CI: 0.19, 0.36) and 0.21 µg/L (95% CI: 0.15, 0.28) from Cycle 2 to Cycle 5, respectively.

**Urinary Concentrations of Organophosphates and Pyrethroids around the World**

The trends in overall urinary concentrations of OP and pyrethroid metabolites differ from those found in American studies and reports. These differences likely reflect the nations'

differing regulations over insecticide usage. For example in the United States, results from the 1999-2002 U.S. National Health and Nutrition Examination Survey (NHANES) found that in a sample of 356 adult men aged 20-55 years old, the unadjusted median urinary concentrations for DEP, DETP, DMP, and DMTP were 0.8 μg/L, 0.5 μg/L, <LOD (of 0.58 μg/L), and 0.6 μg/L, respectively (211). Compared to our study, the levels of DEP and DMTP were higher and the level of DETP was lower in male adults.

Another study (212), using NHANES data from 1999-2008, found that the creatinine-adjusted geometric mean of 5,147 participants aged 12-40 years old was much higher than the results from the previous study (211). This study (212) had geometric means for DEP, DETP, DMP, and DMTP of 3.9 μg/g, 2.7 μg/g, 6.4 μg/g, and 11.3 μg/g, respectively, which were higher than those found in our study.

The latest report of the NHANES published by the Centers for Disease Control and Prevention used data from 2013-14 (213). The report detailed the urinary concentrations of OP and pyrethroid metabolites by demographic categories allowing for a more in-depth look at the trends in concentrations between groups. For approximately 1,600 adults aged 20 years or more, they reported the geometric means for DEP, DETP, DMP, and DMTP being 2.1 μg/L (95% CI: 1.9, 2.4), <LOD (LOD was 0.56 μg/L), 2.3 μg/L (95% CI: 2.0, 2.6), and 1.6 μg/L (95% CI: 1.3, 1.8), respectively. For DEP, DETP, DMP, and DMTP, the medians were 2.2 μg/L (95% CI: 1.9, 2.5), <LOD (LOD was 0.56 μg/L) 2.3 μg/L (95% CI: 2.1, 2.5), and 1.6 μg/L (95% CI: 1.3, 1.8), respectively. For creatinine-adjusted concentrations, they reported the geometric means for DEP, DETP, DMP, and DMTP of 2.2 μg/g (95% CI: 2.0, 2.4), <LOD (LOD was 0.56 μg/L), 2.4 μg/g (95% CI: 2.2, 2.6), and 1.6 μg/g (95% CI: 1.4, 1.9), respectively. For DEP, DETP, DMP, and DMTP, the medians were 2.2 μg/g (95% CI: 1.9, 2.5), <LOD (LOD was 0.56 μg/L) 2.3 μg/g

(95% CI: 2.1, 2.6), and 1.5 μg/g (95% CI: 1.3, 1.7), respectively. Compared to our study, DEP, DMP, and DMTP had higher geometric means and medians. Their data were collected 4 years prior to the data collected for our study, and it supports the observation that OP concentrations had been going down over time.

The above report (213) also detailed the urinary concentrations for 3-PBA and *trans*-DCCA. For *trans*-DCCA, all results were under the LOD of 0.60 μg/L. For adults aged 20+ years, they reported the geometric mean for 3-PBA of 0.67 μg/L (95% CI: 0.60, 0.75) and a median of 0.62 μg/L (95% CI: 0.53, 0.72). For creatinine-adjusted concentrations, they reported a geometric mean of 0.73 μg/g (95% CI: 0.65, 0.82) and a median of 0.60 μg/g (95% CI: 0.55, 0.66). Both unadjusted and creatinine-adjusted concentrations demonstrated that the 3-PBA concentrations of Americans were higher than Canadians 3-PBA concentrations. Compared to the other American study using NHANES data from a previous year (212), 3-PBA concentrations seemed to be increasing over time in America.

Urinary concentrations of OP and pyrethroid differ across other countries as well. In Korea, results from the 2012-2014 Korean National Environmental Health Survey found that for 3-PBA, the creatinine-adjusted geometric mean and median of 6,208 participants were 1.95 μg/g (95% CI: 1.86, 2.04) and 1.88 μg/g (95% CI: 1.80, 1.97), respectively (214). The results from Korea showed that the urinary concentration of 3-PBA was higher than the ones found in the American and Canadian populations.

In Israel, a study of 247 individuals 20-74 years of age (215) showed similar creatinine-adjusted DEP and DETP levels but higher DMP and DMTP levels (about 10 μg/g and 6 μg/g for DMP and DMTP) as compared to our study and American studies. For the Isreali study, higher

concentrations is likely due to the a higher consumption of regionally produced fruits and vegetables, and the use of insecticides, such as chlorpyrifos and parathion-methyl that have been restricted or being phased out of use in both Canada and the US (215,216).

In Canada, the restriction and phasing out of OP insecticides could be one of the major contributors to the decrease in OP concentrations over time. In 2000, Health Canada stated that they would re-evaluate the use of 27 OP active ingredients in Canada (REV99-01). Since then, many OPs have been restricted for use in Canada or phased out by reducing the number of acceptable usages of some specific OPs. For example, one OP class that has seen several re-evaluations is chlorpyrifos. In 2000, chlorpyrifos were restricted from all residential use; in 2007, it was further restricted in select forestry and agricultural use; and in 2020, it was restricted in almost all but a few purposes with the intent to fully phase the OP out by the end of 2023 (217). Other OPs, such as phosmet, dichlorvos, and acephate in 2020 and dimethoate in 2015, have been approved for continued use with more risk mitigation measures being put in place (218–221). This continuing initiative of monitoring the effects of OP use on both environmental and human will likely lead to the near-complete phasing out of this class of insecticide within the next decade.

In Canada, pyrethroid insecticides may have increased in use over time by replacing restricted and phased out OP insecticides; however, Health Canada has also recently begun consideration of re-evaluation of pyrethroid insecticide usage. In 2011, Health Canada stated that they would re-evaluate 10 pyrethroid active ingredients (222). In 2019, permethrin was deemed to be acceptable for continued use with few mitigation measures or amendments (223). In 2018, cyfluthrin, cypermethrin, and deltamethrin were all deemed acceptable for continued use and tetramethrin was given some restrictions for its use (224–227). As most of these decisions have

not been restrictive in nature, it seems that pyrethroid usage will continue to increase as OPs are being phased out. Consequently, pyrethroid metabolite concentrations in humans will likely continue to increase over time.

### Variations of Urinary Concentrations of Organophosphates and Pyrethroids in Sub-Populations

*Sex difference.* This study found that the urinary concentrations of OP and pyrethroid metabolites were higher among females than males. The latest report by NHANES demonstrated differences in concentrations between sex (213). For OPs, they reported the unadjusted geometric means and medians for females had higher levels of DMTP and DMP than for males whereas DEP had similar levels between sexes. For creatinine-adjusted geometric means and medians, the concentrations were higher for females than for males for all 3 OP metabolites. Similar trends were seen for this study and another study using CHMS data, whereby most metabolites had a higher concentration in females than in males (56). To my knowledge, there is no study, either *in vitro* or *in vivo*, that elucidates how females might have higher OP concentrations than males. Drawing from other research, the difference could be females consume more fruits and vegetables, a significant exposure of OPs, than males (56,228,229).

For pyrethroids, the latest report using NHANES data documented a different trend for unadjusted concentrations, whereby the unadjusted geometric means and medians had similar levels between sexes for 3-PBA; however, for the creatinine-adjusted geometric mean and median of 3-PBA, it was similar to OPs as females had higher levels than males (213). A Korean study also found that for 3-PBA, the creatinine-adjusted geometric means and median were higher for females than for males (214). Like with OPs, the likely reason for this difference

between sexes is the higher consumption of pyrethroid residue-containing food such as fruits and vegetables (56,229).

*Age difference.* This study found that the participants aged 70-79 years had a higher OP concentration than the other age groups. This relationship was not seen among the pyrethroids metabolites, which differed from the results from two Korean studies that showed a positive relationship between pyrethroid concentrations and age. One study, using population representative survey data, found that creatinine-adjusted concentrations increases with age (214). Another Korean study, using repeated measures from 1,239 elderly participants, confirmed that the elder population had a greater 3-PBA concentration than younger populations (230). This study (230) also suggested that the reason for increased concentrations at older ages was due to a greater vulnerability to pyrethroids. No studies compared OP concentrations among older age groups.

*Race differences*. The latest report by NHANES detailed the geometric means and medians for the White, Black, Hispanic, and Asian populations (213). For OPs, the unadjusted concentrations showed no race differences. As creatinine-adjustment is important to correct for variable dilution in urinary concentrations seen between race, it can serve as a more accurate measure of concentrations between races (201). For DMP and DMTP, the creatinine-adjusted geometric mean and median for Whites were higher than Blacks but lower than Hispanics and Asians. For DEP, the creatinine-adjusted geometric mean and median were higher than Blacks and Hispanics but lower than Asians. In the current study, all OP metabolites had higher creatinine-adjusted geometric means and medians in the White population than in the non-White population. Previous studies using CHMS data demonstrated non-Whites to have a higher creatinine-adjusted geometric mean than whites; however, this was for the entire population of 6-

70 years of age where young children had a significantly higher geometric mean than any other age group during the study period (56). Potential reasons for different OP concentrations among race groups could be due to differences in diet and in the culturally-specific way to prepare food. A recent study showed that household cooking techniques had a minimal effect of reducing pesticide residue on food items such as fruits and vegetables (231). Additionally, biological difference in urinary excretion could be responsible, at least in part, for the different concentrations found between races (201).

For pyrethroids, the latest report using NHANES data documented that for Whites, the geometric mean for unadjusted concentration of 3-PBA was 0.69 μg/L (95% CI: 0.59, 0.80) and the median was 0.62 μg/L (95% CI: 0.51, 0.78) (213). In the report, the geometric mean and median for Whites were higher than Hispanics and Asians, but lower than Blacks. The creatinine-adjusted geometric mean for Whites was 0.78 μg/g (95% CI: 0.66, 0.92) and the median was 0.66 μg/g (95% CI: 0.56, 0.80). The geometric mean and median were higher than Blacks, Hispanics, and Asians. Another American study of participants from North Carolina, also showed that Black population had a higher unadjusted 3-PBA concentration than the White population (232). Both these American studies differed with the results of our study. Our study demonstrated that the average concentrations of 3-PBA was higher amongst non-Whites than Whites. This difference was also seen for the other 3 pyrethroid metabolites. Reasons for this difference have not been previously investigated. Possible reasons could be differing demographics as the terms Blacks, Asians, and Hispanics all capture a multitude of different races that each could have different pyrethroid metabolite concentrations. As mentioned with OPs, the biological difference in urinary excretion could also play a role in the different concentrations found among races (201).

*Smoking-related difference.* This study found that non-smokers had higher concentrations of pyrethroid metabolites than former or daily smokers. Another study using population representative survey data in South Korea found that creatinine-adjusted urinary concentrations of pyrethroids was negatively associated with smoking (214), as did a Canadian study (233). There is a possibility that smokers are more likely to eat a diet that is poorer in fruits and vegetables (foods with high pyrethroid residue concentrations) compared with non-smokers.

For other covariates such as physical activeness, sedentary behaviour, and education, there are no specific studies looking at how they affect urinary OP or pyrethroid concentrations. In this study, across all OPs and pyrethroids, respondents who were active or who had a post-secondary degree/diploma tended to have higher unadjusted and creatinine-adjusted concentrations than respondents who were non-active or had less than a post-secondary degree/diploma, respectively. Sedentary behaviour was not significantly associated with urinary concentrations of the metabolites; however, respondents who had healthy sedentary behaviour tended to have higher concentrations of DEP and DETP than those who were moderately sedentary or sedentary. For creatinine-adjusted concentrations, there was no trends seen between sedentary behaviour levels across all metabolites.

**Urinary Concentrations of Organophosphates and Pyrethroids and Obesity Measures**

This study found that creatinine-adjusted urinary concentrations of all four OP metabolites were significantly associated with BMI and WC. Sex was an effect modifier for the associations of creatinine-adjusted DEP and DMP with BMI. This interaction showed that there was a significant association between both DEP and DMP and BMI in women but not in men. Sex was also an effect modifier for the association of creatinine-adjusted DEP and WC and the

association was significant in women but not in men. Aforementioned reasons such as females eating more fruits and vegetables might be an explanation.

An American study using NHANES data from 1999-2008 found that there was no relationship between OP metabolites and BMI; however, they noted that different OP metabolites can elicit both advantageous and detrimental metabolic outcomes that are independent of BMI (234). The discrepancy between the two studies should be cautiously interpreted due to the absence of an important confounder that both studies did not adjust for the respondents' recent diets, which is a major OP exposure source and can greatly influence the respondents' urinary concentrations (56).

For pyrethroids, this study found that creatinine-adjusted urinary concentrations of 3-PBA and *trans*-DCCA were significantly and negatively related to BMI, and creatinine-adjusted urinary concentrations of *cis*-DCCA, 3-PBA, and *trans*-DCCA were negatively related to WC. There was no significant relationship for *cis*-DBCA concentrations with either BMI or WC. However, a Korean study of 3671 adults found a non-linear relationship between the concentration of creatinine-adjusted 3-PBA and BMI (116). This relationship was positive at a low level of 3-PBA, but was negative when creatinine-adjusted 3-PBA was above 1.4 μg/L. The Canadian creatinine-adjusted concentrations are far below a concentration of 1.4 μg/L, and the correlation between 3-PBA and BMI was positive. The Korean population also found that those with higher concentration quintiles had a higher odds of being obese or of being overweight as compared to those with healthy BMI (116). Both our study and the Korean study did not adjust for the respondents' recent diets nor the household pyrethroid residue concentrations, which are major pyrethroid exposure sources that can greatly influence the respondents' urinary

concentrations (56,235). There were no studies found that examined the associations of *cis*-DBCA, *cis*-DCCA, and *trans*-DCCA with BMI or WC.

Ye et al. used CHMS data from Cycle 1 (2007-2009) and found that there was a significant relationship (ß: 0.98, 95% CI: 0.97, 0.99) between overall DAP metabolite concentrations and BMI (56). There was a significant relationship (ß: 0.99, 95% CI: 0.98, 0.99) between overall pyrethroid metabolite concentrations and BMI (56). The report illuminated the importance of adjusting for recent diet. The authors found that there was a significant relationship between fruit and vegetable consumption, and increased OP exposure. The regression coefficients for the overall DAP metabolite concentration were 1.21 (95% CI: 1.06, 1.37) and 1.43 (95% CI: 1.26, 1.61) for the middle and high weekly fruit consumption tertiles compared the low tertile, respectively, and were 1.14 (95% CI: 0.99, 1.31) and 1.33 (95% CI: 1.16, 1.52) for the middle and high weekly vegetable consumption tertiles compared the low tertile, respectively. These relationship correlates to an approximately 40% and 30% higher urinary total DAP concentration for respondents in the high fruit and vegetable consumption tertiles as compared to the low fruit and vegetable consumption tertile, respectively.

For pyrethroids, Ye et al. (56) found that the consumption of vegetable, pulses, and nuts was significantly associated with increased urinary pyrethroid metabolite concentration. The relationship correlated to approximately 25% and 40% higher urinary total pyrethroid concentrations for respondents in the high pulses and nuts consumption tertile and vegetable consumption tertiles as compared to the low consumption tertile, respectively. It is worth noting that the frequency of food item eaten per week was calculated by taking the yearly frequency of the food consumption and dividing it by the number of weeks a year. This methodology is subject to a high degree of recall bias, and perhaps involves recency bias, as recalling the number

of times you have eaten a specific food item in a year would likely be imprecise. Additionally, the study looks at the total DAP concentration rather than the individual urinary OP metabolite concentrations, which included DMDTP and DEDTP. The additional thiol group might play a part in the observed relationship that makes it not comparable to the results of the current study. For both BMI and WC, we found that the urinary metabolites without a thiol group, DEP and DMP, had stronger significant associations as compared to the urinary metabolites that had one, DETP and DMTP; however, the results between the metabolites are not comparable as DEP and DMP were stratified for sex due to the presence of effect modification of sex whereas DETP and DMTP were not. If the difference in associations were to stand when stratifying DETP and DMTP by sex, another thiol group could further weaken the association making the actual impact of high fruit and vegetable intake greater with this study's population. Additionally, Ye et al. (56) looked at the total pyrethroid concentration rather than the individual urinary pyrethroid metabolite concentrations, which could hide important information that is specific to each pyrethroid metabolite. Nonetheless, the study (56) has demonstrated that recent fruit and vegetable intake is a potentially important confounder to consider for pyrethroids.

A study conducted in Italy investigated dietary factors in relation to 3-PBA concentrations (163). Among the 55 participants, a higher intake of cooked cruciferous vegetables (broccoli, cabbage, and cauliflower) and leafy vegetables (beet leaves, chicory, and spinach) was significantly associated with a higher urinary 3-PBA concentration, further indicating that high intake of cooked vegetables increases urinary 3-PBA concentrations.

Both urinary OP and pyrethroids metabolites concentrations were also significantly associated with WC. Although waist circumference is a better predictor for adiposity than BMI, their measurements can be correlated to each other and affected by similar factors (236–238).

Urinary concentrations of OP and pyrethroid metabolites tended to have a stronger negative relationship with BMI than with WC. This might be explained as a diet high in fruits and vegetables can elicit a greater inverse effect on WC than on BMI (239). As such, the populations that has high OP and pyrethroid exposure from fruit and vegetable consumption likely benefits from the diet and can experience a significant reduction in WC.

To further reinforce the point of how diet can affect OP concentrations within humans, several studies have examined how an organic diet differs from a conventional one. In respect to OPs, an Australian study with 13 adults looked at whether an organic diet would lower an individual urinary OP concentrations as compared to a conventional diet (240). The study showed that switching to an organic diet for one week was able to significantly reduce urinary OP metabolites levels by nearly 90%. An American study found similar results that urinary OP metabolite concentrations were significantly lower when consuming an organic diet (241).

For pyrethroids, an American study of 4 racially diverse families with 3 to 5 members per family, found a significant decrease in *cis*-DCCA, 3-PBA, and *trans*-DCCA levels following an organic diet intervention (241). A French study observed that for more than 99% of the adult population, diet was the major source of pyrethroid exposure (242). The results of this study may be more relevant to France rather than Canada as most exposure came from cypermethrin and deltamethrin which were found on meats, cereals, fruits, and cauliflowers. These 2 pyrethroids insecticides are not commonly used in Canada (60).

Another major confounder that could have biased the relationship between pyrethroids and obesity measures was pyrethroid's adherence to indoor house dust. An American study of homes and daycares in the United States detected significant amounts of permethrin (median

concentration 1454 ng/g of dust) as well as lesser amount of other pyrethroids in the indoor dust (235). Another American study suggested that pyrethroid degradation occurs more slowly indoor which results in the accumulation of lingering pyrethroid residues (243). The authors of this study found that in a 2005-2006 nationwide representative survey of homes in the United States, permethrin residues were detectable in 89% of homes. Inclusion of household pyrethroid concentrations would help better illuminate the true relationship between chronic pyrethroid exposure and obesity outcomes. Additionally, determining the source of higher household pyrethroid concentration residues might also contribute to our understanding of the relationship.

**Urinary Concentrations of Organophosphates and Pyrethroids and Diabetes Measures**

This study found that urinary concentrations of all four OP metabolites or all four pyrethroid metabolites were not significantly associated with HbA1c levels or the prevalence of self-reported diabetes. The only apparent trend was that the non-thiol containing OPs had higher odds of having diabetes in the higher concentration quartiles as compared to the lowest quartile, whereas the thiol containing OPs had lower odds of having diabetes in the higher concentration quartiles as compared to the lowest quartile. The sample size is relatively small, and there are only 67 to 69 diabetes cases for each logistic regression model. Although each model had at least 10 cases in each level for every covariate, the low case count in addition to the bootstrap sampling could have caused the very wide confidence intervals seen in the models (a subsample could have been taken with 9 cases in a level for each covariate).

Previous studies had similar findings for the relationship between diabetes outcomes and OP metabolites. A recent study of 285 adults aged 40-60 years, including 142 were pesticide sprayers, from Thailand, showed no significant association between OP pesticide exposure and

insulin resistance (244). An American study using data from NHANES 1999-2008 also observed no association between OP exposure and diabetes biomarkers (234).

A few previous studies observed a significant relationship between diabetes outcomes and pyrethroid metabolites. A study used data from 2796 adults aged 20 years or older who participated in NHANES 2007-2010 and found a significant relationship between creatinine-adjusted urinary 3-PBA concentration and the risk of diabetes (245). The fully adjusted model showed that the fourth, third, and second concentration quartiles had ORs of 2.18 (95% CI: 1.18, 4.03), 2.24 (95% CI: 1.35, 3.71), and 1.63 (95% CI: 1.03, 2.57), respectively, when compared to the first concentration quartile for the risk of diabetes. The study also found that a doubling of urinary 3-PBA concentrations increased the odds of having diabetes by 1.14 (95% CI: 1.04, 1.25). This American study had a higher diabetes prevalence as compared to our study, which might contribute to the differences in the results through unaccounted confounders (14.2% as compared to 8.5%). Another study conducted in China examined the relationship between occupational exposures to pyrethroid and diabetes (183). Among the 3080 participants, people who were occupationally exposed to pyrethroids had a 1.48 (95% CI: 1.24, 1.77) higher odds of abnormal glucose regulation than those who were not occupationally exposed (183). A Bolivian study also observed that cumulative pesticide exposure (defined by total number of hours spraying pesticides) was associated with an increased OR of having abnormal glucose regulation in pesticide sprayers (182).

In summary, compared data from Cycle 5 to Cycle 2 CHMS, urinary OP concentrations in Canada decreased over time likely due to the phasing out and restriction of OP insecticides. Urinary pyrethroids concentrations in Canada increased over time likely due to the pyrethroids becoming a more popular substitute for OP insecticides. Females had on average higher urinary

levels of OP and pyrethroid than males. Non-smokers had on average higher urinary levels of pyrethroids than both former and daily smokers. Urinary OP metabolite concentrations were negatively associated with BMI and WC and, which might be greatly affected by recent diet that was not adjusted for in the models. Urinary 3-PBA and *trans*-DCCA metabolite concentrations were negatively associated with both BMI and WC, which might be greatly affected by the recent diet and household pyrethroid residue concentration that were not adjusted for in the models. There was no significant relationship found between diabetes outcomes and urinary OP and pyrethroid concentrations. The specific limitations that were encountered for OPs and pyrethroids during this study are outlined in the limitations.

**8. Strengths and Limitations**

In respect to the study design, there are several inherent limitations. The first limitation is that because the data for this study were cross-sectional, temporality cannot be established as the insecticides concentrations and household questionnaires were measured and recorded at a single point in time. As a result of this, causal effect or order cannot be established as to whether insecticides cause obesity and diabetes or vice versa. Additionally, relying on the concentrations of insecticides from a single spot urine sample does not accurately represent long term exposures to these insecticides. This limitation can be mitigated in future analysis by looking at data across all past and present cycles to analyze trends over time.

The second limitation is non-response bias as the environmental contaminant subsample had an overall weighted response rate of only 47.5%. Although the study does a methodologically rigorous weighting methodology to overcome non-response bias through predictive modelling, it is possible that there is still some bias that could have affected the data.

Consequently, respondents who had chosen not to respond to the survey could be significantly different from the respondents who participated. For example, individuals who were of higher BMI or waist circumference status might have not chosen to participate in the MEC portion of the survey as they were fearful of stigmatization of their weight. The exclusion of these individuals could bias the results by not capturing the morbidly obese population. Non-response bias could have an effect on the results; however, data have shown the effect of non-response bias to be minimal even without compensatory adjustments (246).

The third limitation is that all data from the household questionnaire were self-reported, which is subject to several biases. Social desirability bias and recall bias could have potentially impacted the data gathered from respondents. With social desirability bias, respondents might want to look better in front of the reviewer and could have falsely answered saying they had a higher education level, were highly active, did not smoke, or did not have diabetes to look more desirable. Respondents could have incorrectly estimated the amount of time they were sedentary or active during the week.

The fourth limitation is that there are only 11 primary sampling units, which means that regression models created using CHMS data cannot exceed 11 degrees of freedom. This leads to the limitation of the number of covariates that can be added to a regression model. As explained in the methods, this limitation is why each insecticide metabolite had its own study population and potentially different covariates in their regression models as compared to other urinary metabolites. This was done to ensure that the best fitting models could be built while still respecting the 11 degree of freedom limit.

The fifth limitation is the categorization of the race variable. Initially, this variable was assigned 4 different levels but due to low sample size, the race variable had to be recategorized

to White and non-White. This recategorization potentially causes the loss of important information because different races have different habits including different cooking styles. As urinary insecticide concentration is more of a reflection of recent exposure rather than chronic exposure, recent diet of the respondents plays an important role. Different races may have different ways of preparing foods that could result in less insecticide exposure, such as longer rinsing habits for fruits and vegetables.

The sixth limitation is the inability to control for whether a participant lives in a rural or urban environment. Both urban and rural environments likely predispose the participant to a myriad of different insecticide exposures. The location in which the participant lives also plays a large role in the development of health outcomes like obesity and diabetes (12). For urban environments, participants may be more exposed to insecticide through household insecticide products, insecticide-treated yards, and having access to a larger selection of foods at grocers that contain insecticide residues. Additionally, the built environment of urban settings may predispose an individual to adverse health outcomes like obesity by not having walkable places, higher access to fast food, and other hinderances to physical activity. For rural environments, participants may be more exposed to insecticide through occupational exposures if they grow and/or consume crops that are treated with insecticides. They may also have higher insecticide residue on their clothes which can be adhere to indoor dust predisposing the individual to chronic insecticide exposure. Being able to control for whether a participant lives in a rural or urban setting would allow for a better understanding of the relationship between insecticide exposure and obesity and diabetes, as well as to provide more valid estimates from the linear and logistic regression models.

In regard to the insecticide concentration measures, there are major limitations involved. OP metabolites concentration levels in humans are usually measured using urinary biomarkers to estimate the dose in humans; however, there are significant limitations when using OP biomarkers as an exposure assessment tool. The first issue with this approach is that within-person measurements can be highly variable, resulting in measurements that may be valid but not precise (202,247). Also, within-person measurements substantially vary by season where concentrations can be higher in harvest season than in the colder months of the year (203). Additionally, the time of day when the urine sample is taken affects the urinary OP concentration. Urine taken as part of the first morning void are more concentrated and best reflects individual's average exposure throughout the day (202,247). In the CHMS, the urine sample is taken at the MEC and is likely not the first morning void (and is indeterminable as the time of urine collection is not recorded). The second issue with this approach is that OP metabolites have a very short half-life, meaning that the measurements only represent exposures from the previous 2 days before urinary metabolite sample collection (109,110). Lastly, the OP metabolites, such as DAPs, that are measured in the urine samples can be found in the environment and within food, meaning that if these metabolites are excreted without any metabolic changes, OP exposures that are based on urinary biomarker levels may be overestimated (exposure to the metabolite not to OP) (248–251).

The urinary measurements of pyrethroids also have similar limitations as OPs. Since they are considered non-persistent chemicals, it is harder to discriminate the difference between recent exposure and chronic exposure. Preformed pyrethroid metabolites possibly result in an overestimation of pyrethroid exposure as these metabolites are not the result of human metabolic functions when exposed to pyrethroids; however, a study looking at pyrethroid and their

metabolites levels in food found that preformed pyrethroids metabolites likely do not influence the urinary human pyrethroid metabolite concentrations (252). Temporal variability in pyrethroids concentration is evident as factors, such as place of residence, lifestyle, and occupation, play a major role in pyrethroid exposure (112). It is likely that urinary concentrations of pyrethroids are a result of their recent activities, such as their diet and lifestyle and may not reflect the respondent's chronic exposure. Unlike OPs, it is unclear whether the time of the day at which urine is collected, does significantly change urinary pyrethroid levels due to differing results (112,253).

To overcome these measuring limitations, the proportion of concentration attributable to environmental exposure should be calculated when possible. Additionally, other influencing factors, like the date of when the urine sample is taken, should also be recorded to ensure comparability between studies and the ability to estimate how much of the concentration is due to seasonal variation. Fortunately, the CHMS does record the day when urine samples are taken, and as the cycle is carried out continuously over the course of 2 years, a seasonal variation analysis of insecticide concentrations within Canadians can be conducted for future studies. Seasonal variation would also affect at home/yard pesticide use; however, Cycle 1 of the CHMS included a question about home/yard pesticide use in the past month and there was no difference in the distributions of urinary OP and pyrethroid metabolites between those who did use pesticide and those who did not (56).

To my knowledge, after performing an extensive literature review, this is the first study that examined the relationships between insecticide exposures and obesity and diabetes outcomes in Canadians. Previous studies in Canada have looked at the relationships of OPs and pyrethroids with mental development and lung function (142,204). As such, this study fills an important gap

in the literature by exploring the relationships between insecticide exposure and obesity and diabetes outcomes in the Canadian population. Additionally, this fills a global gap in the literature as there have been very few studies worldwide that have investigated insecticide exposures in humans and their effects on obesity and diabetes.

There were other important strengths to this study. The results are highly generalizable as the survey was designed to be representative of about 97% of the Canadian population. Additionally, this survey also provides concrete measures of urinary biomarkers that are linked with concrete measures of obesity. All measures done in the study were carried out by trained professionals using established measuring methods to ensure that the data are as accurate as possible. Another strength is that the CHMS collected data for an extensive list of variables, and the associations between insecticides and obesity and diabetes outcomes were able to be analyzed while controlling for important confounders such as physical activity and sedentary behaviour.

## 9. Conclusions

This study analyzed data from the CHMS 2015-16 (Cycle 5) and provided nationally representative estimates for the urinary concentrations of organophosphates and pyrethroids in Canadians aged 18-79 years. The geometric means and medians for both unadjusted and creatinine-adjusted concentrations were estimated for 4 OP metabolites (DEP, DETP, DMP, and DMTP), as well as for the 4 pyrethroid metabolites (*cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA). The estimates showed that urinary OP concentrations in Canada were lower in 2015-16 as compared with 2009-11 (Cycle 2 of the CMHS), which is likely due to the phasing out and restriction of OP insecticides. Conversely, urinary pyrethroids concentrations in Canada increased from 2009-11 to 2015-16 as pyrethroids seemed to be popular substitutes for OP

insecticides. For both insecticide classes, females were more exposed than males. Negative significant relationships were found between both BMI and WC and urinary OP metabolite concentrations. There were also negative significant relationships found between both BMI and WC and urinary 3-PBA and *trans*-DCCA metabolite concentrations. These relationships should be interpreted with caution as respondents' recent diet and other factors, such as household pyrethroid residue concentrations, were not adjusted for in the models. In regard to diabetes outcomes and urinary OP and pyrethroids concentrations, the models tended to show positive associations, but they were not statistically significant.

Research using urinary biomarkers of the exposure to insecticide classes such as pyrethroids and OPs are subject to many limitations when estimates are derived from a single urine sample. Urinary insecticide metabolites concentrations may vary throughout the day resulting in increased intra-person variability. Additionally, insecticides have short half-lives meaning that the concentrations measured in the study are more an indicator of recent exposure rather than chronic exposure. Future studies that examine relationships between insecticide exposure should seek to take multiple urine measurements during a single day to adjust for intra-person variability, as well as multiple urine measurements over the course of weeks or months to assess a chronic insecticide exposure.

The impact of recent diet is another important variable to consider in future studies of insecticide exposure in relation to human health. The CHMS should consider adding questions during the MEC portion of the survey to capture information on recent diet over the course of the prior week since relevant food consumption such as vegetables, fruits, and nuts, are related to both the insecticide exposures and health outcomes of interest. Access to this information will allow better adjustments when modelling associations between health conditions and any

chemical that has a short half-life and is diet-related. Additionally, future studies should seek to combine cycles of large surveys such as the NHANES and the CHMS to increase the number of usable degrees of freedom in regression models and to increase the study's sample size.

Another consideration for future studies would be to examine the temporal trend of insecticide exposure throughout the year. Seasonal variations in diet, household pyrethroid residue, and home/yard insecticide use may greatly impact a respondent's urinary insecticide metabolite concentrations. Adjusting for seasonal variation by measuring a respondent's urine sample multiple times in a year would allow a better understanding of how insecticide exposure varies by season. If there is a significant difference, it can serve as an important variable to use in models to generate more accurate estimates. It could also inform health policies by addressing specific seasonal factors that may increase insecticide exposure in order to stem the rising pyrethroid exposure seen in Canadians.

## 10. References


1. Health Canada. Canadian Guidelines for Body Weight Classification in Adults [Internet]. [cited 2020 Nov 28]. Available from: http://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/healthy-weights/canadian-guidelines-body-weight-classification-adults/quick-reference-tool-professionals.html

2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014 Aug 30;384(9945):766–81.

3. Lebenbaum M, Zaric GS, Thind A, Sarma S. Trends in obesity and multimorbidity in Canada. Prev Med. 2018 Nov 1;116:173–9.

4. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health. 2009 Mar 25;9(1):88.

5. Reuser M, Bonneux LG, Willekens FJ. Smoking Kills, Obesity Disables: A Multistate Approach of the US Health and Retirement Survey. Obesity. 2009;17(4):783–9.

6. Jia H, Lubetkin EI. The impact of obesity on health-related quality-of-life in the general adult US population. J Public Health. 2005 Jun 1;27(2):156–64.

7. Berthoud H-R, Klein S. Advances in Obesity: Causes, Consequences, and Therapy. Gastroenterology. 2017 May 1;152(7):1635–7.

8. Song D, Li Y, Lu X, Sun M, Liu H, Yu G, et al. Palladium-copper nanowires-based biosensor for the ultrasensitive detection of organophosphate pesticides. Anal Chim Acta. 2017 Aug 22;982:168–75.

9. Casida JE, Quistad GB. Organophosphate Toxicology: Safety Aspects of Nonacetylcholinesterase Secondary Targets. Chem Res Toxicol. 2004 Aug 1;17(8):983–98.

10. Curl CL, Fenske RA, Kissel JC, Shirai JH, Moate TF, Griffith W, et al. Evaluation of Take-Home Organophosphorus Pesticide Exposure among Agricultural Works and Their Children. Environ Health Perspect. 2002 Dec;110(12):A 787.

11. Rothlein J, Rohlman D, Lasarev M, Phillips J, Muniz J, McCauley L. Organophosphate pesticide exposure and neurobehavioral performance in agricultural and nonagricultural Hispanic workers. Environ Health Perspect. 2006 May;114(5):691–6.

12. Papas MA, Alberg AJ, Ewing R, Helzlsouer KJ, Gary TL, Klassen AC. The Built Environment and Obesity. Epidemiol Rev. 2007 Jan 1;29(1):129–43.

13. Slotkin TA. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? Reprod Toxicol. 2011 Apr 1;31(3):297–301.

14. Meyer A, Seidler FJ, Aldridge JE, Tate CA, Cousins MM, Slotkin TA. Critical Periods for Chlorpyrifos-Induced Developmental Neurotoxicity: Alterations in Adenylyl Cyclase Signaling in Adult Rat Brain Regions after Gestational or Neonatal Exposure. Environ Health Perspect. 2004 Mar;112(3):295–301.

15. Meggs WJ, Brewer KL. Weight gain associated with chronic exposure to chlorpyrifos in rats. J Med Toxicol. 2007 Sep 1;3(3):89–93.

16. Lassiter TL, Ryde IT, Levin ED, Seidler FJ, Slotkin TA. Neonatal exposure to parathion alters lipid metabolism in adulthood: Interactions with dietary fat intake and implications for neurodevelopmental deficits. Brain Res Bull. 2010 Jan 15;81(1):85–91.

17. Brander SM, Gabler MK, Fowler NL, Connon RE, Schlenk D. Pyrethroid Pesticides as Endocrine Disruptors: Molecular Mechanisms in Vertebrates with a Focus on Fishes. Environ Sci Technol. 2016 Sep 6;50(17):8977–92.

18. Alonso MB, Feo ML, Corcellas C, Vidal LG, Bertozzi CP, Marigo J, et al. Pyrethroids: A new threat to marine mammals? Environ Int. 2012 Oct 15;47:99–106.

19. Kim J, Park Y, Yoon KS, Clark JM, Park Y. Permethrin Alters Adipogenesis in 3T3-L1 Adipocytes and Causes Insulin Resistance in C2C12 Myotubes. J Biochem Mol Toxicol. 2014;28(9):418–24.

20. Shen P, Hsieh T-H, Yue Y, Sun Q, Clark JM, Park Y. Deltamethrin increases the fat accumulation in 3T3-L1 adipocytes and Caenorhabditis elegans. Food Chem Toxicol. 2017 Mar 1;101:149–56.

21. Tu W, Xu C, Lu B, Lin C, Wu Y, Liu W. Acute exposure to synthetic pyrethroids causes bioconcentration and disruption of the hypothalamus–pituitary–thyroid axis in zebrafish embryos. Sci Total Environ. 2016 Jan 15;542:876–85.

22. Wallner-Liebmann S, Koschutnig K, Reishofer G, Sorantin E, Blaschitz B, Kruschitz R, et al. Insulin and Hippocampus Activation in Response to Images of High-Calorie Food in Normal Weight and Obese Adolescents. Obesity. 2010;18(8):1552–7.

23. Hossain MM, Suzuki T, Sato I, Takewaki T, Suzuki K, Kobayashi H. The Modulatory Effect of Pyrethroids on Acetylcholine Release in the Hippocampus of Freely Moving Rats. NeuroToxicology. 2004 Sep 1;25(5):825–33.

24. Oswal A, Yeo G. Leptin and the Control of Body Weight: A Review of Its Diverse Central Targets, Signaling Mechanisms, and Role in the Pathogenesis of Obesity. Obesity. 2010;18(2):221–9.

25. Eil C, Nisula BC. The binding properties of pyrethroids to human skin fibroblast androgen receptors and to sex hormone binding globulin. J Steroid Biochem. 1990 Mar 1;35(3):409–14.

26. Rodríguez J-L, Ares I, Martínez M, Martínez-Larrañaga M-R, Anadón A, Martínez M-A. Bioavailability and nervous tissue distribution of pyrethroid insecticide cyfluthrin in rats. Food Chem Toxicol. 2018 Aug 1;118:220–6.

27. Haines DA, Saravanabhavan G, Werry K, Khoury C. An overview of human biomonitoring of environmental chemicals in the Canadian Health Measures Survey: 2007–2019. Int J Hyg Environ Health. 2017 Mar 1;220(2, Part A):13–28.

28. Fiore MF, de Lima ST, Carmichael WW, McKinnie SMK, Chekan JR, Moore BS. Guanitoxin, re-naming a cyanobacterial organophosphate toxin. Harmful Algae. 2020 Feb 1;92:101737.

29. Hyde EG, Carmichael WW. Anatoxin-a(s), a naturally occurring organophosphate, is an irreversible active site-directed inhibitor of acetylcholinesterase (EC 3.1.1.7). J Biochem Toxicol. 1991;6(3):195–201.

30. Neumann R, Peter HH. Insecticidal organophosphates: Nature made them first. Experientia. 1987 Dec 1;43(11):1235–7.

31. Vidyasagar J, Karunakar N, Reddy MS, Rajnarayana K, Surender T, Krishna DR. Oxidative stress and antioxidant status in acute organophosphorous insecticide poisoning. Indian J Pharmacol. 2004 Mar 1;36(2):76.

32. Savolainen K. Understanding the toxic actions of organophosphates. Handb Pestic Toxicol Vol 2. 2001;1013–41.

33. Karalliedde L. Organophosphorus poisoning and anaesthesia. Anaesthesia. 1999 Nov 1;54(11):1073–88.

34. Costa LG. Organophosphorus Compounds at 80: Some Old and New Issues. Toxicol Sci. 2018 Mar 1;162(1):24–35.

35. Petroianu GA. Toxicity of phosphr esters: Willy Lange (1900-1976) and Gerda von Krueger (1907-after 1970). Pharmazie. 2010 Oct;(10):776–80.

36. Lange W, Krueger G v. Über Ester der Monofluorphosphorsäure. Berichte Dtsch Chem Ges B Ser. 1932;65(9):1598–601.

37. Davis FR. The Toxicity of Organophosphate Chemicals [Internet]. Banned. Yale University Press; [cited 2020 Oct 1]. Available from:

http://yale.universitypressscholarship.com/view/10.12987/yale/9780300205176.001.0001/upso-9780300205176-chapter-4

38. Nauen R, Bretschneider T. New modes of action of insecticides. Pestic Outlook. 2002 Dec 18;13(6):241–5.

39. World Health Organization. Public health impact of pesticides used in agriculture [Internet]. World Health Organization; 1990 [cited 2020 Oct 2]. Available from: https://apps.who.int/iris/handle/10665/39772

40. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: Systematic review. BMC Public Health. 2007 Dec;7(1):1–15.

41. Patel V, Ramasundarahettige C, Vijayakumar L, Thakur J, Gajalakshmi V, Gururaj G, et al. Suicide mortality in India: a nationally representative survey. The Lancet. 2012 Jun 23;379(9834):2343–51.

42. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. QJM Int J Med. 2000 Nov 1;93(11):715–31.

43. Richardson RJ, Makhaeva GF. Organophosphorus Compounds. 2014 Jan 1;714–9.

44. Costa LG. Toxic Effects of Pesticides. In: Casarret and Doull's Toxicology, The Basic Science of Poisons [Internet]. Seventh Edition. The McGraw-Hill Companies; 2008 [cited 2020 Oct 23]. p. 883–930. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=958&sectionid=53483747

45. Peter J, Sudarsan T, Moran J. Clinical features of organophosphate poisoning: a review of different classification systems and approaches. Indian J Crit Care Med. 2014 Nov 20;18(11):735.

46. Okudera H. Clinical features on nerve gas terrorism in Matsumoto. J Clin Neurosci. 2002 Jan 1;9(1):17–21.

47. Yanagisawa N, Morita H, Nakajima T. Sarin experiences in Japan: Acute toxicity and long-term effects. J Neurol Sci. 2006 Nov 1;249(1):76–85.

48. Sadaka Y, Broides A, Tzion R, Lifshitz M. Organophosphate acetylcholine esterase inhibitor poisoning from a home-made shampoo. J Emerg Trauma Shock. 2011 Jul 1;4(3):433–433.

49. Peiris JB, Fernando R, De Abrew K. Respiratory failure from severe organophosphate toxicity due to absorption through the skin. Forensic Sci Int. 1988 Feb 1;36(3–4):251–3.

50. Soummer A, Megarbane B, Boroli F, Arbelot C, Saleh M, Moesch C, et al. Severe and prolonged neurologic toxicity following subcutaneous chlorpyrifos self-administration: A case report. Clin Toxicol 15563650. 2011 Feb;49(2):124–7.

51. Meggs W. Permanent Paralysis at Sites of Dermal Exposure to Chlorpyrifos. J Toxicol -- Clin Toxicol. 2003 Oct;41(6):883–6.

52. Health Canada. Pest Management Regulatory Agency Annual Report 2018–2019 [Internet]. 2020 [cited 2020 Oct 22]. Available from: https://www.canada.ca/en/health-

canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/corporate-plans-reports/annual-report-2018-2019.html#a2

53. Cynthia L. Curl, Shirley A.A. Beresford, Richard A. Fenske, Annette L. Fitzpatrick, Chensheng Lu, Jennifer A. Nettleton, et al. Estimating Pesticide Exposure from Dietary Intake and Organic Food Choices: The Multi-Ethnic Study of Atherosclerosis (MESA). Environ Health Perspect. 2015 May 1;123(5):475–83.

54. Kumar S, Kaushik G, Dar MA, Nimesh S, Lopez-Chuken UJ, Villarreal-Chiu JF. Microbial Degradation of Organophosphate Pesticides: A Review. Pedosphere. 2018 Apr 1;28(2):190–208.

55. Ntantu Nkinsa P, Muckle G, Ayotte P, Lanphear BP, Arbuckle TE, Fraser WD, et al. Organophosphate pesticides exposure during fetal development and IQ scores in 3 and 4-year old Canadian children. Environ Res. 2020 Nov 1;190:110023.

56. Ye M, Beach J, Martin JW, Senthilselvan A. Associations between dietary factors and urinary concentrations of organophosphate and pyrethroid metabolites in a Canadian general population. Int J Hyg Environ Health. 2015 Oct 1;218(7):616–26.

57. Government of Canada. Pest Control Products Act [Internet]. 2020 [cited 2020 Nov 1]. Available from: http://laws.lois.justice.gc.ca/eng/acts/P-9.01/page-1.html

58. Health Canada. Maximum Residue Limits for Pesticides [Internet]. [cited 2020 Nov 1]. Available from: http://pr.rp.hc.sc.gc.ca/mrl-lrm/index-eng.php

59. Health Canada. Fifth Report on Human Biomonitoring of Environmental Chemicals in Canada - Canada.ca [Internet]. [cited 2020 Oct 25]. Available from: http://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/fifth-report-human-biomonitoring/page-4.html#s13-1

60. Government of Canada HC. Pesticide Label Search - Health Canada [Internet]. 2010 [cited 2020 Aug 21]. Available from: https://pr-rp.hc-sc.gc.ca/ls-re/index-eng.php

61. Van der Zee EA, Luiten PGM. Muscarinic acetylcholine receptors in the hippocampus, neocortex and amygdala: a review of immunocytochemical localization in relation to learning and memory. Prog Neurobiol. 1999 Aug 1;58(5):409–71.

62. Gupta RC. Toxicology of Organophosphate and Carbamate Compounds. Academic Press; 2011. 781 p.

63. Hulse EJ, Davies JOJ, Simpson AJ, Sciuto AM, Eddleston M. Respiratory Complications of Organophosphorus Nerve Agent and Insecticide Poisoning. Implications for Respiratory and Critical Care. Am J Respir Crit Care Med. 2014 Nov 24;190(12):1342–54.

64. Lotti M. Chapter 72 - Clinical Toxicology of Anticholinesterase Agents in Humans. In: Krieger R, editor. Hayes' Handbook of Pesticide Toxicology (Third Edition) [Internet]. New York: Academic Press; 2010 [cited 2020 Oct 2]. p. 1543–89. Available from: http://www.sciencedirect.com/science/article/pii/B9780123743671000720

65. Banks CN, Lein PJ. A review of experimental evidence linking neurotoxic organophosphorus compounds and inflammation. NeuroToxicology. 2012 Jun 1;33(3):575–84.

66. Senanayake N, Karalliedde L. Neurotoxic Effects of Organohosphorus Insecticides. N Engl J Med. 1987 Mar 26;316(13):761–3.

67. Wadia RS, Sadagopan C, Amin RB, Sardesai HV. Neurological manifestations of organophosphorous insecticide poisoning. J Neurol Neurosurg Psychiatry. 1974 Jul;37(7):841–7.

68. Eddleston M, Mohamed F, Davies JOJ, Eyer P, Worek F, Sheriff MHR, et al. Respiratory failure in acute organophosphorus pesticide self-poisoning. QJM Mon J Assoc Physicians. 2006 Aug;99(8):513–22.

69. Jayawardane P, Dawson AH, Weerasinghe V, Karalliedde L, Buckley NA, Senanayake N. The spectrum of intermediate syndrome following acute organophosphate poisoning: a prospective cohort study from Sri Lanka. PLoS Med. 2008 Jul 1;5(7):1143–54.

70. Jin Y-H, Jeong T-O, Lee J-B. Isolated bilateral vocal cord paralysis with intermediate syndrome after organophosphate poisoning. Clin Toxicol 15563650. 2008 Jun;46(5):482–4.

71. Indudharan R, Win MN, Noor AR. Laryngeal paralysis in organophosphorous poisoning. J Laryngol Otol. 1998 Jan;112(1):81–2.

72. Brahmi N, Mokline A, Kouraichi N, Ghorbel H, Blel Y, Thabet H, et al. Prognostic value of human erythrocyte acetyl cholinesterase in acute organophosphate poisoning. Am J Emerg Med. 2006 Nov 1;24(7):822–7.

73. Glynn P. A mechanism for organophosphate-induced delayed neuropathy. Toxicol Lett. 2006 Mar 15;162(1):94–7.

74. van Tienhoven M, Atkins J, Li Y, Glynn P. Human Neuropathy Target Esterase Catalyzes Hydrolysis of Membrane Lipids. J Biol Chem. 2002 Jun 7;277(23):20942–8.

75. Dowd SR, Bier ME, Patton-Vogt JL. Turnover of Phosphatidylcholine in Saccharomyces cerevisiae. J Biol Chem. 2000 Nov 14;276:3756–63.

76. Baburina I, Jackowski S. Cellular Responses to Excess Phospholipid. J Biol Chem. 1999 Apr 2;274(14):9400–8.

77. Kretzschmar D, Hasan G, Sharma S, Heisenberg M, Benzer S. The Swiss Cheese Mutant Causes Glial Hyperwrapping and Brain Degeneration in Drosophila. J Neurosci. 1997 Oct 1;17(19):7425–32.

78. Aygun D, Onar MK, Altintop BL. The clinical and electrophysiological features of a delayed polyneuropathy developing subsequently after acute organophosphate poisoning and it's correlation with the serum acetylcholinesterase. Electromyogr Clin Neurophysiol. 2003 Nov;43(7):421–7.

79. Miranda J, McConnell R, Wesseling C, Cuadra R, Delgado E, Torres E, et al. Muscular strength and vibration thresholds during two years after acute poisoning with organophosphate insecticides. Occup Environ Med. 2004 Jan;61(1):e4.

80. Ward TR, Mundy WR. Organophosphorus compounds preferentially affect second messenger systems coupled to M2/M4 receptors in rat frontal cortex. Brain Res Bull. 1996 Jan 1;39(1):49–55.

81. Adigun, Abayomi A., Wrench, Nicola, Seidler, Frederic J., Slotkin, Theodore A. Neonatal Organophosphorus Pesticide Exposure Alters the Developmental Trajectory of Cell-Signaling Cascades Controlling Metabolism: Differential Effects of Diazinon and Parathion. Environ Health Perspect. 2010 Feb 1;118(2):210–5.

82. Adigun AA, Wrench N, Seidler FJ, Slotkin TA. Neonatal dexamethasone treatment leads to alterations in cell signaling cascades controlling hepatic and cardiac function in adulthood. Neurotoxicol Teratol. 2010 Mar 1;32(2):193–9.

83. Meyer A, Seidler FJ, Slotkin TA. Developmental effects of chlorpyrifos extend beyond neurotoxicity: critical periods for immediate and delayed-onset effects on cardiac and hepatic cell signaling. Environ Health Perspect. 2004 Feb;112(2):170–8.

84. Zhang H, Liu J, Pope CN. Age-related effects of chlorpyrifos on muscarinic receptor-mediated signaling in rat cortex. Arch Toxicol. 2002 Jan 1;75(11):676–84.

85. Bouchard Maryse F., Chevrier Jonathan, Harley Kim G., Kogut Katherine, Vedar Michelle, Calderon Norma, et al. Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year-Old Children. Environ Health Perspect. 2011 Aug 1;119(8):1189–95.

86. Engel SM, Bradman A, Wolff MS, Rauh VA, Harley KG, Yang JH, et al. Prenatal Organophosphorus Pesticide Exposure and Child Neurodevelopment at 24 Months: An Analysis of Four Birth Cohorts. Environ Health Perspect. 2016 Jun 1;124(6):822–30.

87. Engel SM, Wetmur J, Chen J, Zhu C, Barr DB, Canfield RL, et al. Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood. Environ Health Perspect. 2011 Aug 1;119(8):1182–8.

88. Rauh Virginia, Arunajadai Srikesh, Horton Megan, Perera Frederica, Hoepner Lori, Barr Dana B., et al. Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide. Environ Health Perspect. 2011 Aug 1;119(8):1196–201.

89. González-Alzaga B, Hernández AF, Rodríguez-Barranco M, Gómez I, Aguilar-Garduño C, López-Flores I, et al. Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from South-Eastern Spain. Environ Int. 2015 Dec 1;85:229–37.

90. Cartier C, Warembourg C, Maner-Idrissi GL, Lacroix A, Florence R, Monfort C, et al. Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother–Child PELAGIE Cohort (France). Environ Health Perspect. 2016 May 1;124(5):674–80.

91. Donauer S, Altaye M, Xu Y, Sucharew H, Succop P, Calafat AM, et al. An Observational Study to Evaluate Associations Between Low-Level Gestational Exposure to

Organophosphate Pesticides and Cognition During Early Childhood. Am J Epidemiol. 2016 Sep 1;184(5):410–8.

92. Jusko Todd A., van den Dries Michiel A., Pronk Anjoeka, Shaw Pamela A., Guxens Mònica, Spaan Suzanne, et al. Organophosphate Pesticide Metabolite Concentrations in Urine during Pregnancy and Offspring Nonverbal IQ at Age 6 Years. Environ Health Perspect. 127(1):017007.

93. Montgomery MP, Kamel F, Saldana TM, Alavanja MCR, Sandler DP. Incident Diabetes and Pesticide Exposure among Licensed Pesticide Applicators: Agricultural Health Study, 1993–2003. Am J Epidemiol. 2008 May 15;167(10):1235–46.

94. Abdollahi M, Donyavi M, Pournourmohammadi S, Saadat M. Hyperglycemia associated with increased hepatic glycogen phosphorylase and phosphoenolpyruvate carboxykinase in rats following subchronic exposure to malathion. Comp Biochem Physiol Part C Toxicol Pharmacol. 2004 Apr 1;137(4):343–7.

95. Abdollahi M, Chan TS, Subrahmanyam V, O'Brien PJ. Effects of phosphodiesterase 3,4,5 inhibitors on hepatocyte cAMP levels, glycogenolysis, gluconeogenesis and suceptibility to a mitochondrial toxin. Mol Cell Biochem. 2003 Oct 1;252(1):205–11.

96. Rothman DL, Magnusson I, Cline G, Gerard D, Kahn CR, Shulman RG, et al. Decreased muscle glucose transport/phosphorylation is an early defect in the pathogenesis of non-insulin-dependent diabetes mellitus. Proc Natl Acad Sci. 1995 Feb 14;92(4):983–7.

97. Gómez-Valadés AG, Vidal-Alabró A, Molas M, Boada J, Bermúdez J, Bartrons R, et al. Overcoming Diabetes-Induced Hyperglycemia through Inhibition of Hepatic

Phosphoenolpyruvate Carboxykinase (GTP) with RNAi. Mol Ther. 2006 Feb 1;13(2):401–10.

98. Ercan-Fang N, Gannon MC, Rath VL, Treadway JL, Taylor MR, Nuttall FQ. Integrated effects of multiple modulators on human liver glycogen phosphorylase a. Am J Physiol-Endocrinol Metab. 2002 Jul 1;283(1):E29–37.

99. Duttaroy A, Zimliki CL, Gautam D, Cui Y, Mears D, Wess J. Muscarinic Stimulation of Pancreatic Insulin and Glucagon Release Is Abolished in M3 Muscarinic Acetylcholine Receptor–Deficient Mice. Diabetes. 2004 Jul 1;53(7):1714–20.

100. van Koppen CJ, Kaiser B. Regulation of muscarinic acetylcholine receptor signaling. Pharmacol Ther. 2003 May 1;98(2):197–220.

101. Gilon P, Henquin J-C. Mechanisms and Physiological Significance of the Cholinergic Control of Pancreatic β-Cell Function. Endocr Rev. 2001 Oct 1;22(5):565–604.

102. Kwong TC. Organophosphate Pesticides: Biochemistry and Clinical Toxicology. Ther Drug Monit. 2002 Feb;24(1):144–9.

103. Vale JA. Toxicokinetic and toxicodynamic aspects of organophosphorus (OP) insecticide poisoning. Toxicol Lett. 1998 Dec 28;102–103:649–52.

104. Krieger R. Hayes' Handbook of Pesticide Toxicology. Academic Press; 2010. 2407 p.

105. Mileson BE, Chambers JE, Chen WL, Dettbarn W, Ehrich M, Eldefrawi AT, et al. Common Mechanism of Toxicity: A Case Study of Organophosphorus Pesticides. Toxicol Sci. 1998 Jan 1;41(1):8–20.

106. Kappers WA, Edwards RJ, Murray S, Boobis AR. Diazinon Is Activated by CYP2C19 in Human Liver. Toxicol Appl Pharmacol. 2001 Nov 15;177(1):68–76.

107. Tang J, Cao Y, Rose RL, Brimfield AA, Dai D, Goldstein JA, et al. Metabolism of Chlorpyrifos by Human Cytochrome P450 Isoforms and Human, Mouse, and Rat Liver Microsomes. Drug Metab Dispos. 2001 Sep 1;29(9):1201–4.

108. Mutch E, Daly AK, Leathart JBS, Blain PG, Williams FM. Do multiple cytochrome P450 isoforms contribute to parathion metabolism in man? Arch Toxicol. 2003 Jun 1;77(6):313–20.

109. Griffin P, Mason H, Heywood K, Cocker J. Oral and dermal absorption of chlorpyrifos: a human volunteer study. Occup Environ Med. 1999 Jan;56(1):10–3.

110. Garfitt SJ, Jones K, Mason HJ, Cocker J. Oral and dermal exposure to propetamphos: a human volunteer study. Toxicol Lett. 2002 Aug 5;134(1):115–8.

111. Hodgson E. In vitro human phase I metabolism of xenobiotics I: Pesticides and related compounds used in agriculture and public health, may 2003. J Biochem Mol Toxicol. 2003;17(4):201–6.

112. Wielgomas B. Variability of urinary excretion of pyrethroid metabolites in seven persons over seven consecutive days—Implications for observational studies. Toxicol Lett. 2013 Jul 31;221(1):15–22.

113. Katsuda Y. Development of and future prospects for pyrethroid chemistry. Pestic Sci. 1999;55(8):775–82.

114. Gajendiran A, Abraham J. An overview of pyrethroid insecticides. Front Biol. 2018 Apr 1;13(2):79–90.

115. QYReseach Group. Global Synthetic Pyrethroids Market Research Report 2017 [Internet]. 2017 [cited 2020 Aug 18]. Available from: https://www.marketresearch.com/QYResearch-Group-v3531/Global-Synthetic-Pyrethroids-Research-10909246/

116. Yoo M, Lim Y-H, Kim T, Lee D, Hong Y-C. Association between urinary 3-phenoxybenzoic acid and body mass index in Korean adults: 1st Korean National Environmental Health Survey. Ann Occup Environ Med. 2016 Jan 13;28(1):2.

117. Ujihara K. The history of extensive structural modifications of pyrethroids. J Pestic Sci. 2019 Oct;44(4):215–24.

118. Toshio N. Nerve membrane Na+ channels as targets of insecticides. Trends Pharmacol Sci. 1992 Jan 1;13:236–41.

119. Ogata N, Ohishi Y. Molecular Diversity of Structure and Function of the Voltage-Gated $Na^+$ Channels. Jpn J Pharmacol. 2002;88(4):365–77.

120. Ahlbom J, Fredriksson A, Eriksson P. Neonatal exposure to a type-I pyrethroid (bioallethrin) induces dose—response changes in brain muscarinic receptors and behaviour in neonatal and adult mice. Brain Res. 1994 May 9;645(1):318–24.

121. Aziz MH, Agrawal AK, Adhami VM, Shukla Y, Seth PK. Neurodevelopmental consequences of gestational exposure (GD14–GD20) to low dose deltamethrin in rats. Neurosci Lett. 2001 Mar 16;300(3):161–5.

122. Husain R, Malaviya M, Seth PK, Husain R. Differential responses of regional brain polyamines followingin utero exposure to synthetic pyrethroid insecticides: A preliminary report. Bull Environ Contam Toxicol. 1992 Sep 1;49(3):402–9.

123. Malaviya M, Husain R, Seth PK, Husain R. Perinatal effects of two pyrethroid insecticides on brain neurotransmitter function in the neonatal rat. Vet Hum Toxicol. 1993 Apr;35(2):119–22.

124. Talts U, Fredriksson A, Eriksson P. Changes in behavior and muscarinic receptor density after neonatal and adult exposure to bioallethrin. Neurobiol Aging. 1998 Nov 1;19(6):545–52.

125. Xue Z, Li X, Su Q, Xu L, Zhang P, Kong Z, et al. Effect of Synthetic Pyrethroid Pesticide Exposure During Pregnancy on the Growth and Development of Infants. Asia Pac J Public Health. 2013 Jul 1;25(4_suppl):72S-79S.

126. Imamura L, Hasegawa H, Kurashina K, Matsuno T, Tsuda M. Neonatal exposure of newborn mice to pyrethroid (permethrin) represses activity-dependent c-fos mRNA expression in cerebellum. Arch Toxicol. 2002 Jul 1;76(7):392–7.

127. Jin Y, Liu J, Wang L, Chen R, Zhou C, Yang Y, et al. Permethrin exposure during puberty has the potential to enantioselectively induce reproductive toxicity in mice. Environ Int. 2012 Jul 1;42:144–51.

128. Yuan C, Wang C, Gao S-Q, Kong T-T, Chen L, Li X-F, et al. Effects of permethrin, cypermethrin and 3-phenoxybenzoic acid on rat sperm motility in vitro evaluated with computer-assisted sperm analysis. Toxicol In Vitro. 2010 Mar 1;24(2):382–6.

129. Elbetieha A, Da'as SI, Khamas W, Darmani H. Evaluation of the Toxic Potentials of Cypermethrin Pesticide on Some Reproductive and Fertility Parameters in the Male Rats. Arch Environ Contam Toxicol N Y. 2001 Nov;41(4):522–8.

130. Shukla Y, Taneja P. Mutagenic evaluation of deltamethrin using rodent dominant lethal assay. Mutat Res Toxicol Environ Mutagen. 2000 May 8;467(2):119–27.

131. Zhang S-Y, Ito Y, Yamanoshita O, Yanagiba Y, Kobayashi M, Taya K, et al. Permethrin May Disrupt Testosterone Biosynthesis via Mitochondrial Membrane Damage of Leydig Cells in Adult Male Mouse. Endocrinology. 2007 Aug 1;148(8):3941–9.

132. Zhang S-Y, Ueyama J, Ito Y, Yanagiba Y, Okamura A, Kamijima M, et al. Permethrin may induce adult male mouse reproductive toxicity due to cis isomer not trans isomer. Toxicology. 2008 Jun 27;248(2):136–41.

133. Perry MJ, Venners SA, Barr DB, Xu X. Environmental pyrethroid and organophosphorus insecticide exposures and sperm concentration. Reprod Toxicol. 2007 Jan 1;23(1):113–8.

134. Kamijima M, Hibi H, Gotoh M, Taki K, Saito I, Wang H, et al. A Survey of Semen Indices in Insecticide Sprayers. J Occup Health. 2004;46(2):109–18.

135. Chen H, Xiao J, Hu G, Zhou J, Xiao H, Wang X. Estrogenicity of Organophosphorus and Pyrethroid Pesticides. J Toxicol Environ Health A. 2002 Oct 11;65(19):1419–35.

136. Shafer TJ, Rijal SO, Gross GW. Complete inhibition of spontaneous activity in neuronal networks in vitro by deltamethrin and permethrin. NeuroToxicology. 2008 Mar 1;29(2):203–12.

137. Scollon EJ, Starr JM, Crofton KM, Wolansky MJ, DeVito MJ, Hughes MF. Correlation of tissue concentrations of the pyrethroid bifenthrin with neurotoxicity in the rat. Toxicology. 2011 Nov 28;290(1):1–6.

138. Ding G, Shi R, Gao Y, Zhang Y, Kamijima M, Sakai K, et al. Pyrethroid Pesticide Exposure and Risk of Childhood Acute Lymphocytic Leukemia in Shanghai. Environ Sci Technol. 2012 Dec 18;46(24):13480–7.

139. Chen S, Gu S, Wang Y, Yao Y, Wang G, Jin Y, et al. Exposure to pyrethroid pesticides and the risk of childhood brain tumors in East China. Environ Pollut. 2016 Nov 1;218:1128–34.

140. Han J, Zhou L, Luo M, Liang Y, Zhao W, Wang P, et al. Nonoccupational Exposure to Pyrethroids and Risk of Coronary Heart Disease in the Chinese Population. Environ Sci Technol. 2017 Jan 3;51(1):664–70.

141. Wolansky MJ, Gennings C, Crofton KM. Relative Potencies for Acute Effects of Pyrethroids on Motor Function in Rats. Toxicol Sci. 2006 Jan 1;89(1):271–7.

142. Oulhote Y, Bouchard MF. Urinary Metabolites of Organophosphate and Pyrethroid Pesticides and Behavioral Problems in Canadian Children [Internet]. [cited 2020 Aug 13]. Available from: https://search-proquest-com.proxy.bib.uottawa.ca/docview/1661375402?rfr_id=info%3Axri%2Fsid%3Aprimo

143. Gupta A, Agarwal R, Shukla GS. Functional impairment of blood-brain barrier following pesticide exposure during early development in rats. Hum Exp Toxicol Lond. 1999 Mar;18(3):174–9.

144. Wagner SL. Fatal asthma in a child after use of an animal shampoo containing pyrethrin. West J Med. 2000 Aug;173(2):86–7.

145. Tang W, Wang D, Wang J, Wu Z, Li L, Huang M, et al. Pyrethroid pesticide residues in the global environment: An overview. Chemosphere. 2018 Jan 1;191:990–1007.

146. Rafique N, Tariq SR, Ahmed D. Monitoring and distribution patterns of pesticide residues in soil from cotton/wheat fields of Pakistan. Environ Monit Assess. 2016 Nov 26;188(12):695.

147. Mawussi G, Scorza Júnior RP, Dossa EL, Alaté K-KA. Insecticide residues in soil and water in coastal areas of vegetable production in Togo. Environ Monit Assess. 2014 Nov 1;186(11):7379–85.

148. Riederer AM, Smith KD, Barr DB, Hayden SW, Hunter RE, Ryan PB. Current and Historically Used Pesticides in Residential Soil from 11 Homes in Atlanta, Georgia, USA. Arch Environ Contam Toxicol. 2010 May 1;58(4):908–17.

149. Delgado-Moreno L, Lin K, Veiga-Nascimento R, Gan J. Occurrence and Toxicity of Three Classes of Insecticides in Water and Sediment in Two Southern California Coastal Watersheds. J Agric Food Chem. 2011 Sep 14;59(17):9448–56.

150. Feo ML, Ginebreda A, Eljarrat E, Barceló D. Presence of pyrethroid pesticides in water and sediments of Ebro River Delta. J Hydrol. 2010 Nov 8;393(3):156–62.

151. Weston DP, Ramil HL, Lydy MJ. Pyrethroid insecticides in municipal wastewater - Weston - 2013 - Environmental Toxicology and Chemistry - Wiley Online Library [Internet]. [cited 2020 Aug 20]. Available from: https://setac.onlinelibrary.wiley.com/doi/abs/10.1002/etc.2338

152. Weston DP, Holmes RW, Lydy MJ. Residential runoff as a source of pyrethroid pesticides to urban creeks. Environ Pollut. 2009 Jan 1;157(1):287–94.

153. Fantke P, Wieland P, Wannaz C, Friedrich R, Jolliet O. Dynamics of pesticide uptake into plants: From system functioning to parsimonious modeling. Environ Model Softw. 2013 Feb 1;40:316–24.

154. Aldana-Madrid ML, Valenzuela-Quintanar AI, Silveira-Gramont MI, Rodríguez-Olibarría G, Grajeda-Cota P, Zuno-Floriano FG, et al. Residual Pyrethroids in Fresh Horticultural Products in Sonora, Mexico. Bull Environ Contam Toxicol. 2011 Aug 30;87(4):436.

155. Leng G, Berger-Preiß E, Levsen K, Ranft U, Sugiri D, Hadnagy W, et al. Pyrethroids used indoor - ambient monitoring of pyrethroids following a pest control operation. Int J Hyg Environ Health. 2005 May 13;208(3):193–9.

156. Kolaczinski JH, Curtis CF. Chronic illness as a result of low-level exposure to synthetic pyrethroid insecticides: a review of the debate. Food Chem Toxicol. 2004 May 1;42(5):697–706.

157. Aulakh RS, Gill JPS, Bedi JS, Sharma JK, Joia BS, Ockerman HW. Organochlorine pesticide residues in poultry feed, chicken muscle and eggs at a poultry farm in Punjab, India. J Sci Food Agric. 2006;86(5):741–4.

158. Dallegrave A, Pizzolato TM, Barreto F, Eljarrat E, Barceló D. Methodology for trace analysis of 17 pyrethroids and chlorpyrifos in foodstuff by gas chromatography–tandem mass spectrometry. Anal Bioanal Chem. 2016 Nov 1;408(27):7689–97.

159. Rawn DFK, Judge J, Roscoe V. Application of the QuEChERS method for the analysis of pyrethrins and pyrethroids in fish tissues. Anal Bioanal Chem. 2010 Jul 1;397(6):2525–31.

160. Johnson RM, Ellis MD, Mullin CA, Frazier M. Pesticides and honey bee toxicity — USA. Apidologie. 2010 May 1;41(3):312–31.

161. Bouwman H, Kylin H. Malaria Control Insecticide Residues in Breast Milk: The Need to Consider Infant Health Risks. Environ Health Perspect. 2009 Oct;117(10):1477–80.

162. Morgan MK. Children's Exposures to Pyrethroid Insecticides at Home: A Review of Data Collected in Published Exposure Measurement Studies Conducted in the United States. Int J Environ Res Public Health. 2012 Aug;9(8):2964–85.

163. Fortes C, Mastroeni S, Pilla MA, Antonelli G, Lunghini L, Aprea C. The relation between dietary habits and urinary levels of 3-phenoxybenzoic acid, a pyrethroid metabolite. Food Chem Toxicol. 2013 Feb 1;52:91–6.

164. United States Environmental Protection Agency. Pyrethrins and Pyrethroids | Ingredients Used in Pesticide Products | US EPA [Internet]. [cited 2020 Sep 20]. Available from: https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids

165. World Health Organization. WHO | Safety of pyrethroids for public health use [Internet]. WHO. World Health Organization; [cited 2020 Sep 18]. Available from: http://www.who.int/whopes/resources/who_cds_whopes_gcdpp_2005.10/en/

166. Québec. Règlement sur la qualité de l'eau potable [Internet]. RLRQ c Q-2, r. 40. Available from: http://legisquebec.gouv.qc.ca/fr/ShowDoc/cr/Q-2,%20r.%2040

167. Barr DB, Olsson AO, Wong L, Udunka S, Baker SE, Whitehead RD, et al. Urinary Concentrations of Metabolites of Pyrethroid Insecticides in the General U.S. Population: National Health and Nutrition Examination Survey 1999–2002. Environ Health Perspect. 2010 Jun 1;118(6):742–8.

168. Elliott M, Janes NF, Kimmel EC, Casida JE. Metabolic fate of pyrethrin I, Pyrethrin II, and allethrin administered orally to rats. J Agric Food Chem. 1972 Apr;20(2):300–13.

169. Soderlund DM, Clark JM, Sheets LP, Mullin LS, Piccirillo VJ, Sargent D, et al. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. Toxicology. 2002 Feb 1;171(1):3–59.

170. Khambay BPS, Jewess PJ. 6.1 - Pyrethroids. In: Gilbert LI, editor. Comprehensive Molecular Insect Science [Internet]. Amsterdam: Elsevier; 2005 [cited 2020 Aug 21]. p. 1–29. Available from: http://www.sciencedirect.com/science/article/pii/B0444519246000752

171. Narahashi T. Nerve Membrane Ion Channels as the Target Site of Insecticides [Internet]. Vol. 2, Mini-Reviews in Medicinal Chemistry. 2002 [cited 2020 Aug 21]. p. 419–32. Available from: https://www.eurekaselect.com/81402/article

172. Song JH, Narahashi T. Modulation of sodium channels of rat cerebellar Purkinje neurons by the pyrethroid tetramethrin. J Pharmacol Exp Ther. 1996 Apr 1;277(1):445–53.

173. Ramadan AA, Bakry NM, Marei ASM, Eldefrawi AT, Eldefrawi ME. Action of pyrethroids on GABAA receptor function. Pestic Biochem Physiol. 1988 Oct 1;32(2):97–105.

174. Narahashi T. Chapter 31 - Neurophysiological Effects of Insecticides. In: Krieger R, editor. Hayes' Handbook of Pesticide Toxicology (Third Edition) [Internet]. New York: Academic Press; 2010 [cited 2020 Aug 21]. p. 799–817. Available from: http://www.sciencedirect.com/science/article/pii/B9780123743671000318

175. Ray DE, Sutharsan S, Forshaw PJ. Actions of pyrethroid insecticides on voltage-gated chloride channels in neuroblastoma cells. Neurotoxicology. 1997;18(3):755–60.

176. Oortgiesen M, van Kleef RGDM, Vijverberg HPM. Effects of pyrethroids on neurotransmitter-operated ion channels in cultured mouse neuroblastoma cells. Pestic Biochem Physiol. 1989 Jun 1;34(2):164–73.

177. Thornton JE, Cheung CC, Clifton DK, Steiner RA. Regulation of Hypothalamic Proopiomelanocortin mRNA by Leptin in ob/ob Mice. Endocrinology. 1997 Nov 1;138(11):5063–6.

178. Garey J, Wolff MS. Estrogenic and Antiprogestagenic Activities of Pyrethroid Insecticides. Biochem Biophys Res Commun. 1998 Oct 29;251(3):855–9.

179. Blouin K, Boivin A, Tchernof A. Androgens and body fat distribution. J Steroid Biochem Mol Biol. 2008 Feb 1;108(3):272–80.

180. Cremer JE, Cunningham VJ, Seville MP. Relationships between Extraction and Metabolism of Glucose, Blood Flow, and Tissue Blood Volume in Regions of Rat Brain. J Cereb Blood Flow Metab. 1983 Sep 1;3(3):291–302.

181. Cremer JE, Seville MP. Changes in regional cerebral blood flow and glucose metabolism associated with symptoms of pyrethroid toxicity. Neurotoxicology. 1985;6(3):1–12.

182. Hansen MR, Jørs E, Lander F, Condarco G, Schlünssen V. Is Cumulated Pyrethroid Exposure Associated With Prediabetes? A Cross-sectional Study. J Agromedicine. 2014 Oct 2;19(4):417–26.

183. Wang J, Zhu Y, Cai X, Yu J, Yang X, Cheng J. Abnormal glucose regulation in pyrethroid pesticide factory workers. Chemosphere. 2011 Feb 1;82(7):1080–2.

184. Casida JE, Quistad GB. Golden Age of Insecticide Research: Past, Present, or Future? Annu Rev Entomol. 1998 Jan 1;43(1):1–16.

185. Soderlund DM. Molecular Mechanisms of Insecticide Resistance. In: Sjut V, editor. Molecular Mechanisms of Resistance to Agrochemicals [Internet]. Berlin, Heidelberg: Springer; 1997 [cited 2020 Aug 22]. p. 21–56. (Chemistry of Plant Protection). Available from: https://doi.org/10.1007/978-3-662-03458-3_2

186. Mallick P, Moreau M, Song G, Efremenko AY, Pendse SN, Creek MR, et al. Development and Application of a Life-Stage Physiologically Based Pharmacokinetic (PBPK) Model to the Assessment of Internal Dose of Pyrethroids in Humans. Toxicol Sci. 2020 Jan 1;173(1):86–99.

187. Agency for Toxic Substances & Disease Registry. ATSDR - Toxicological Profile: Pyrethrins and Pyrethroids [Internet]. [cited 2020 Sep 25]. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=787&tid=153

188. Meeker JD, Barr DB, Hauser R. Human semen quality and sperm DNA damage in relation to urinary metabolites of pyrethroid insecticides. Hum Reprod. 2008 Aug 1;23(8):1932–40.

189. Wei B, Mohan KR, Weisel CP. Exposure of flight attendants to pyrethroid insecticides on commercial flights: Urinary metabolite levels and implications. Int J Hyg Environ Health. 2012 Jul 1;215(4):465–73.

190. Kaneko H, Ohkawa H, Miyamoto J. Absorption and Metabolism of Dermally Applied Phenothrin in Rats. J Pestic Sci. 1981;6(2):169–82.

191. Leng G, Leng A, Kuhn K-H, Lewalter J. Human dose-excretion studies with the pyrethroid insecticide cyfluthrin : urinary metabolite profile following inhalation. Xenobiotica. 1997;27(12):1273–83.

192. Leng G, Kuhn K-H, Idel H. Biological monitoring of pyrethroids in blood and pyrethroid metabolites in urine: applications and limitations. Sci Total Environ. 1997 Jun 20;199(1–2):173–81.

193. Statistics Canada. Canadian Health Measures Survey (CHMS) [Internet]. 2015 [cited 2020 May 4]. Available from: https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=251160

194. Statistics Canada. Questionnaire(s) and reporting guide(s) - Canadian Health Measures Survey January 2016 to December 2017 (Cycle 5) [Internet]. 2015 [cited 2020 Nov 6]. Available from: https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvInstrumentList&Id=251160

195. Statistics Canada. Canadian Health Measures Survey (CHMS) Data User Guide: Cycle 5. 2020;129.

196. Statistics Canada. Canadian Health Measures Survey (CHMS) Data User Guide: Cycle 2. 2020;129.

197. Statistics Canada. Canadian Health Measures Survey Cycle 5: Data Dictionary - Household (Rounded) October 2018.

198. Statistics Canada. Canadian Health Measures Survey (CHMS) Derived Variable (DV) Specifications: Cycle 5; Household and Clinic Data.

199. Canadian Society for Exercise Physiology. CSEP Physical Activity Training for Health® (CSEP-PATH®) Resource Manual, 2nd Edition. Canadian Society for Exercise Physiology; 2020.

200. National Center for Biotechnology, U. S. National Library of Medicine. Instructions for Measuring Waist Circumference, According to NHANES III Protocol - Clinical

Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults [Internet]. [cited 2020 Nov 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK2004/

201. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, James PL. Urinary Creatinine Concentrations in the U.S. Population: Implications for Urinary Biologic Monitoring Measurements. Environ Health Perspect. 2005 Feb 1;113(2):192–200.

202. Kissel JC, Curl CL, Kedan G, Lu C, Griffith W, Barr DB, et al. Comparison of organophosphorus pesticide metabolite levels in single and multiple daily urine samples collected from preschool children in Washington State. J Expo Anal Environ Epidemiol. 2005 Mar;15(2):164–71.

203. Attfield KR, Hughes MD, Spengler JD, Lu C. Within- and Between-Child Variation in Repeated Urinary Pesticide Metabolite Measurements over a 1-Year Period. Environ Health Perspect. 2014 Feb 1;122(2):201–6.

204. Ye M, Beach J, Martin JW, Senthilselvan A. Urinary concentrations of pyrethroid metabolites and its association with lung function in a Canadian general population. Occup Environ Med. 2016 Feb 1;73(2):119–26.

205. Hornung RW, Reed LD. Estimation of Average Concentration in the Presence of Nondetectable Values. Appl Occup Environ Hyg. 1990 Jan 1;5(1):46–51.

206. PARTICIPACTION. Canadian 24-Hour Movement Guidelines for Adults (aged 18-64) [Internet]. [cited 2020 Nov 29]. Available from:

https://participaction.cdn.prismic.io/participaction/50ee8fd4-73d5-48d3-9659-e7bc226a0af0_24HMovementGuidelines-ENG-Adults+18-64+-+Final.pdf

207. Tremblay MS, Carson V, Chaput J-P, Connor Gorber S, Dinh T, Duggan M, et al. Canadian 24-Hour Movement Guidelines for Children and Youth: An Integration of Physical Activity, Sedentary Behaviour, and Sleep. Appl Physiol Nutr Metab. 2016 Jun;41(6 (Suppl. 3)):S311–27.

208. Lean MEJ, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995 Jul 15;311(6998):158–61.

209. Cummings P. The relative merits of risk ratios and odds ratios. Arch Pediatr Adolesc Med. 2009 May;163(5):438–45.

210. SAS. NLMeans [Internet]. [cited 2021 May 21]. Available from: https://support.sas.com/kb/62/addl/fusion_62362_5_nlmeans.sas.txt

211. Omoike OE, Lewis RC, Meeker JD. Association between urinary biomarkers of exposure to organophosphate insecticides and serum reproductive hormones in men from NHANES 1999–2002. Reprod Toxicol. 2015 Jun 1;53:99–104.

212. Migneron-Foisy V, Bouchard MF, Freeman EE, Saint-Amour D. Myopia and Exposure to Organophosphate and Pyrethroid Pesticides in the General United States Population. Invest Ophthalmol Vis Sci. 2017 Sep 1;58(11):4915–24.

213. Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals Update. 2021;595.

214. Hwang M, Lee Y, Choi K, Park C. Urinary 3-phenoxybenzoic acid levels and the association with thyroid hormones in adults: Korean National Environmental Health Survey 2012–2014. Sci Total Environ. 2019 Dec 15;696:133920.

215. Berman T, Goldsmith R, Göen T, Spungen J, Novack L, Levine H, et al. Urinary concentrations of organophosphate pesticide metabolites in adults in Israel: Demographic and dietary predictors. Environ Int. 2013 Oct 1;60:183–9.

216. Bilenko N, Fraser D, Vardi H, Shai I, Shahar DR. Mediterranean diet and cardiovascular diseases in an Israeli population. Prev Med. 2005 Mar 1;40(3):299–305.

217. Health Canada. Re-evaluation Note REV2021-02, Update on the Re-evaluation of Chlorpyrifos [Internet]. 2021 [cited 2021 Jun 6]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-note/2021/n-methyl-carbamate/chlorpyrifos.html

218. Health Canada. Re-evaluation Decision RVD2020-11, Phosmet and its associated end-use products [Internet]. 2020 [cited 2021 Jun 6]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2020/phosmet.html

219. Health Canada. Re-evaluation Decision RVD2020-08, Dichlorvos and Its Associated End-use Products [Internet]. 2020 [cited 2021 Jun 6]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-

publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2020/dichlorvos.html

220. Health Canada. Re-evaluation Decision RVD2020-07, Acephate and Its Associated End-use Products [Internet]. 2020 [cited 2021 Jun 6]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2020/acephate.html

221. Health Canada. Re-evaluation Decision RVD2015-04, Dimethoate [Internet]. 2017 [cited 2021 Jun 6]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2015/document-dimethoate-rvd2015-04.html

222. Health Canada. Re-evaluation Note REV2011-05, Re-evaluation of Pyrethroids, Pyrethrins and Related Active Ingredients [Internet]. 2011 [cited 2021 Jun 11]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-note/2011/pyrethroids-pyrethrins-related-active-ingredients-rev2011-05.html

223. Health Canada. Re-evaluation Decision RVD2019-11, Permethrin and Its Associated End-use Products [Internet]. 2019 [cited 2021 Jun 11]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2019/permethrin.html

224. Health Canada. Re-evaluation Decision RVD2018-35, Cyfluthrin and Its Associated End-use Products [Internet]. 2018 [cited 2021 Jun 11]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2018/cyfluthrin.html

225. Health Canada. Re-evaluation Decision RVD2018-22, Cypermethrin and Its Associated End-use Products [Internet]. 2018 [cited 2021 Jun 11]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2018/cypermethrin.html

226. Health Canada. Re-evaluation Decision RVD2018-27, Deltamethrin and its Associated End-use Products [Internet]. 2018 [cited 2021 Jun 11]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2018/deltamethrine.html

227. Health Canada. Re-evaluation Decision RVD2018-01, Tetramethrin and Its Associated End-use Products [Internet]. 2018 [cited 2021 Jun 11]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2018/tetramethrin.html

228. Prättälä R, Paalanen L, Grinberga D, Helasoja V, Kasmel A, Petkeviciene J. Gender differences in the consumption of meat, fruit and vegetables are similar in Finland and the Baltic countries. Eur J Public Health. 2007 Oct 1;17(5):520–5.

229. Emanuel AS, McCully SN, Gallagher KM, Updegraff JA. Theory of Planned Behavior explains gender difference in fruit and vegetable consumption. Appetite. 2012 Dec 1;59(3):693–7.

230. Kim JH, Kim S, Hong Y-C. Household insecticide use and urinary 3-phenoxybenzoic acid levels in an elder population: a repeated measures data. J Expo Sci Environ Epidemiol. 2020 Oct 6;1–15.

231. Chung SW. How effective are common household preparations on removing pesticide residues from fruit and vegetables? A review. J Sci Food Agric. 2018;98(8):2857–70.

232. Morgan M, Jones P, Sobus J, Boyd Barr D. Predictors of Urinary 3-Phenoxybenzoic Acid Levels in 50 North Carolina Adults. Int J Environ Res Public Health. 2016 Nov;13(11):1172.

233. Fortin M-C, Bouchard M, Carrier G, Dumas P. Biological monitoring of exposure to pyrethrins and pyrethroids in a metropolitan population of the Province of Quebec, Canada. Environ Res. 2008 Jul 1;107(3):343–50.

234. Ranjbar M, Rotondi MA, Ardern CI, Kuk JL. The Influence of Urinary Concentrations of Organophosphate Metabolites on the Relationship between BMI and Cardiometabolic Health Risk. J Obes. 2015 Aug 20;2015:e687914.

235. Starr J, Graham S, Stout D, Andrews K, Nishioka M. Pyrethroid pesticides and their metabolites in vacuum cleaner dust collected from homes and day-care centers. Environ Res. 2008 Nov 1;108(3):271–9.

236. Dalton M, Cameron AJ, Zimmet PZ, Shaw JE, Jolley D, Dunstan DW, et al. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. J Intern Med. 2003 Dec;254(6):555–63.

237. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. Eur Heart J. 2007 Apr;28(7):850–6.

238. Zhu S, Heshka S, Wang Z, Shen W, Allison DB, Ross R, et al. Combination of BMI and Waist Circumference for Identifying Cardiovascular Risk Factors in Whites. Obes Res. 2004 Apr;12(4):633–45.

239. Schwingshackl L, Hoffmann G, Kalle-Uhlmann T, Arregui M, Buijsse B, Boeing H. Fruit and Vegetable Consumption and Changes in Anthropometric Variables in Adult Populations: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. PLoS ONE [Internet]. 2015 Oct 16 [cited 2021 Jun 7];10(10). Available from: http://link.gale.com/apps/doc/A431814674/AONE?sid=bookmark-AONE&xid=6ff0cda0

240. Oates L, Cohen M, Braun L, Schembri A, Taskova R. Reduction in urinary organophosphate pesticide metabolites in adults after a week-long organic diet. Environ Res. 2014 Jul 1;132:105–11.

241. Hyland C, Bradman A, Gerona R, Patton S, Zakharevich I, Gunier RB, et al. Organic diet intervention significantly reduces urinary pesticide levels in U.S. children and adults. Environ Res. 2019 Apr 1;171:568–75.

242. Vanacker M, Quindroit P, Angeli K, Mandin C, Glorennec P, Brochot C, et al. Aggregate and cumulative chronic risk assessment for pyrethroids in the French adult population. Food Chem Toxicol. 2020 Sep 1;143:111519.

243. Stout II DM, Bradham KD, Egeghy PP, Jones PA, Croghan CW, Ashley PA, et al. American Healthy Homes Survey: A National Study of Residential Pesticides Measured from Floor Wipes. Environ Sci Technol. 2009 Jun 15;43(12):4294–300.

244. Seesen M, Lucchini RG, Siriruttanapruk S, Sapbamrer R, Hongsibsong S, Woskie S, et al. Association between Organophosphate Pesticide Exposure and Insulin Resistance in Pesticide Sprayers and Nonfarmworkers. Int J Environ Res Public Health. 2020 Jan;17(21):8140.

245. Park J, Park SK, Choi Y-H. Environmental pyrethroid exposure and diabetes in U.S. adults. Environ Res. 2019 May 1;172:399–407.

246. Hendra R, Hill A. Rethinking Response Rates: New Evidence of Little Relationship Between Survey Response Rates and Nonresponse Bias. Eval Rev. 2019 Oct 1;43(5):307–30.

247. Griffith W, Curl CL, Fenske RA, Lu CA, Vigoren EM, Faustman EM. Organophosphate pesticide metabolite levels in pre-school children in an agricultural community: within-

and between-child variability in a longitudinal study. Environ Res. 2011 Aug;111(6):751–6.

248. Lu C, Bravo R, Caltabiano LM, Irish RM, Weerasekera G, Barr DB. The presence of dialkylphosphates in fresh fruit juices: implication for organophosphorus pesticide exposure and risk assessments. J Toxicol Environ Health A. 2005 Feb 13;68(3):209–27.

249. Quirós-Alcalá L, Bradman A, Smith K, Weerasekera G, Odetokun M, Barr DB, et al. Organophosphorous pesticide breakdown products in house dust and children's urine. J Expo Sci Environ Epidemiol. 2012 Nov;22(6):559–68.

250. Zhang X, Driver JH, Li Y, Ross JH, Krieger RI. Dialkylphosphates (DAPs) in fruits and vegetables may confound biomonitoring in organophosphorus insecticide exposure and risk assessment. J Agric Food Chem. 2008 Nov 26;56(22):10638–45.

251. Timchalk C, Busby A, Campbell JA, Needham LL, Barr DB. Comparative pharmacokinetics of the organophosphorus insecticide chlorpyrifos and its major metabolites diethylphosphate, diethylthiophosphate and 3,5,6-trichloro-2-pyridinol in the rat. Toxicology. 2007 Jul 31;237(1–3):145–57.

252. Morgan MK, MacMillan DK, Zehr D, Sobus JR. Pyrethroid insecticides and their environmental degradates in repeated duplicate-diet solid food samples of 50 adults. J Expo Sci Environ Epidemiol. 2018 Jan;28(1):40–5.

253. Sams C, Jones K. Biological monitoring for exposure to deltamethrin: A human oral dosing study and background levels in the UK general population. Toxicol Lett. 2012 Aug 13;213(1):35–8.

# 11. Appendices

**Appendix 1. Geometric means and selected percentiles of urinary organophosphate and pyrethroid metabolites concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and cycle 5 (2016–2017).**

Appendices 1a-1k report the unadjusted and creatinine-adjusted geometric means and medians for the study populations of the CHMS cycles 1, 2 and 5. The measurements were also stratified by sex to give a better picture of the different concentration levels seen between sexes. These estimates included participants under the age of 18 years, and were used to make the comparisons in the first part of the discussion.

**Appendix 1a. Dimethylphosphate (DMP) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2556 | 83.0 (78.3-86.8) | 3.3 (2.9-3.7) | <LOD | 3.5 (3.0-4.0) | 17 (15-20) | 26 (22-29) |
| 5 (2016 – 2017) | 2633 | 80.9 (75.1-85.6) | 1.7 (1.4-2.1) | <LOD | 1.6 (1.3-1.9) | 8.6 (6.2-11) | 14 (10-18) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2546 | 83.0 (78.3-86.8) | 3.2 (2.9-3.6) | <LOD | 3.0 (2.7-3.3) | 15 (11-18) | 24 (19-30) |
| 5 (2016 – 2017) | 2606 | 80.9 (75.1-85.6) | 1.7 (1.4–2.0) | <LOD | 1.5 (1.3-1.8) | 7.2 (5.3-9.0) | 12 (8.7-15) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1280 | 82.5 (76.3-87.4) | 3.3 (2.8-3.8) | <LOD | 3.4 (2.8-4.0) | 17 (13-21) | 26 (21-31) |
| 5 (2016 – 2017) | 1308 | 77.6 (69.2-84.3) | 1.6 (1.3–2.1) | <LOD | 1.5 (0.97-2.0) | 8.4 (6.5-10) | 13 (9.4-18) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1276 | 82.5 (77.6-84.3) | 2.8 (2.5-3.1) | <LOD | 2.5 (2.1-2.9) | 15 (11-18) | 24 (19-30) |
| 5 (2016 – 2017) | 1298 | 77.6 (69.2-84.3) | 1.4 (1.1-1.8) | <LOD | 1.3 (1.0-1.6) | 5.7 (4.5-6.9) | 9.4 (6.3-13) |
| **Female, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1276 | 83.4 (77.9– 87.8) | 3.4 (2.9–3.9) | <LOD | 3.6 (2.8-4.5) | 17 (14-20) | 24 (17-31) |
| 5 (2016 – 2017) | 1325 | 84.1 (79.6-87.8) | 1.8 (1.6-2.2) | <LOD | 1.6 (1.4-1.8) | 9.9[c] (6.1-14) | 16 (10-21) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1270 | 83.4 (77.9-87.8) | 3.8 (3.2-4.6) | <LOD | 3.4 (2.6-4.2) | 16 (11-21) | 28 (20-36) |
| 5 (2016 – 2017) | 1308 | 84.1 (79.6-87.8) | 2.0 (1.7-2.4) | <LOD | 1.8 (1.5-2.0) | 8.8 (6.2-11) | 13[c] (7.7-18) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection

Note: The LODs for Cycles 1, 2, and 5 are 0.8, 1, and 0.58 µg/L, respectively.

[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

[b] Data are not available, as participants under the age of six years were not included in Cycle 1.

[c] Use data with caution.

**Appendix 1b. Dimethylthiophosphate (DMTP) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2559 | 80.0 (75.1-84.0) | 2.7 (2.3-3.2) | <LOD | 2.8 (2.2-3.5) | 23 (17-28) | 37 (27-47) |
| 5 (2016 – 2017) | 2645 | 70.6 (64.8-75.8) | 1.3 (1.1-1.5) | <LOD | 1.1 (0.89-1.3) | 10 (8.8-12) | 20 (15-25) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2549 | 80.0 (75.1-84.0) | 2.7 (2.3-3.1) | <LOD | 2.5 (1.8-3.1) | 21 (17-25) | 35 (31-39) |
| 5 (2016 – 2017) | 2618 | 70.6 (64.8-75.8) | 1.3 (1.1–1.5) | <LOD | 1.0 (0.88-1.1) | 10 (7.0-13) | 19[c] (12-27) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1281 | 80.2 (73.8-85.4) | 2.5 (2.1-3.0) | <LOD | 2.4 (1.8-3.0) | 22[c] (13-32) | 37[c] (17-57) |
| 5 (2016 – 2017) | 1315 | 70.6 (60.7-78.9) | 1.3 (1.0–1.6) | <LOD | 1.1[c] (0.65-1.5) | 9.9 (7.3-12) | 16[c] (8.3-24) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1277 | 80.2 (73.8-85.4) | 2.1 (1.8-2.5) | <LOD | 1.9 (1.5-2.4) | 16 (11-22) | 28 (18-38) |
| 5 (2016 – 2017) | 1305 | 70.6 (60.7-78.9) | 1.1 (0.91-1.4) | <LOD | 0.88 (0.62-1.1) | 7.3[c] (3.7-11) | 19[c] (7.3-30) |
| **Female, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1278 | 79.7 (74.4–84.2) | 2.9 (2.4–3.6) | <LOD | 3.2 (2.4-4.1) | 23 (17-30) | 37 (29 – 45) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 (2016 – 2017) | 1330 | 70.6 (64.3-76.2) | 1.3 (1.1-1.6) | <LOD | 1.1 (0.82-1.4) | 11 (8.4-13) | 21 (16-25) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1272 | 79.7 (74.4-84.2) | 3.3 (2.6-4.2) | <LOD | 3.3 (2.3-4.4) | 27 (20-35) | 37 (25-50) |
| 5 (2016 – 2017) | 1313 | 70.6 (64.3-76.2) | 1.4 (1.2-1.7) | <LOD | 1.1 (0.89-1.3) | 12 (8.2-16) | 21[c] (10-33) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection
Note: The LODs for Cycles 1, 2, and 5 are 0.6, 0.6, and 0.44 µg/L, respectively.
[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[b] Data are not available, as participants under the age of six years were not included in Cycle 1.
[c] Use data with caution.

**Appendix 1c. Dimethyldithiophosphate (DMDTP) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2537 | 49.1 (44.2-53.9) | - | <LOD | <LOD | 2.9 (2.4-3.5) | 6.5 (5.2-7.8) |
| 5 (2016 – 2017) | 2618 | 51.8 (46.9-56.6) | - | <LOD | 0.097 (<LOD-0.12) | 1.4 (0.94-1.9) | 4.1[c] (2.6-5.6) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2527 | 49.1 (44.2-53.9) | - | <LOD | <LOD | 3.3 (2.4-4.2) | 7.2 (5.2-9.3) |
| 5 (2016 – 2017) | 2591 | 51.8 (46.9-56.6) | - | <LOD | 0.11 (<LOD-0.13) | 1.4 (1.1-1.8) | 3.9[c] (1.4-6.4) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1271 | 42.2 (37.4-47.2) | - | <LOD | <LOD | 2.6[c] (1.5-3.7) | 5.7 (3.8-7.6) |
| 5 (2016 – 2017) | 1296 | 70.6 (60.7-78.9) | - | <LOD | <LOD | 1.2[c] (0.64-1.7) | 4.1[c] (1.2-7.0) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1267 | 42.2 (37.4-47.2) | - | <LOD | <LOD | 2.0 (1.5-2.5) | 4.4 (3.0-5.8) |
| 5 (2016 – 2017) | 1286 | 49.5 (43.2-55.8) | - | <LOD | <LOD | 1.2[c] (0.61-1.8) | N/A[d] |
| **Female, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1266 | 55.8 (49.5–61.8) | - | <LOD | 0.33 (<LOD-0.42) | 3.4 (2.5-4.2) | 7.8 (5.5–10) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 (2016 – 2017) | 1322 | 54.0 (46.4-61.4) | 0.17 (0.14-2.1) | <LOD | 0.099[c] (<LOD-0.14) | 1.5[c] (0.48-2.5) | 3.8[c] (1.9-5.7) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1260 | 55.8 (49.5-61.8) | - | <LOD | 0.40[c] (<LOD-0.55) | 4.6 (3.2-6.0) | 9.4 (7.5-11) |
| 5 (2016 – 2017) | 1305 | 54.0 (46.4-61.4) | 0.19 (0.14-0.24) | <LOD | 0.13[c] (<LOD-0.19) | N/A[d] | 4.9[c] (1.5-8.4) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection
Note: The LODs for Cycles 1, 2, and 5 are 0.09, 0.3, and 0.093 µg/L, respectively.
[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[b] Data are not available, as participants under the age of six years were not included in Cycle 1.
[c] Use data with caution.
[d] Data are too unreliable to be published.

**Appendix 1d. Diethylphosphate (DEP) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2556 | 83.3 (79.1-86.7) | 2.8 (2.6-3.1) | <LOD | 2.8 (2.5-3.1) | 11 (8.4-13) | 19 (16-21) |
| 5 (2016 – 2017) | 2646 | 97.8 (95.9-98.8) | 2.2 (2.0-2.5) | 0.52 (0.44-0.60) | 2.1 (1.8-2.4) | 9.9 (8.4-11) | 14 (10-17) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2546 | 83.3 (79.1-86.7) | 2.7 (2.5-2.9) | <LOD | 2.6 (2.3-2.9) | 9.5 (8.3-11) | 14 (11-17) |
| 5 (2016 – 2017) | 2619 | 97.8 (95.9-98.8) | 2.1 (2.0–2.3) | 0.66 (0.52-0.80) | 2.1 (1.8-2.3) | 7.1 (6.7-7.5) | 10 (8.8-11) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1279 | 85.3 (81.7-88.3) | 2.9 (2.6-3.3) | <LOD | 2.9 (2.5-3.4) | 10 (8.4-12) | 18[c] (11-26) |
| 5 (2016 – 2017) | 1315 | 97.9 (95.9-98.9) | 2.2 (1.9–2.6) | 0.53 (0.44-0.61) | 2.1 (1.6-2.6) | 9.8 (7.9-12) | 15 (11-20) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1275 | 85.3 (81.7-88.3) | 2.4 (2.1-2.7) | <LOD | 2.2 (1.8-2.5) | 9.1 (6.9-11) | 14 (9.5-18) |
| 5 (2016 – 2017) | 1305 | 97.6 (95.9-98.9) | 1.9 (1.6-2.2) | 0.55 (0.40-0.71) | 1.8 (1.4-2.1) | 7.1 (6.1-8.1) | 9.5 (8.1-11) |
| **Female, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1277 | 81.2 (75.4–85.9) | 2.7 (2.4–3.1) | <LOD | 2.6 (2.2-2.9) | 12[c] (7.5-17) | 19 (15-23) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 (2016 – 2017) | 1331 | 97.7 (93.6-99.2) | 2.2 (1.9-2.6) | 0.51 (0.37-0.64) | 2.1 (1.7-2.5) | 9.7 (7.6-12) | 12 (8.3-16) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1271 | 81.2 (75.4-85.9) | 3.1 (2.7-3.5) | <LOD | 2.9 (2.5-3.3) | 9.9 (7.5-12) | 14 (9.9-19) |
| 5 (2016 – 2017) | 1314 | 97.7 (93.6-99.2) | 2.4 (2.1-2.7) | 0.80 (0.58-1.0) | 2.4 (2.0-2.7) | 7.1 (6.5-7.7) | 11 (9.1-12) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection
Note: The LODs for Cycles 1, 2, and 5 are 0.5, 1, and 0.29 µg/L, respectively.
[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[b] Data are not available, as participants under the age of six years were not included in Cycle 1.
[c] Use data with caution.

**Appendix 1e. Diethylthiophosphate (DETP) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 2511 | 72.7 (68.1-76.8) | 0.66 (0.60-0.72) | <LOD | 0.60 (0.51-0.70) | 2.7 (1.9-3.4) | 5.3[c] (3.2-7.4) |
| 5 (2016 – 2017) | 2610 | 75.5 (70.3-80.1) | 0.37 (0.33-0.42) | <LOD | 0.32 (0.27-0.38) | 2.6 (2.1-3.2) | 4.4 (3.6-5.2) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 2501 | 72.7 (68.1-76.8) | 0.60 (0.54-0.66) | <LOD | 0.59 (0.50-0.68) | 2.8 (2.1-3.4) | 4.1 (3.5-4.7) |
| 5 (2016 – 2017) | 2583 | 75.5 (70.3-80.1) | 0.36 (0.32-0.40) | <LOD | 0.34 (0.29-0.39) | 2.3 (1.7-2.8) | 3.8 (2.8-4.7) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1261 | 73.1 (67.9-77.7) | 0.63 (0.57-0.71) | <LOD | 0.58 (0.49-0.67) | 2.5 (1.9-3.1) | 3.5[c] (1.6-5.5) |
| 5 (2016 – 2017) | 1294 | 75.7 (66.1-83.3) | 0.37 (0.29-0.48) | <LOD | 0.33 (0.22-0.45) | 2.4[c] (1.1-3.7) | 4.5 (2.9-6.2) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1257 | 73.1 (67.9-77.7) | 0.50 (0.44-0.57) | <LOD | 0.44 (0.32-0.55) | 2.1 (1.5-2.7) | 3.3 (2.2-4.4) |
| 5 (2016 – 2017) | 1284 | 75.7 (66.1-83.3) | 0.32 (0.26-0.40) | <LOD | 0.29 (0.19-0.39) | 1.9 (1.3-2.4) | 3.0[c] (1.5-4.6) |
| **Female, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 (2009–2011) | 1250 | 72.2 (65.9–77.8) | 0.68 (0.59-0.79) | <LOD | 0.61 (0.46-0.76) | N/A[d] | 5.6[c] (1.6–9.5) |
| 5 (2016 – 2017) | 1316 | 75.3 (70.9-79.3) | 0.37 (0.29-0.47) | <LOD | 0.32 (0.24-0.40) | 2.7[c] (1.4-4.1) | 4.3[c] (1.5-7.1) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1244 | 72.2 (65.9-77.8) | 0.72 (0.60-0.87) | <LOD | 0.69 (0.55-0.82) | 3.6 (2.8-4.5) | 5.2[c] (2.9-7.5) |
| 5 (2016 – 2017) | 1299 | 75.3 (70.9-79.3) | 0.40 (0.32-0.49) | <LOD | 0.36 (0.28-0.44) | 2.9[c] (1.6-4.1) | 3.9[c] (1.9-6.0) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection

Note: The LODs for Cycles 1, 2, and 5 are 0.08, 0.3, and 0.13 µg/L, respectively.

[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

[b] Data are not available, as participants under the age of six years were not included in Cycle 1.

[c] Use data with caution.

[d] Data are too unreliable to be published.

**Appendix 1f. Diethyldithiophosphate (DEDTP) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2557 | 3.4[c] (1.8-6.4) | - | <LOD | <LOD | <LOD | <LOD |
| 5 (2016 – 2017) | 2643 | 5.8[c] (3.7-9.0) | - | <LOD | <LOD | <LOD | 0.072 (<LOD-0.091) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2547 | 3.4[c] (1.8-6.4) | - | <LOD | <LOD | <LOD | <LOD |
| 5 (2016 – 2017) | 2616 | 5.8[c] (3.7-9.0) | - | <LOD | <LOD | <LOD | 0.13 (<LOD-0.16) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1279 | N/A[d] | - | <LOD | <LOD | <LOD | <LOD |
| 5 (2016 – 2017) | 1312 | 5.9[c] (3.0-11.4) | - | <LOD | <LOD | <LOD | 0.074[c] (<LOD-0.10) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1275 | N/A[d] | - | <LOD | <LOD | <LOD | <LOD |
| 5 (2016 – 2017) | 1302 | 5.9[c] (3.0-11.4) | - | <LOD | <LOD | <LOD | 0.12 (<LOD-0.15) |
| **Female, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1278 | N/A[d] | - | <LOD | <LOD | <LOD | <LOD |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 (2016 – 2017) | 1331 | 5.7 (3.9-8.1) | - | <LOD | <LOD | <LOD | 0.071 (<LOD-0.081) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1272 | N/A[d] | - | <LOD | <LOD | <LOD | <LOD |
| 5 (2016 – 2017) | 1314 | 5.7 (3.9-8.1) | - | <LOD | <LOD | <LOD | 0.15 (<LOD-0.17) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection
Note: The LODs for Cycles 1, 2, and 5 are 0.06, 0.3, and 0.067 µg/L, respectively.
[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[b] Data are not available, as participants under the age of six years were not included in Cycle 1.
[c] Use data with caution.
[d] Data are too unreliable to be published.

**Appendix 1g. 3-Phenoxybenzoic acid (3-PBA) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2516 | 100 | 0.43 (0.35-0.53) | 0.079 (0.066-0.091) | 0.36 (0.29-0.43) | 2.6[c] (1.6-3.6) | 5.9[c] (2.2-9.5) |
| 5 (2016 – 2017) | 2706 | 100 (99.9-100) | 0.53 (0.42-0.66) | 0.091 (0.065-0.12) | 0.46 (0.37-0.55) | 3.6[c] (1.7-5.4) | 9.7[c] (3.6-16) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2506 | 100 | 0.42 (0.34-0.51) | 0.10 (0.093-0.11) | 0.33 (0.26-0.39) | 2.3[c] (1.2-3.4) | N/A[d] |
| 5 (2016 – 2017) | 2676 | 100 (99.9-100) | 0.52 (0.43-0.62) | 0.11 (0.088-0.13) | 0.39 (0.33-0.44) | 3.2 (2.1-4.2) | N/A[d] |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1256 | 100 | 0.37 (0.30-0.46) | 0.073 (0.053-0.092) | 0.33 (0.27-0.39) | 1.9[c] (0.85-3.0) | N/A[d] |
| 5 (2016 – 2017) | 1348 | 100 (99.9-100) | 0.46 (0.37-0.56) | 0.074[c] (0.044-0.10) | 0.41 (0.30-0.52) | 2.6 (1.7-3.4) | 4.3[c] (2.5-6.1) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1253 | 100 | 0.31 (0.26-0.38) | 0.088 (0.072-0.10) | 0.26 (0.21-0.32) | 1.3[c] (0.69-1.9) | 2.7[c] (0.77-4.6) |
| 5 (2016 – 2017) | 1333 | 100 (99.9-100) | 0.39 (0.34-0.46) | 0.099 (0.083-0.12) | 0.29 (0.22-0.36) | 2.3[c] (1.5-3.2) | 3.7 (2.9-4.5) |
| **Female, 3-79 years** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1260 | 100 | 0.49 (0.37-0.64) | 0.084 (0.069-0.10) | 0.38 (0.27-0.48) | 3.9[c] (1.6-6.2) | N/A[d] |
| 5 (2016 – 2017) | 1358 | 100 (99.7-100) | 0.62 (0.46-0.83) | 0.096 (0.082-0.11) | 0.49 (0.36-0.61) | N/A[d] | 15[c] (6.1-24) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1254 | 100 | 0.56 (0.44-0.72) | 0.11 (0.093-0.13) | 0.41 (0.31-0.51) | N/A[d] | N/A[d] |
| 5 (2016 – 2017) | 1343 | 100 (99.7-100) | 0.68 (0.53-0.88) | 0.15 (0.12-0.17) | 0.50 (0.41-0.59) | N/A[d] | 18[c] (6.3-29) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection

Note: The LODs for Cycles 1, 2, and 5 are 0.01, 0.01, and 0.012 µg/L, respectively.

[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

[b] Data are not available, as participants under the age of six years were not included in Cycle 1.

[c] Use data with caution.

[d] Data are too unreliable to be published.

**Appendix 1h. 4-Fluoro-3-phenoxybenzoic acid (4-F-3-PBA) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2539 | 58.6 (53.1-63.9) | - | <LOD | 0.0091 (<LOD-0.010) | 0.049[c] (0.028-0.070) | 0.11[c] (0.040-0.17) |
| 5 (2016 – 2017) | 2649 | 34.5 (28.3-41.4) | - | <LOD | <LOD | 0.048 (0.036-0.060) | 0.082 (0.055-11) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2529 | 58.6 (53.1-63.9) | - | <LOD | 0.0099 (<LOD-0.012) | 0.048[c] (0.030-0.066) | N/A[d] |
| 5 (2016 – 2017) | 2619 | 34.5 (28.3-41.4) | - | <LOD | <LOD | 0.034 (0.026-0.043) | 0.084[c] (0.045-0.12) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1268 | 57.4 (52.0-62.6) | - | <LOD | 0.0090 (<LOD-0.012) | 0.055[c] (0.032-0.079) | 0.10[c] (0.044-0.16) |
| 5 (2016 – 2017) | 1319 | 34.2 (26.0-43.5) | - | <LOD | <LOD | 0.049[c] (0.027-0.072) | 0.082 (0.060-0.10) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1264 | 57.4 (52.0-62.6) | - | <LOD | 0.0079 (<LOD-0.010) | 0.036[c] (0.019-0.054) | N/A[d] |
| 5 (2016 – 2017) | 1304 | 34.2 (26.0-43.5) | - | <LOD | <LOD | 0.036[c] (0.021-0.052) | 0.085[c] (0.036-0.13) |
| **Female, 3-79 years** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1271 | 59.8 (52.5-66.6) | - | <LOD | 0.0092 (0.0083-0.010) | 0.049[c] (0.015-0.082) | N/A[d] |
| 5 (2016 – 2017) | 1330 | 34.9 (28.3-42.1) | - | <LOD | <LOD | 0.044[c] (0.031-0.057) | N/A[d] |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1265 | 59.8 (52.5-66.6) | - | <LOD | 0.0099 (0.0093-0.011) | 0.050[c] (0.024-0.076) | N/A[d] |
| 5 (2016 – 2017) | 1315 | 34.9 (28.3-42.1) | - | <LOD | <LOD | 0.032 (0.021-0.044) | N/A[d] |

CI: confidence interval; GM: geometric mean; LOD: limit of detection
Note: The LODs for Cycles 1, 2, and 5 are 0.008, 0.008, and 0.0060 µg/L, respectively.
[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[b] Data are not available, as participants under the age of six years were not included in Cycle 1.
[c] Use data with caution.
[d] Data are too unreliable to be published.

**Appendix 1i. *cis*-3-(2-2,-Dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid (*cis*-DBCA) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2535 | 59.6 (52.5-66.3) | 0.012 (0.010-0.014) | <LOD | 0.0094 (0.0084-0.010) | 0.066 (0.045-0.087) | 0.15[c] (0.076-0.23) |
| 5 (2016 – 2017) | 2633 | 79.5 (73.6-84.3) | 0.019 (0.016-0.023) | <LOD | 0.019 (0.016-0.021) | 0.11 (0.083-0.13) | 0.18 (0.13-0.22) |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2525 | 59.6 (52.5-66.3) | 0.011 (0.0097-0.013) | <LOD | 0.0099 (0.0091-0.011) | 0.060[c] (0.035-0.085) | 0.12[c] (0.069-0.17) |
| 5 (2016 – 2017) | 2603 | 79.5 (73.6-84.3) | 0.019 (0.016-0.022) | <LOD | 0.017 (0.014-0.020) | 0.097 (0.076-0.12) | 0.16 (0.13-0.19) |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1272 | 61.7 (54.5-68.4) | 0.012 (0.010-0.015) | <LOD | 0.0096 (0.0068-0.012) | 0.070[c] (0.044-0.095) | 0.14[c] (0.048-0.23) |
| 5 (2016 – 2017) | 1305 | 78.7 (71.6-84.4) | 0.019 (0.015-0.023) | <LOD | 0.018 (0.015-0.020) | 0.12 (0.077-0.15) | 0.20 (0.13-0.26) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1268 | 61.7 (54.5-68.4) | 0.010 (0.0085-0.012) | <LOD | 0.0098 (0.0082-0.011) | 0.059[c] (0.036-0.081) | 0.11[c] (0.043-0.18) |
| 5 (2016 – 2017) | 1290 | 78.7 (71.6-84.4) | 0.016 (0.014-0.019) | <LOD | 0.015 (0.012-0.018) | 0.079 (0.051-0.11) | 0.15 (0.098-0.20) |
| **Female, 3-79 years** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1263 | 57.5 (48.6-66.0) | 0.011 (0.0092-0.013) | <LOD | 0.0092 (0.0069-0.011) | N/A[d] | N/A[d] |
| 5 (2016 – 2017) | 1328 | 80.2 (73.3-85.8) | 0.020 (0.016-0.024) | <LOD | 0.019 (0.016-0.022) | 0.10 (0.082-0.12) | 0.17 (0.12-0.22) |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1257 | 57.5 (48.6-66.0) | 0.013 (0.011-0.015) | <LOD | 0.010[c] (0.0062-0.014) | 0.066[c] (0.027-0.10) | 0.14[c] (0.071-0.21) |
| 5 (2016 – 2017) | 1313 | 80.2 (73.3-85.8) | 0.021 (0.018-0.026) | <LOD | 0.021 (0.017-0.025) | 0.098 (0.083-0.11) | 0.16 (0.11-0.22) |

CI: confidence interval; GM: geometric mean; LOD: limit of detection

Note: The LODs for Cycles 1, 2, and 5 are 0.006, 0.006, and 0.0059 µg/L, respectively.

[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

[b] Data are not available, as participants under the age of six years were not included in Cycle 1.

[c] Use data with caution.

[d] Data are too unreliable to be published.

**Appendix 1j. *cis*-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*cis*-DCCA) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2553 | 99.4 (98.0-99.8) | 0.12 (0.10-0.15) | 0.024 (0.021-0.028) | 0.093 (0.076-0.11) | 0.85[c] (0.47-1.2) | 2.2[c] (0.78-3.6) |
| 5 (2016 – 2017) | 2715 | 100 (99.9-100.0) | 0.18 (0.13-0.24) | 0.029[c] (0.016-0.042) | 0.15 (0.11-0.19) | 1.1[c] (0.43-1.8) | N/A[d] |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2543 | 99.4 (98.0-99.8) | 0.12 (0.10-0.15) | 0.028 (0.025-0.031) | 0.087 (0.072-0.10) | 0.83[c] (0.42-1.2) | N/A[d] |
| 5 (2016 – 2017) | 2685 | 100 (99.9-100.0) | 0.17 (0.13-0.23) | 0.036 (0.026-0.045) | 0.14 (0.10-0.17) | 1.0 (0.71-1.4) | N/A[d] |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1277 | 99.2 (96.8-99.8) | 0.10 (0.087-0.13) | 0.024 (0.018-0.029) | 0.088 (0.068-0.11) | 0.55 (0.43-0.68) | 1.2[c] (0.39-2.1) |
| 5 (2016 – 2017) | 1355 | 100 (99.9-100) | 0.16 (0.12-0.22) | 0.027[c] (0.011-0.042) | 0.13 (0.089-0.18) | 1.1[c] (0.61-1.5) | 2.5[c] (0.96-4.0) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1273 | 99.2 (96.8-99.8) | 0.088 (0.075-0.10) | 0.026 (0.023-0.029) | 0.068 (0.053-0.083) | 0.41[c] (0.23-0.59) | 0.96[c] (0.46-1.5) |
| 5 (2016 – 2017) | 1340 | 100 (99.9-100) | 0.14 (0.10-0.18) | 0.029 (0.020-0.038) | 0.10 (0.065-0.13) | 0.92[c] (0.55-1.3) | 1.8[c] (1.1-2.5) |
| **Female, 3-79 years** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1276 | 99.6 (97.9-99.9) | 0.15 (0.11-0.20) | 0.025 (0.020-0.030) | 0.099 (0.077-0.12) | N/A[d] | N/A[d] |
| 5 (2016 – 2017) | 1360 | 99.9 (99.9-100) | 0.19[c] (0.13-0.29) | 0.034[c] (0.021-0.048) | 0.17 (0.12-0.22) | N/A[d] | N/A[d] |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1270 | 99.6 (97.9-99.9) | 0.17 (0.13-0.22) | 0.034 (0.029-0.039) | 0.034 (0.029-0.039) | N/A[d] | N/A[d] |
| 5 (2016 – 2017) | 1345 | 99.9 (99.9-100) | 0.21 (0.15-0.30) | 0.051 (0.039-0.062) | 0.17 (0.13-0.21) | N/A[d] | N/A[d] |

CI: confidence interval; GM: geometric mean; LOD: limit of detection

Note: The LODs for Cycles 1, 2, and 5 are 0.007, 0.007, and 0.0045 µg/L, respectively.

[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

[b] Data are not available, as participants under the age of six years were not included in Cycle 1.

[c] Use data with caution.

[d] Data are too unreliable to be published.

**Appendix 1k. *trans*-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*trans*-DCCA) — Geometric means and selected percentiles of urine concentrations (µg/L) for the Canadian population aged 3–79 years, Canadian Health Measures Survey Cycle 1 (2007–2009), Cycle 2 (2009–2011), and Cycle 5 (2016–2017).** (59)

| Cycle | N | Detection Frequency (95% CI) | GM[a] (95% CI) | 10th (95% CI) | 50th (95% CI) | 90th (95% CI) | 95th (95% CI) |
|---|---|---|---|---|---|---|---|
| **Total, 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2558 | 99.4 (97.8-99.9) | 0.29 (0.23-0.36) | 0.051 (0.043-0.059) | 0.22 (0.17-0.26) | 2.0[c] (0.90-3.2) | 6.8[c] (2.1-11) |
| 5 (2016 – 2017) | 2719 | 99.6 (98.7-99.9) | 0.27 (0.20-0.37) | 0.038[c] (0.023-0.052) | 0.23 (0.18-0.28) | 2.2[c] (0.95-3.4) | N/A[d] |
| **Total, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 2548 | 99.4 (97.8-99.9) | 0.28 (0.23-0.35) | 0.062 (0.054-0.070) | 0.19 (0.15-0.24) | 1.9[c] (0.72-3.1) | N/A[d] |
| 5 (2016 – 2017) | 2689 | 99.6 (98.7-99.9) | 0.26 (0.20-0.34) | 0.050 (0.038-0.062) | 0.21 (0.15-0.26) | 2.0[c] (1.1-3.0) | N/A[d] |
| **Male 3-79 years** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1279 | 99.3 (96.4-99.9) | 0.25 (0.20-0.31) | 0.048 (0.036-0.060) | 0.21 (0.17-0.25) | 1.3[c] (0.82-1.8) | N/A[d] |
| 5 (2016 – 2017) | 1355 | 99.7 (99.1-99.9) | 0.25 (0.19-0.33) | 0.036[c] (0.0098-0.062) | 0.21 (0.16-0.26) | 2.1[c] (1.3-3.0) | 4.5[c] (1.6-7.3) |
| **Male, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009–2011) | 1275 | 99.3 (96.4-99.9) | 0.21 (0.18-0.25) | 0.055 (0.045-0.064) | 0.17 (0.13-0.20) | 1.0[c] (0.53-1.5) | N/A[d] |
| 5 (2016 – 2017) | 1340 | 99.7 (99.1-99.9) | 0.21 (0.17-0.28) | 0.045 (0.030-0.060) | 0.17[c] (0.11-0.23) | 1.5[c] (0.6-2.3) | 3.5 (2.3-4.8) |
| **Female, 3-79 years** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1279 | 99.6 (97.9-99.9) | 0.34 (0.25-0.46) | 0.052 (0.040-0.064) | 0.22 (0.16-0.28) | N/A[d] | N/A[d] |
| 5 (2016 – 2017) | 1364 | 99.5 (96.8-99.9) | 0.29[c] (0.19-0.43) | 0.039 (0.029-0.050) | 0.24 (0.17-0.31) | N/A[d] | N/A[d] |
| **Female, 3-79 years (Creatinine adjusted (µg/g))** | | | | | | | |
| 1 (2007 – 2009)[b] | - | - | - | - | - | - | - |
| 2 (2009– 2011) | 1273 | 99.6 (97.9-99.9) | 0.38 (0.29-0.51) | 0.070 (0.058-0.083) | 0.24 (0.18-0.30) | N/A[d] | N/A[d] |
| 5 (2016 – 2017) | 1349 | 99.5 (96.8-99.9) | 0.32 (0.22-0.45) | 0.058 (0.045-0.070) | 0.25 (0.20-0.31) | N/A[d] | N/A[d] |

CI: confidence interval; GM: geometric mean; LOD: limit of detection

Note: The LODs for Cycles 1, 2, and 5 are 0.01, 0.01, and 0.0094 µg/L, respectively.

[a] If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

[b] Data are not available, as participants under the age of six years were not included in Cycle 1.

[c] Use data with caution.

[d] Data are too unreliable to be published.

**Appendix 2. Exclusion Criteria for pertinent measures during MEC visits** (195)**.**

| **Measure** | **Exclusion Criteria** | |
|---|---|---|
| | **Automatic application exclusions** | **Staff Decision** |
| Standing Height | None | Acute or chronic condition preventing respondent from standing upright unassisted (e.g., cast on leg). |
| Weight | None | Fibreglass/plaster cast which cannot be removed. |
| Waist Circumference | Pregnancy | Acute or chronic condition (e.g., unable to correctly landmark a wheelchair bound respondent, a colostomy bag which interferes with taking an accurate measurement). |
| Urine | Wheelchair bound and has a catheter | Important language barrier preventing proper instruction for collection. Mental/physical disability preventing providing a sample. |

**Appendix 3. Sampling Weights** (195)

Weighting factors were incorporated into the survey to ensure that estimates from the survey data could be representative of the population. The weight given to each respondent corresponds to the number of Canadians the respondent represents in the Canadian population. The survey weight is given to each participant is the inverse of the probability of that respondent being selected for the survey. For analysis, the bootstrap method is used to approximate the sample variance. 500 replicates are produced to generate 500 bootstrap weights for use with CHMS data. As for the respondent weight, many steps are taking to calculate the weight.

The first step involves the calculation of the selection weight for each collection site within given regions. The collection site selection weight is calculated as the following:

*Sum of persons in all sites contained within the regions (number of persons in the site) x (Number of sites selected within the region).*

Next, a dwelling weight is calculated by taken the inverse of the probability of selection of the dwelling within the stratum it belongs to. A proportion of dwellings identified during collection are deemed as out of scope and are simply removed from the sample. The dwelling selection weight is then multiplied by the collection site selection weight. The dwelling selection weight is calculated as the following:

*1 / [(Count of all dwellings in the strata) / (Count of all dwelling in the sample from the strata)]*

Next, the weight of non-respondent households was redistributed to the respondent within homogenous response groups. These response groups are created through a score method of scores derived through logistic regression. The logistic regression model is created to estimate

the response probability of household (based on factors such as geographic locations, number of attempts to contact the household, and elapsed time between first and last contact) and the resulting probabilities are used to divide households into groups of similar response probabilities. Within each homogenous response group, an adjustment factor is calculated, and the weight of each respondent household is multiplied by this adjustment factor to create the adjusted household weight. The non-response household adjustment factor is calculated as the following:

*Sum of weights for all dwellings (households) / Sum of weights for all respondent households.*

The next step involves the creation of the respondent's individual weight. To convert the adjusted household weight to a person weight, the adjusted household weight is multiplied by the inverse of the probability of selection of the person selected in the household (this probability is dependent on the age and the number of persons in the household).

The next adjustment is for non-response at the questionnaire level. To create appropriate adjustment factors, logistic regression models to create homogenous response groups are employed using the same methodology as the non-response at the household level. Persons who did not respond to the questionnaire are removed and the remaining respondents have their weight multiplied by this adjustment factor. The non-response questionnaire adjustment factor is calculated as the following:

*Sum of weights for all selected persons / Sum of weights for all selected persons responding to the questionnaire.*

Non-response at the MEC level follows the same methodology as non-response at questionnaire level. The non-response MEC adjustment factor is calculated as the following:

*Sum of weights for all persons responding to the questionnaire / Sum of weights for all persons participating at the MEC*

Another non-response adjusted is performed specifically for the urine subsample using the same methodology as the other non-response adjustments. The non-response urine environmental contaminant adjustment factor is calculated as the following:

*Sum of weight of persons selected for the subsample / Sum of weights of person selected for the subsample and had a valid measure.*

Next, calibration was performed to ensure the sum of the final weights corresponds to the estimates of the population for each age group and sex by geographical region. The calibration was performed using the mean of the monthly estimates for each cross-tabulation of regional boundaries and age-sex groups. To control for extreme outliers that would strongly influence the point and variance estimates, winsorization was employed to adjust these extreme weights downward. Winsorization is done by taking outlier weights and replacing them by the highest non-outlier weight for that age and sex group. Afterwards, all weights are then adjusted so that the surplus weight from the outliers can be redistributed. All non-outlier weights are multiplied by the winsorized adjustment factor to create winsorized adjusted weights. The winsorized adjustment factor is calculated as the following:

*Sum of original final weights / Sum of non-outlier weights*

Lastly another calibration is done using the same methodology as the first calibration step. In summary, the entire weighting process is the following:

1) Collection site selection weight
2) Dwelling selection weight

3) Non-response household adjustment

4) Conversion to person weight

5) Non-response questionnaire adjustment

6) Non-response MEC adjustment

7) Non-response urine environmental contaminant adjustment

8) First Calibration

9) Winsorization

10) Second Calibration

**Appendix 4. Geometric means and medians (95% confidence intervals) of urinary organophosphate and pyrethroids concentrations in Canadians 18 years or older in the CHMS 2015-16.**

Appendices 4a-4d present the baseline characteristics for unadjusted OP concentrations. The geometric means of DEP, DETP, DMP, and DETP were 1.992 µg/L (95% CI: 1.711, 2.320), 0.335 µg/L (95% CI: 0.284, 0.362), 1.545 µg/L (95% CI: 1.298, 1.840), and 1.141 µg/L (95% CI: 0.980, 1.329), respectively. The medians of DEP, DETP, DMP, and DETP were 1.880 µg/L (95% CI: 1.500, 2.264), 0.302 µg/L (95% CI: 0.242, 0.362), 1.469 µg/L (95% CI: 1.244, 1.694), and 1.002 µg/L (95% CI: 0.782, 1.222), respectively.

For unadjusted OP metabolite concentrations, the geometric mean tended to be higher across all OPs for individuals who were aged 70 years or older, white, active, or those who had a post-secondary degree/diploma. There was also high sampling variability among OP metabolites' geometric means for the 70+ age group, those who had diabetes or those who did not have a post-secondary degree/diploma. The median tended to be higher across all OPs for individuals who were aged 70 years or older, white, or those who had a post-secondary degree/diploma. There was also high sampling variability among OP metabolites' medians for those who had diabetes, who were sedentary, who had less than a high school education, or who smoked daily. These differences in distributions of unadjusted OP metabolite concentrations among the categories of the characteristics were not statistically significant.

**Appendix 4a. Geometric means and medians (95% confidence intervals) of urinary diethylphosphate (DEP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/L) | Median (µg/L) | p-value** |
|---|---|---|---|---|
| **Total** | 1113 (100.0) | 1.992 (1.711, 2.320) | 1.880 (1.500, 2.264) | |
| **Sex** | | | | 0.487 |
| Male | 561 (50.5) | 2.003 (1.623, 2.472) | 1.914 (1.394, 2.433) | |
| Female | 552 (49.5) | 1.981 (1.629, 2.408) | 1.843 (1.417, 2.269) | |
| **Age (yrs)** | | | | 0.958 |
| 18-49 | 660 (56.7) | 2.025 (1.635, 2.508) | 1.844 (1.277, 2.411) | |
| 50-59 | 122 (18.4) | 1.852 (1.367, 2.510) | 2.133 (1.626, 2.599) | |
| 60-69 | 219 (17.7) | 1.889 (1.427, 2.502) | 1.772 (0.973, 2.570)[E] | |
| 70-79 | 112 (7.2) | 2.394 (1.454, 3.941)[E] | 2.255 (1.589, 2.922) | |
| **Body mass index** | | | | 0.269 |
| Underweight and healthy | 402 (42.0) | 1.814 (1.302, 2.527) | 1.626 (1.184, 2.068) | |
| Overweight | 381 (29.9) | 2.221 (1.651, 2.987) | 2.282 (1.890, 2.675) | |
| Obese class | 329 (28.1) | 2.041 (1.553, 2.682) | 2.046 (1.316, 2.775)[E] | |
| **Waist circumference** | | | | 0.044 |
| Underweight and healthy | 406 (41.5) | 1.805 (1.262, 2.583) | 1.633 (1.129, 2.137) | |
| Overweight | 226 (17.9) | 1.973 (1.622, 2.401) | 2.094 (1.626, 2.562) | |
| Obese class | 481 (40.6) | 2.211 (1.707, 2.866) | 2.140 (1.654, 2.627) | |
| **Diabetes** | | | | 0.643 |
| No | 1044 (91.9) | 1.928 (1.613, 2.304) | 1.823 (1.412, 2.235) | |
| Yes | 69 (8.1) | 2.888 (1.362, 6.121)[F] | 2.284 (0.410, 4.159)[F] | |
| **Race** | | | | 0.279 |
| White | 856 (70.5) | 2.070 (1.750, 2.449) | 2.012 (1.628, 2.397) | |
| Non-White | 257 (29.5) | 1.816 (1.218, 2.709)[E] | 1.635 (0.957, 2.312) | |
| **Physical activity** | | | | 0.060 |
| Active | 609 (52.2) | 2.272 (1.600, 3.225) | 2.368 (1.766, 2.970) | |
| Inactive | 504 (47.8) | 1.726 (1.171, 2.545)[E] | 1.592 (1.334, 1.850) | |
| **Sedentary behaviour** | | | | 0.965 |
| Healthy | 497 (47.8) | 2.064 (1.594, 2.672) | 2.063 (1.508, 2.617) | |
| Moderately sedentary | 467 (39.1) | 1.916 (1.402, 2.618) | 1.809 (1.090, 2.527)[E] | |
| Sedentary | 149 (13.1) | 1.966 (1.460, 2.646) | 1.768 (1.027, 2.509)[E] | |
| **Highest level of education** | | | | 0.055 |
| Less than secondary school | 105 (6.6) | 1.709 (1.126, 2.595)[E] | 1.405 (0.736, 2.074)[E] | |
| Secondary school | 294 (27.7) | 1.646 (0.994, 2.726)[E] | 1.434 (0.949, 1.919) | |
| Post-secondary degree/diploma | 714 (65.7) | 2.193 (1.731, 2.777) | 2.138 (1.656, 2.620) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.198 |
| Non-smoker | 579 (50.5) | 2.059 (1.692, 2.505) | 1.881 (1.436, 2.326) | |
| Former smoker | 331 (30.7) | 1.923 (1.488, 2.486) | 1.943 (1.485, 2.402) | |
| Daily smoker | 203 (18.8) | 1.930 (1.498, 2.487) | 1.843 (1.116, 2.570)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 4b. Geometric means and medians (95% confidence intervals) of urinary diethylthiophosphate (DETP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/L) | Median (µg/L) | p-value** |
|---|---|---|---|---|
| **Total** | 1094 (100.0) | 0.335 (0.284, 0.395) | 0.302 (0.242, 0.362) | |
| **Sex** | | | | 0.617 |
| Male | 547 (50.1) | 0.336 (0.257, 0.438) | 0.295 (0.192, 0.398) | |
| Female | 547 (49.9) | 0.335 (0.265, 0.432) | 0.305 (0.221, 0.389) | |
| **Age (yrs)** | | | | 0.036 |
| 18-49 | 646 (56.3) | 0.333 (0.261, 0.425) | 0.281 (0.210, 0.352) | |
| 50-59 | 122 (18.6) | 0.298 (0.203, 0.439)[E] | 0.305 (0.168, 0.443)[E] | |
| 60-69 | 215 (17.8) | 0.335 (0.233, 0.483)[E] | 0.345 (0.161, 0.529)[E] | |
| 70-79 | 111 (7.3) | 0.471 (0.218, 1.018)[F] | 0.541 (0.353, 0.729) | |
| **Body mass index** | | | | 0.372 |
| Underweight and healthy | 397 (42.0) | 0.383 (0.251, 0.584)[E] | 0.324 (0.192, 0.455)[E] | |
| Overweight | 372 (29.8) | 0.314 (0.231, 0.427) | 0.287 (0.162, 0.413)[E] | |
| Obese class | 325 (28.2) | 0.294 (0.204, 0.425) | 0.241 (0.110, 0.372)[E] | |
| **Waist circumference** | | | | 0.096 |
| Underweight and healthy | 399 (41.4) | 0.397 (0.245, 0.641)[E] | 0.338 (0.178, 0.497)[E] | |
| Overweight | 222 (17.9) | 0.275 (0.158, 0.479)[E] | 0.245 (0.162, 0.327) | |
| Obese class | 473 (40.7) | 0.308 (0.234, 0.405) | 0.274 (0.164, 0.383)[E] | |
| **Diabetes** | | | | 0.605 |
| No | 1027 (92.0) | 0.339 (0.286, 0.401) | 0.301 (0.237, 0.365) | |
| Yes | 67 (8.0) | 0.296 (0.161, 0.543)[E] | 0.290 (0.045, 0.536)[F] | |
| **Race** | | | | 0.520 |
| White | 842 (70.2) | 0.345 (0.282, 0.422) | 0.324 (0.220, 0.428) | |
| Non-White | 252 (29.8) | 0.313 (0.208, 0.472)[E] | 0.279 (0.188, 0.370) | |
| **Physical activity** | | | | 0.005 |
| Active | 600 (52.2) | 0.367 (0.284, 0.472) | 0.333 (0.231, 0.434) | |
| Inactive | 494 (47.8) | 0.304 (0.214, 0.432) | 0.259 (0.181, 0.337) | |
| **Sedentary behaviour** | | | | 0.968 |
| Healthy | 489 (47.8) | 0.384 (0.269, 0.548) | 0.333 (0.227, 0.439) | |
| Moderately sedentary | 464 (39.2) | 0.293 (0.201, 0.428)[E] | 0.253 (0.170, 0.336) | |
| Sedentary | 141 (13.0) | 0.305 (0.214, 0.435) | 0.252 (0.087, 0.416)[E] | |

| | | | | |
|---|---|---|---|---|
| **Highest level of education** | | | | 0.398 |
| Less than secondary school | 106 (6.8) | 0.281 (0.165, 0.477)[E] | 0.254 (0.142, 0.366)[E] | |
| Secondary school | 288 (27.5) | 0.248 (0.113, 0.544)[F] | 0.210 (0.144, 0.276) | |
| Post-secondary degree/diploma | 700 (65.7) | 0.387 (0.274, 0.546) | 0.374 (0.249, 0.498) | |
| | | | | |
| **Smoking status** | | | | <0.001 |
| Non-smoker | 565 (49.8) | 0.388 (0.278, 0.543) | 0.352 (0.256, 0.448) | |
| Former smoker | 328 (31.0) | 0.334 (0.266, 0.419) | 0.308 (0.208, 0.408) | |
| Daily smoker | 201 (19.2) | 0.230 (0.082, 0.644)[F] | 0.187 (0.090, 0.285)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 4c. Geometric means and medians (95% confidence intervals) of urinary dimethylphosphate (DMP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/L) | Median (µg/L) | p-value** |
|---|---|---|---|---|
| **Total** | 1108 (100.0) | 1.545 (1.298, 1.840) | 1.469 (1.244, 1.694) | |
| **Sex** | | | | 0.648 |
| Male | 558 (50.4) | 1.461 (1.101, 1.940) | 1.366 (0.886, 1.856) | |
| Female | 550 (49.6) | 1.636 (1.356, 1.974) | 1.529 (1.333, 1.724) | |
| **Age (yrs)** | | | | 0.172 |
| 18-49 | 657 (56.6) | 1.522 (1.258, 1.841) | 1.488 (1.265, 1.710) | |
| 50-59 | 122 (18.6) | 1.531 (1.050, 2.231)[E] | 1.424 (0.767, 2.080)[E] | |
| 60-69 | 216 (17.5) | 1.399 (0.927, 2.112)[E] | 1.425 (0.716, 2.134)[E] | |
| 70-79 | 113 (7.3) | 2.263 (1.057, 4.846)[F] | 2.141 (0.817, 3.465)[E] | |
| **Body mass index** | | | | 0.063 |
| Underweight and healthy | 402 (42.2) | 1.638 (1.277, 2.101) | 1.568 (1.170, 1.966) | |
| Overweight | 378 (29.8) | 1.649 (1.271, 2.139) | 1.416 (1.006, 1.826) | |
| Obese class | 328 (28.0) | 1.322 (0.788, 2.216)[E] | 1.265 (0.876, 1.654) | |
| **Waist circumference** | | | | 0.408 |
| Underweight and healthy | 405 (41.6) | 1.487 (1.226, 1.803) | 1.498 (1.198, 1.798) | |
| Overweight | 227 (18.1) | 1.772 (1.120, 2.804)[E] | 1.656 (1.038, 2.275)[E] | |
| Obese class | 476 (40.3) | 1.513 (1.123, 2.037) | 1.373 (0.998, 1.748) | |
| **Diabetes** | | | | 0.326 |
| No | 1040 (91.9) | 1.531 (1.277, 1.834) | 1.475 (1.254, 1.696) | |
| Yes | 68 (8.1) | 1.725 (1.127, 2.642)[E] | 1.395 (0.152, 2.637)[F] | |
| **Race** | | | | 0.584 |
| White | 851 (70.4) | 1.660 (1.278, 2.156)[E] | 1.542 (1.228, 1.857) | |
| Non-White | 257 (29.6) | 1.303 (0.806, 2.106) | 1.309 (0.919, 1.700) | |
| **Physical activity** | | | | 0.447 |
| Active | 606 (52.3) | 1.637 (1.188, 2.255) | 1.438 (1.020, 1.857) | |
| Inactive | 502 (47.7) | 1.451 (1.186, 1.775) | 1.485 (1.256, 1.713) | |
| **Sedentary behaviour** | | | | 0.205 |
| Healthy | 497 (48.1) | 1.524 (1.289, 1.801) | 1.557 (1.343, 1.770) | |
| Moderately sedentary | 464 (38.8) | 1.540 (1.106, 2.144) | 1.409 (0.908, 1.911) | |
| Sedentary | 147 (13.1) | 1.646 (1.148, 2.359) | 1.361 (0.620, 2.103)[E] | |
| **Highest level of education** | | | | 0.431 |
| Less than secondary school | 106 (6.7) | 1.340 (0.875, 2.051)[E] | 1.175 (0.511, 1.839)[E] | |

| | | | | |
|---|---|---|---|---|
| Secondary school | 292 (27.8) | 1.143 (0.504, 2.592)[F] | 1.105 (0.853, 1.357) | |
| Post-secondary degree/diploma | 710 (65.5) | 1.782 (1.268, 2.506) | 1.683 (1.393, 1.973) | |
| **Smoking status** | | | | 0.003 |
| Non-smoker | 576 (50.5) | 1.670 (1.382, 2.018) | 1.576 (1.391, 1.761) | |
| Former smoker | 331 (30.8) | 1.570 (1.115, 2.211) | 1.529 (0.949, 2.109)[E] | |
| Daily smoker | 201 (18.7) | 1.220 (0.585, 2.544)[F] | 1.057 (0.580, 1.535)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 4d. Geometric means and medians (95% confidence intervals) of urinary dimethylthiophosphate (DMTP) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Characteristic | No. (%)* | Geometric Mean (µg/L) | Median (µg/L) | p-value** |
|---|---|---|---|---|
| **Total** | 1112 (100.0) | 1.141 (0.980, 1.329) | 1.002 (0.782, 1.222) | |
| **Sex** | | | | 0.824 |
| Male | 561 (50.6) | 1.154 (0.885, 1.504) | 0.997 (0.561, 1.433)[E] | |
| Female | 551 (49.4) | 1.129 (0.911, 1.398) | 1.016 (0.709, 1.323) | |
| **Age (yrs)** | | | | 0.002 |
| 18-49 | 660 (56.8) | 1.118 (0.912, 1.369) | 0.985 (0.775, 1.195) | |
| 50-59 | 121 (18.4) | 0.998 (0.565, 1.762)[E] | 0.911 (0.000, 1.870)[F] | |
| 60-69 | 218 (17.5) | 1.180 (0.923, 1.510) | 1.318 (0.971, 1.666) | |
| 70-79 | 113 (7.3) | 1.738 (0.699, 4.320)[F] | 1.567 (0.577, 2.556)[E] | |
| **Body mass index** | | | | 0.064 |
| Underweight and healthy | 401 (41.8) | 1.307 (0.851, 2.008)[E] | 1.071 (0.468, 1.675)[E] | |
| Overweight | 381 (29.9) | 1.184 (0.870, 1.611) | 1.030 (0.569, 1.492)[E] | |
| Obese class | 330 (28.3) | 0.898 (0.473, 1.706)[E] | 0.823 (0.464, 1.182)[E] | |
| **Waist circumference** | | | | 0.102 |
| Underweight and healthy | 405 (41.3) | 1.209 (0.863, 1.693) | 1.011 (0.459, 1.564)[E] | |
| Overweight | 227 (18.1) | 1.279 (0.909, 1.851) | 1.176 (0.718, 1.633)[E] | |
| Obese class | 480 (40.6) | 1.017 (0.699, 1.479)[E] | 0.989 (0.681, 1.296) | |
| **Diabetes** | | | | 0.951 |
| No | 1043 (91.9) | 1.162 (1.010, 1.335) | 1.019 (0.794, 1.245) | |
| Yes | 69 (8.1) | 0.935 (0.478, 1.830)[E] | 0.853 (0.114, 1.591)[F] | |
| **Race** | | | | <0.001 |
| White | 856 (70.6) | 1.340 (0.917, 1.959) | 1.270 (0.812, 1.729) | |
| Non-White | 256 (29.4) | 0.777 (0.258, 2.335)[F] | 0.535 (0.226, 0.843)[E] | |
| **Physical activity** | | | | 0.093 |
| Active | 608 (52.1) | 1.215 (0.950, 1.553) | 1.038 (0.666, 1.410) | |
| Inactive | 504 (47.9) | 1.066 (0.812, 1.400) | 0.995 (0.713, 1.277) | |
| **Sedentary behaviour** | | | | 0.811 |
| Healthy | 496 (47.8) | 1.188 (0.875, 1.611) | 1.018 (0.660, 1.376) | |
| Moderately sedentary | 468 (39.1) | 1.155 (0.808, 1.537) | 1.025 (0.455, 1.595)[E] | |
| Sedentary | 148 (13.1) | 1.059 (0.684, 1.641)[E] | 0.796 (0.358, 1.235)[E] | |
| **Highest level of education** | | | | 0.027 |

| | | | | |
|---|---|---|---|---|
| Less than secondary school | 106 (6.7) | 0.835 (0.341, 2.043)[F] | 0.867 (0.333, 1.401)[E] | |
| Secondary school | 294 (27.8) | 0.862 (0.379, 1.962)[F] | 0.606 (0.302, 0.911)[E] | |
| Post-secondary degree/diploma | 712 (65.5) | 1.327 (0.940, 1.874) | 1.177 (0.783, 1.570) | |
| **Smoking status** | | | | <0.001 |
| Non-smoker | 578 (50.6) | 1.286 (0.952, 1.737) | 1.168 (0.753, 1.583) | |
| Former smoker | 332 (30.6) | 1.314 (0.892, 1.935)[E] | 1.080 (0.624, 1.535)[E] | |
| Daily smoker | 202 (18.8) | 0.660 (0.129, 3.376)[F] | 0.547 (0.216, 0.878)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

Appendices 4e-4h present the baseline characteristics for unadjusted pyrethroids concentrations. The geometric means of *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA were 0.017 µg/L (95% CI: 0.014, 0.021), 0.188 µg/L (95% CI: 0.125, 0.281), 0.538 µg/L (95% CI: 0.402, 0.721), and 0.272 µg/L (95% CI: 0.184, 0.401), respectively. The medians of *cis*-DBCA, *cis*-DCCA, 3-PBA, and *trans*-DCCA were 0.017 µg/L (95% CI: 0.014, 0.020), 0.163 µg/L (95% CI: 0.110, 0.216), 0.467 µg/L (95% CI: 0.347, 0.586), and 0.233 µg/L (95% CI: 0.169, 0.297), respectively.

For unadjusted pyrethroid metabolites, the geometric mean for each of the urinary pyrethroids tended to be higher for individuals who were female, non-white, active, sedentary, or who had a post-secondary degree/diploma, who had diabetes, or did not smoke. The geometric means showed a higher sampling variability for those who were 50-79 years old, inactive, sedentary, who had a BMI of 25 or higher, who had diabetes, had no post-secondary degree/diploma, or who smoked daily. The medians of unadjusted pyrethroid metabolites showed similar tendencies. However, these differences in distributions of the four urinary pyrethroids were not statistically significant.

**Appendix 4e. Geometric means and medians (95% confidence intervals) of urinary *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*cis*-DBCA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)[*] | Geometric Mean (µg/L) | Median (µg/L) | p-value[**] |
|---|---|---|---|---|
| **Total** | 1095 (100.0) | 0.017 (0.014, 0.021) | 0.017 (0.014, 0.020) | |
| **Sex** | | | | 0.796 |
| Male | 550 (49.4) | 0.017 (0.013, 0.021) | 0.016 (0.013, 0.019) | |
| Female | 545 (50.6) | 0.018 (0.014, 0.023) | 0.018 (0.014, 0.023) | |
| **Age (yrs)** | | | | 0.065 |
| 18-49 | 656 (57.0) | 0.019 (0.014, 0.025) | 0.018 (0.015, 0.022) | |
| 50-59 | 120 (18.4) | 0.012 (0.005, 0.033)[F] | 0.013 (0.007, 0.020)[E] | |
| 60-69 | 214 (17.5) | 0.017 (0.012, 0.023)[E] | 0.018 (0.010, 0.026)[E] | |
| 70-79 | 105 (7.1) | 0.022 (0.011, 0.041)[E] | 0.018 (0.008, 0.028)[E] | |
| **Body mass index** | | | | 0.019 |
| Underweight and healthy | 391 (41.9) | 0.017 (0.012, 0.023) | 0.018 (0.014, 0.022) | |
| Overweight | 380 (29.8) | 0.016 (0.011, 0.023)[E] | 0.015 (0.012, 0.019) | |
| Obese class | 324 (28.3) | 0.020 (0.013, 0.031)[E] | 0.022 (0.015, 0.030) | |
| **Waist circumference** | | | | 0.055 |
| Underweight and healthy | 396 (40.6) | 0.017 (0.013, 0.022) | 0.017 (0.014, 0.020) | |
| Overweight | 230 (18.0) | 0.014 (0.007, 0.026)[E] | 0.014 (0.007, 0.021)[E] | |
| Obese class | 469 (41.4) | 0.019 (0.014, 0.027) | 0.020 (0.016, 0.024) | |
| **Diabetes** | | | | 0.271 |
| No | 1023 (91.7) | 0.017 (0.013, 0.021) | 0.017 (0.014, 0.020) | |
| Yes | 72 (8.3) | 0.021 (0.010, 0.043)[E] | 0.017 (0.004, 0.030)[F] | |
| **Race** | | | | 0.026 |
| White | 837 (70.2) | 0.016 (0.013, 0.021) | 0.016 (0.012, 0.020) | |
| Non-White | 258 (29.8) | 0.019 (0.013, 0.028) | 0.018 (0.014, 0.023) | |
| **Physical activity** | | | | 0.068 |
| Active | 595 (51.7) | 0.018 (0.014, 0.023) | 0.018 (0.015, 0.020) | |
| Inactive | 500 (48.3) | 0.016 (0.011, 0.024)[E] | 0.016 (0.009, 0.022)[E] | |
| **Sedentary behaviour** | | | | 0.699 |
| Healthy | 484 (46.5) | 0.018 (0.013, 0.024) | 0.018 (0.013, 0.022) | |
| Moderately sedentary | 459 (39.9) | 0.016 (0.012, 0.021) | 0.017 (0.014, 0.019) | |
| Sedentary | 152 (13.6) | 0.018 (0.012, 0.028)[E] | 0.018 (0.008, 0.028)[E] | |
| **Highest level of education** | | | | 0.984 |
| Less than secondary school | 101 (6.4) | 0.014 (0.010, 0.021)[E] | 0.015 (0.011, 0.020) | |
| Secondary school | 287 (27.7) | 0.016 (0.011, 0.023)[E] | 0.016 (0.009, 0.023)[E] | |
| Post-secondary degree/diploma | 707 (65.8) | 0.018 (0.014, 0.023) | 0.017 (0.014, 0.020) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.003 |
| Non-smoker | 570 (50.6) | 0.020 (0.014, 0.029) | 0.019 (0.014, 0.024) | |
| Former smoker | 322 (30.2) | 0.015 (0.010, 0.023)[E] | 0.016 (0.011 0.022) | |
| Daily smoker | 203 (19.2) | 0.014 (0.008, 0.027)[E] | 0.014 (0.008, 0.021) | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 4f. Geometric means and medians (95% confidence intervals) of urinary *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane (*cis*-DCCA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)* | Geometric Mean (µg/L) | Median (µg/L) | p-value** |
|---|---|---|---|---|
| **Total** | 1141 (100.0) | 0.188 (0.125, 0.281)[E] | 0.163 (0.110, 0.216) | |
| **Sex** | | | | 0.487 |
| Male | 577 (50.4) | 0.167 (0.100, 0.279)[E] | 0.146 (0.081, 0.211)[E] | |
| Female | 564 (49.6) | 0.212 (0.127, 0.354)[E] | 0.180 (0.111, 0.248)[E] | |
| **Age (yrs)** | | | | 0.958 |
| 18-49 | 681 (57.2) | 0.193 (0.116, 0.322)[E] | 0.169 (0.101, 0.238)[E] | |
| 50-59 | 126 (18.3) | 0.189 (0.106, 0.339)[E] | 0.187 (0.054, 0.319)[E] | |
| 60-69 | 219 (17.0) | 0.164 (0.101, 0.267)[E] | 0.150 (0.090, 0.209)[E] | |
| 70-79 | 115 (7.5) | 0.197 (0.122, 0.318)[E] | 0.159 (0.069, 0.248)[E] | |
| **Body mass index** | | | | 0.269 |
| Underweight and healthy | 410 (41.6) | 0.197 (0.114, 0.340)[E] | 0.170 (0.091, 0.248)[E] | |
| Overweight | 393 (30.5) | 0.187 (0.123, 0.283)[E] | 0.168 (0.097, 0.239)[E] | |
| Obese class | 338 (27.9) | 0.175 (0.110, 0.280)[E] | 0.148 (0.077, 0.220)[E] | |
| **Waist circumference** | | | | 0.044 |
| Underweight and healthy | 413 (41.1) | 0.191 (0.108, 0.338)[E] | 0.169 (0.085, 0.252)[E] | |
| Overweight | 236 (18.3) | 0.205 (0.135, 0.311)[E] | 0.181 (0.101, 0.260)[E] | |
| Obese class | 492 (40.6) | 0.177 (0.115, 0.271)[E] | 0.156 (0.090, 0.222)[E] | |
| **Diabetes** | | | | 0.643 |
| No | 1066 (91.7) | 0.185 (0.119, 0.288)[E] | 0.159 (0.105, 0.213) | |
| Yes | 75 (8.3) | 0.221 (0.148, 0.329)[E] | 0.221 (0.103, 0.340)[E] | |
| **Race** | | | | 0.225 |
| White | 875 (70.7) | 0.177 (0.112, 0.278)[E] | 0.155 (0.093, 0.217)[E] | |
| Non-White | 266 (29.3) | 0.216 (0.136, 0.344)[E] | 0.182 (0.105, 0.260)[E] | |
| **Physical activity** | | | | 0.013 |
| Active | 627 (52.6) | 0.208 (0.133, 0.323)[E] | 0.186 (0.091, 0.280)[E] | |
| Inactive | 514 (47.4) | 0.168 (0.095, 0.298)[E] | 0.146 (0.095, 0.198) | |
| **Sedentary behaviour** | | | | 0.965 |
| Healthy | 510 (47.4) | 0.197 (0.127, 0.305)[E] | 0.159 (0.078, 0.240)[E] | |
| Moderately sedentary | 478 (39.6) | 0.170 (0.109, 0.267)[E] | 0.169 (0.113, 0.225) | |
| Sedentary | 153 (13.0) | 0.212 (0.101, 0.446)[F] | 0.161 (0.062, 0.260)[E] | |
| **Highest level of education** | | | | 0.055 |
| Less than secondary school | 106 (6.5) | 0.131 (0.052, 0.332)[F] | 0.143 (0.088, 0.197)[E] | |
| Secondary school | 300 (27.2) | 0.163 (0.076, 0.350)[F] | 0.145 (0.044, 0.247)[E] | |
| Post-secondary degree/diploma | 735 (66.3) | 0.206 (0.139, 0.306)[E] | 0.173 (0.116, 0.229) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.198 |
| Non-smoker | 591 (50.3) | 0.212 (0.144, 0.312)[E] | 0.182 (0.124, 0.240) | |
| Former smoker | 340 (30.3) | 0.172 (0.105, 0.281)[E] | 0.148 (0.080, 0.216)[E] | |
| Daily smoker | 210 (19.4) | 0.157 (0.080, 0.309)[E] | 0.162 (0.081, 0.243)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 4g. Geometric means and medians (95% confidence intervals) of urinary 3-phenoxybenzoic acid (3-PBA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)* | Geometric Mean (µg/L) | Median (µg/L) | p-value** |
|---|---|---|---|---|
| **Total** | 1139 (100.0) | 0.538 (0.402, 0.721) | 0.467 (0.347, 0.586) | |
| **Sex** | | | | 0.176 |
| Male | 574 (50.5) | 0.443 (0.249, 0.788)[E] | 0.430 (0.287, 0.573) | |
| Female | 565 (49.5) | 0.656 (0.391, 1.102)[E] | 0.494 (0.320, 0.668) | |
| **Age (yrs)** | | | | 0.800 |
| 18-49 | 678 (56.9) | 0.577 (0.387, 0.862)[E] | 0.487 (0.333, 0.641) | |
| 50-59 | 126 (18.4) | 0.511 (0.299, 0.874)[E] | 0.457 (0.211, 0.702)[E] | |
| 60-69 | 220 (17.2) | 0.452 (0.261, 0.785)[E] | 0.385 (0.185, 0.586)[E] | |
| 70-79 | 115 (7.5) | 0.534 (0.352, 0.811)[E] | 0.413 (0.254, 0.572)[E] | |
| **Body mass index** | | | | 0.638 |
| Underweight and healthy | 409 (41.8) | 0.642 (0.379, 1.086)[E] | 0.547 (0.350, 0.745) | |
| Overweight | 393 (30.6) | 0.466 (0.297, 0.733)[E] | 0.450 (0.295, 0.605) | |
| Obese class | 337 (27.6) | 0.483 (0.300, 0.777)[E] | 0.415 (0.303, 0.527) | |
| **Waist circumference** | | | | 0.721 |
| Underweight and healthy | 414 (41.4) | 0.574 (0.371, 0.889)[E] | 0.523 (0.360, 0.686) | |
| Overweight | 235 (18.2) | 0.564 (0.395, 0.805) | 0.454 (0.277, 0.632) | |
| Obese class | 490 (40.4) | 0.493 (0.347, 0.700) | 0.450 (0.355, 0.545) | |
| **Diabetes** | | | | 0.583 |
| No | 1066 (92.3) | 0.525 (0.377, 0.732) | 0.466 (0.340, 0.591) | |
| Yes | 73 (7.7) | 0.721 (0.317, 1.641)[F] | 0.570 (0.000, 1.305)[F] | |
| **Race** | | | | 0.354 |
| White | 874 (70.6) | 0.499 (0.350, 0.712) | 0.440 (0.324, 0.556) | |
| Non-White | 265 (29.4) | 0.645 (0.422, 0.986)[E] | 0.583 (0.427, 0.740) | |
| **Physical activity** | | | | 0.106 |
| Active | 627 (53.1) | 0.588 (0.401, 0.861)[E] | 0.507 (0.338, 0.676) | |
| Inactive | 512 (46.9) | 0.487 (0.301, 0.787)[E] | 0.414 (0.274, 0.553) | |
| **Sedentary behaviour** | | | | 0.974 |
| Healthy | 508 (47.6) | 0.557 (0.396, 0.784) | 0.476 (0.320, 0.632) | |
| Moderately sedentary | 478 (39.4) | 0.501 (0.377, 0.665) | 0.467 (0.361, 0.572) | |
| Sedentary | 153 (13.0) | 0.588 (0.301, 1.149)[E] | 0.404 (0.153, 0.654)[E] | |
| **Highest level of education** | | | | 0.175 |
| Less than secondary school | 107 (6.6) | 0.395 (0.170, 0.917)[F] | 0.400 (0.240, 0.560)[E] | |
| Secondary school | 298 (27.3) | 0.480 (0.257, 0.894)[E] | 0.388 (0.196, 0.581)[E] | |
| Post-secondary degree/diploma | 734 (66.1) | 0.582 (0.429, 0.789) | 0.479 (0.344, 0.614) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.493 |
| Non-smoker | 592 (50.0) | 0.570 (0.431, 0.754) | 0.509 (0.400, 0.618) | |
| Former smoker | 338 (30.4) | 0.501 (0.350, 0.718) | 0.384 (0.227, 0.540)[E] | |
| Daily smoker | 209 (19.6) | 0.519 (0.290, 0.929)[E] | 0.420 (0.191, 0.649)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 4h. Geometric means and medians (95% confidence intervals) of urinary *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid (*trans*-DCCA) concentrations in Canadians 18 years or older in the CHMS 2015-16.**

| Variable | No. (%)[*] | Geometric Mean (µg/L) | Median (µg/L) | p-value[**] |
|---|---|---|---|---|
| **Total** | 1141 (100.0) | 0.272 (0.184, 0.401)[E] | 0.233 (0.169, 0.297) | |
| **Sex** | | | | 0.412 |
| Male | 575 (50.2) | 0.243 (0.151, 0.390)[E] | 0.208 (0.143, 0.274) | |
| Female | 566 (49.8) | 0.305 (0.179, 0.518)[E] | 0.256 (0.160, 0.353)[E] | |
| **Age (yrs)** | | | | 0.333 |
| 18-49 | 679 (57.0) | 0.293 (0.176, 0.487)[E] | 0.237 (0.148, 0.325)[E] | |
| 50-59 | 126 (18.3) | 0.254 (0.127, 0.510)[E] | 0.260 (0.082, 0.437)[E] | |
| 60-69 | 220 (17.2) | 0.237 (0.143, 0.393)[E] | 0.192 (0.096, 0.288)[E] | |
| 70-79 | 116 (7.5) | 0.249 (0.156, 0.398)[E] | 0.185 (0.088, 0.282)[E] | |
| **Body mass index** | | | | 0.940 |
| Underweight and healthy | 410 (41.6) | 0.322 (0.173, 0.599)[E] | 0.263 (0.164, 0.361)[E] | |
| Overweight | 393 (30.5) | 0.249 (0.160, 0.387)[E] | 0.210 (0.142, 0.278) | |
| Obese class | 338 (27.9) | 0.233 (0.128, 0.424)[E] | 0.221 (0.110, 0.333)[E] | |
| **Waist circumference** | | | | 0.642 |
| Underweight and healthy | 414 (41.1) | 0.309 (0.171, 0.558)[E] | 0.263 (0.151, 0.375)[E] | |
| Overweight | 235 (18.1) | 0.283 (0.203, 0.395) | 0.203 (0.128, 0.278)[E] | |
| Obese class | 492 (40.8) | 0.235 (0.138, 0.399)[E] | 0.229 (0.163, 0.296) | |
| **Diabetes** | | | | 0.924 |
| No | 1066 (91.7) | 0.270 (0.178, 0.409)[E] | 0.229 (0.162, 0.296) | |
| Yes | 75 (8.3) | 0.295 (0.190, 0.457)[E] | 0.322 (0.121, 0.523)[E] | |
| **Race** | | | | 0.968 |
| White | 875 (70.7) | 0.257 (0.166, 0.398)[E] | 0.231 (0.148, 0.315) | |
| Non-White | 266 (29.3) | 0.310 (0.199, 0.483)[E] | 0.244 (0.178, 0.309) | |
| **Physical activity** | | | | 0.013 |
| Active | 627 (52.7) | 0.305 (0.197, 0.474)[E] | 0.262 (0.165, 0.358)[E] | |
| Inactive | 514 (47.3) | 0.239 (0.130, 0.441)[E] | 0.197 (0.123, 0.271)[E] | |
| **Sedentary behaviour** | | | | 0.975 |
| Healthy | 509 (47.3) | 0.286 (0.186, 0.440)[E] | 0.237 (0.159, 0.316) | |
| Moderately sedentary | 479 (39.7) | 0.250 (0.163, 0.382)[E] | 0.229 (0.152, 0.306) | |
| Sedentary | 153 (13.0) | 0.295 (0.136, 0.636)[F] | 0.184 (0.027, 0.342)[F] | |
| **Highest level of education** | | | | 0.086 |
| Less than secondary school | 106 (6.5) | 0.204 (0.096, 0.434)[F] | 0.167 (0.058, 0.277)[E] | |
| Secondary school | 300 (27.2) | 0.235 (0.108, 0.512)[F] | 0.194 (0.102, 0.287)[E] | |
| Post-secondary degree/diploma | 735 (66.3) | 0.297 (0.205, 0.431)[E] | 0.245 (0.170, 0.320) | |

| | | | | |
|---|---|---|---|---|
| **Smoking status** | | | | 0.970 |
| Non-smoker | 591 (50.3) | 0.305 (0.210, 0.442)[E] | 0.265 (0.194, 0.336) | |
| Former smoker | 340 (30.3) | 0.243 (0.146, 0.403)[E] | 0.204 (0.112, 0.295)[E] | |
| Daily smoker | 210 (19.4) | 0.242 (0.134, 0.436)[E] | 0.206 (0.111, 0.301)[E] | |

[*] (%) are based off the weighted population size.

[**] p values represent the differences in distribution between the various levels. Two leveled distributions were evaluated using the Kolmogorov-Smirnov Test and three or more leveled distributions were evaluated using the Kruskal-Wallis Test.

[E] Interpret data with caution due to high coefficient of variation (>16.6%)

[F] Interpret data with extreme caution as the estimate does not meet Statistics Canada's quality standards due to high coefficient of variation (>33.3%)

**Appendix 5. Risk ratios (RRs) and 99% confidence intervals (CIs) for the 4th, 3rd, and 2nd quartiles compared to the 1st quartile for urinary concentrations in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

**Appendix 5.a Risk ratios (RRs) and 99% confidence intervals (CIs) for the 4th, 3rd, and 2nd quartiles compared to the 1st quartile for urinary concentrations of organophosphates in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Metabolite** | **RR (99% CI)** | **p-value** | **RR (99% CI)** | **p-value** |
| **DEP[a]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.71 (-0.67, 4.08) | 0.44 | 2.77 (0.49, 5.05) | 0.05 |
| Quartile 3 | 1.87 (-0.80, 4.54) | 0.40 | 1.05 (0.16, 1.94) | 0.88 |
| Quartile 2 | 1.03 (-0.90, 2.97) | 0.96 | 1.92 (0.01, 3.83) | 0.22 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 1.83 (-0.29, 3.95) | 0.31 | 2.64 (0.29, 5.00) | 0.07 |
| Quartile 3 | 1.69 (-0.43, 3.80) | 0.40 | 0.91 (0.05, 1.77) | 0.78 |
| Quartile 2 | 1.07 (-1.14, 3.28) | 0.93 | 1.67 (0.12, 3.21) | 0.27 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 2.64 (-1.00, 6.29) | 0.25 | 3.99 (-0.36, 8.35) | 0.08 |
| Quartile 3 | 2.42 (-0.73, 5.57) | 0.25 | 1.28 (-0.28, 2.84) | 0.65 |
| Quartile 2 | 1.86 (-2.14, 5.87) | 0.58 | 1.64 (0.19, 3.10) | 0.25 |
| Quartile 1 | Reference | | Reference | |
| **DETP[b]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 0.89 (-0.48, 2.25) | 0.83 | 0.64 (-0.24, 1.52) | 0.29 |
| Quartile 3 | 1.17 (-0.57, 2.90) | 0.81 | 0.97 (-0.26, 2.19) | 0.94 |
| Quartile 2 | 0.91 (-0.88, 2.70) | 0.90 | 0.71 (-0.13, 1.54) | 0.36 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 0.94 (-0.37, 2.25) | 0.91 | 0.57 (-0.25, 1.39) | 0.18 |
| Quartile 3 | 1.16 (-0.52, 2.84) | 0.81 | 0.89 (-0.44, 2.22) | 0.83 |
| Quartile 2 | 1.12 (-1.26, 3.50) | 0.90 | 0.80 (-0.13, 1.74) | 0.59 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 1.01 (-0.65, 2.67) | 0.99 | 0.55 (-0.43, 1.53) | 0.24 |
| Quartile 3 | 1.31 (-0.75, 3.38) | 0.70 | 1.02 (-0.49, 2.53) | 0.97 |

| | | | | |
|---|---|---|---|---|
| Quartile 2 | 1.19 (-1.52, 3.91) | 0.85 | 0.84 (-0.10, 1.78) | 0.66 |
| Quartile 1 | Reference | | Reference | |
| **DMP[c]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.98 (0.41, 3.55) | 0.11 | 0.76 (-0.65, 2.17) | 0.66 |
| Quartile 3 | 1.31 (-0.36, 2.98) | 0.63 | 1.66 (-0.49, 3.81) | 0.43 |
| Quartile 2 | 2.79 (-1.13, 6.72) | 0.24 | 0.80 (-0.49, 2.09) | 0.69 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 2.14 (0.28, 4.01) | 0.11 | 0.71 (-0.79, 2.20) | 0.61 |
| Quartile 3 | 1.33 (-0.39, 3.06) | 0.62 | 1.52 (-0.92, 3.96) | 0.58 |
| Quartile 2 | 3.10 (-1.68, 7.87) | 0.26 | 0.72 (-0.53, 1.96) | 0.56 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 2.94 (-0.98, 6.85) | 0.20 | 1.05 (-1.07, 3.18) | 0.95 |
| Quartile 3 | 1.36 (-0.80, 3.52) | 0.67 | 1.77 (-0.94, 4.49) | 0.46 |
| Quartile 2 | 3.24 (-2.64, 9.12) | 0.33 | 0.58 (-0.38, 1.55) | 0.27 |
| Quartile 1 | Reference | | Reference | |
| **DMTP[d]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 0.69 (0.03, 1.35) | 0.22 | 0.76 (-0.32, 1.83) | 0.56 |
| Quartile 3 | 0.73 (-0.42, 1.89) | 0.55 | 0.78 (-0.79, 2.35) | 0.72 |
| Quartile 2 | 0.83 (-0.68, 2.34) | 0.78 | 1.15 (-0.50, 2.80) | 0.81 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 0.72 (-0.06, 2.35) | 0.35 | 0.71 (-0.40, 1.81) | 0.49 |
| Quartile 3 | 0.61 (-0.29, 1.51) | 0.26 | 0.66 (-0.79, 2.11) | 0.55 |
| Quartile 2 | 0.78 (-0.80, 1.49) | 0.71 | 1.02 (-0.55, 2.59) | 0.97 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 0.86 (-0.34, 2.06) | 0.77 | 0.86 (-0.54, 2.26) | 0.80 |
| Quartile 3 | 0.58 (-0.33, 1.48) | 0.23 | 0.66 (-0.89, 2.21) | 0.57 |
| Quartile 2 | 0.86 (-1.20, 2.91) | 0.86 | 0.95 (-0.74, 2.65) | 0.94 |
| Quartile 1 | Reference | | Reference | |

**Abbreviations:** DEP, diethylphosphate; DETP, diethylthiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate

[a] Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, body mass index and education. n=1113.

[b] Model 3 is adjusted for age, sex, body mass index and sedentary behaviour. n=1094.

[c] Model 3 is adjusted for age, sex, body mass index and education. n=1108.

[d] Model 3 is adjusted for age, sex, body mass index and sedentary behaviour. n=1087.

**Appendix 5.b Relative risk (RR) and 99% confidence intervals (CIs) for the 4th, 3rd, and 2nd quartiles compared to the 1st urinary concentrations of pyrethroids in relation to having diabetes in Canadians 18 years or older in the CHMS 2015-16.**

| | Unadjusted | | Creatinine-Adjusted | |
|---|---|---|---|---|
| **Variable** | **RR (99% CI)** | **p-value** | **RR (99% CI)** | **p-value** |
| ***cis*-DBCA[a]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.55 (-0.44, 3.53) | 0.48 | 1.00 (-0.20, 2.20) | 0.99 |
| Quartile 3 | 0.87 (-0.42, 2.16) | 0.79 | 1.03 (-0.67, 2.72) | 0.97 |
| Quartile 2 | 1.43 (-0.48, 3.34) | 0.56 | 0.95 (-0.31, 2.21) | 0.92 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 1.90 (-0.56, 4.36) | 0.35 | 1.20 (-0.59, 3.00) | 0.77 |
| Quartile 3 | 1.04 (-0.57, 2.64) | 0.95 | 1.02 (-0.76, 2.79) | 0.98 |
| Quartile 2 | 1.64 (-0.43, 3.70) | 0.43 | 1.00 (-0.41, 2.41) | 0.99 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 1.80 (-0.50, 4.10) | 0.37 | 1.15 (-0.62, 2.93) | 0.82 |
| Quartile 3 | 1.05 (-0.56, 2.66) | 0.94 | 1.13 (-1.20, 3.46) | 0.88 |
| Quartile 2 | 1.83 (-0.54, 4.21) | 0.37 | 0.98 (-0.63, 2.59) | 0.97 |
| Quartile 1 | Reference | | Reference | |
| ***cis*-DCCA[b]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.57 (-1.17, 4.32) | 0.59 | 1.34 (0.00, 2.69) | 0.51 |
| Quartile 3 | 1.45 (-0.50, 3.39) | 0.55 | 1.08 (-0.61, 2.77) | 0.90 |
| Quartile 2 | 1.59 (-0.61, 3.78) | 0.49 | 1.13 (-0.06, 2.33) | 0.77 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |
| Quartile 4 | 1.58 (-1.24, 4.40) | 0.60 | 1.25 (-0.11, 2.60) | 0.64 |
| Quartile 3 | 1.48 (-0.46, 3.42) | 0.92 | 0.99 (-0.75, 2.72) | 0.99 |
| Quartile 2 | 1.44 (-0.62, 3.51) | 0.58 | 0.93 (-0.12, 1.98) | 0.87 |
| Quartile 1 | Reference | | Reference | |
| **Model 3** | | | | |
| Quartile 4 | 1.73 (-1.05, 4.51) | 0.50 | 1.31 (-0.01, 2.63) | 0.55 |
| Quartile 3 | 1.82 (-0.92, 4.56) | 0.44 | 0.98 (-0.91, 2.87) | 0.98 |
| Quartile 2 | 1.73 (-0.85, 4.31) | 0.47 | 0.70 (-0.17, 1.57) | 0.37 |
| Quartile 1 | Reference | | Reference | |
| **3-PBA[c]** | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.35 (-0.78, 3.47) | 0.68 | 1.49 (0.23, 2.75) | 0.32 |
| Quartile 3 | 0.65 (-0.58, 1.88) | 0.47 | 0.41 (-0.14, 0.95) | 0.01 |
| Quartile 2 | 1.19 (-0.42, 2.81) | 0.76 | 0.93 (-0.24, 2.11) | 0.89 |
| Quartile 1 | Reference | | Reference | |
| **Model 2** | | | | |

| | | | | |
|---|---|---|---|---|
| Quartile 4 | 1.45 (-0.83, 3.72) | 0.61 | 1.55 (0.40, 2.70) | 0.22 |
| Quartile 3 | 0.72 (-0.59, 2.03) | 0.58 | 0.43 (-0.21, 1.07) | 0.02 |
| Quartile 2 | 1.11 (-0.55, 2.76) | 0.87 | 0.80 (-0.12, 1.71) | 0.57 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 1.80 (-1.87, 5.48) | 0.57 | 1.88 (-0.27, 4.04) | 0.29 |
| Quartile 3 | 0.88 (-0.83, 2.59) | 0.86 | 0.46 (-0.33, 1.25) | 0.08 |
| Quartile 2 | 1.32 (-1.31, 3.94) | 0.76 | 0.82 (-0.12, 1.76) | 0.62 |
| Quartile 1 | Reference | | Reference | |
| **trans-DCCA**[d] | | | | |
| **Model 1** | | | | |
| Quartile 4 | 1.50 (0.12, 1.53) | 0.71 | 1.21 (-0.23, 2.65) | 0.39 |
| Quartile 3 | 0.80 (-0.29, 1.89) | 0.73 | 1.29 (-0.83, 3.41) | 0.88 |
| Quartile 2 | 0.83 (0.12, 1.53) | 0.53 | 0.78 (-0.10, 1.67) | 0.55 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 2** | | | | |
| Quartile 4 | 1.61 (0.07, 3.14) | 0.31 | 1.21 (-0.04, 2.45) | 0.67 |
| Quartile 3 | 0.93 (-0.29, 2.14) | 0.87 | 1.41 (-0.67, 3.50) | 0.61 |
| Quartile 2 | 0.84 (0.24, 1.44) | 0.50 | 0.79 (-0.10, 1.68) | 0.54 |
| Quartile 1 | Reference | | Reference | |
| | | | | |
| **Model 3** | | | | |
| Quartile 4 | 2.08 (-0.16, 4.31) | 0.21 | 1.68 (-0.19, 3.55) | 0.35 |
| Quartile 3 | 1.20 (-0.21, 2.61) | 0.72 | 1.69 (-0.94, 4.33) | 0.50 |
| Quartile 2 | 0.99 (0.05, 1.92) | 0.97 | 1.05 (-0.26, 2.36) | 0.93 |
| Quartile 1 | Reference | | Reference | |

**Abbreviations:** *cis*-DBCA, *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropane carboxylic acid; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid; 3-PBA, 3-Phenoxybenzoic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxylic acid

**a** Model 1 is unadjusted, Model 2 is adjusted for age and sex, Model 3 is adjusted for age, sex, body mass index, and education. n=1095.

[b] Model 3 is adjusted for age, sex, body mass index and sedentary behaviour. n=1141.

[c] Model 3 is adjusted for age, sex, body mass index and education. n=1139.

[d] Model 3 is adjusted for age, sex, body mass index and education. n=1141.