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Review

Pesticide exposures and respiratory health in general populations

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ABSTRACT

Human exposures to pesticides can occur in the workplace, in the household and through the ambient environment. While several articles have reviewed the impact of pesticide exposures on human respiratory health in occupational settings, to the best of our knowledge, this article is the first one to review published studies on the association between pesticide exposures and human respiratory health in the general populations. In this article, we critically reviewed evidences up to date studying the associations between non-occupational pesticide exposures and respiratory health in general populations. This article also highlighted questions arising from these studies, including our recent analyses using the data from the Canadian Health Measures Survey (CHMS), for future research. We found few studies have addressed the impact of environmental pesticide exposures on respiratory health, especially on lung function, in general populations. In the studies using the data from CHMS Cycle 1, exposures to OP insecticides, pyrethroid insecticides, and the organochlorine pesticide DDT were associated with impaired lung function in the Canadian general population, but no significant associations were observed for the herbicide 2,4-D. Future research should focus on the potential age-specific and pesticide-specific effect on respiratory health in the general population, and repeated longitudinal study design is critical for assessing the temporal variations in pesticide exposures. Research findings from current studies of non-occupational pesticide exposures and their health impact in general population will help to improve the role of regulatory policies in mitigating pesticide-related public health problems, and thereafter providing greater benefit to the general population.

Contents

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Introduction

Human exposures to pesticides can occur in the workplace, in the household and through the ambient environment. According to the United States Environment Protection Agency (US EPA) Pesticide Program, approximately two billion pounds of pesticides is used every year in North American (US EPA, 2011), but only 1% reaches its target (Gavrilescu, 2005), suggesting the majority of pesticides will enter the environment without producing the intended benefit. Pesticide run-off from farm land and subsequent movement into water bodies further increases the spread of pesticides in the environment (Damalas and Eleftherohorinos, 2011; Davis et al., 1992) thereby increasing the likelihood of exposure to non-target organisms and the general public. Consumption of food containing pesticide residues is a recognized source of pesticide exposures in the general population (Schettgen et al., 2002; Ye et al., 2015b). It has been estimated that up to 50% of fruits, vegetables, and cereals grown in the European Union (EU) contain pesticide residues, and that one out of 20 food items in EU markets is known to exceed EU legal limits for pesticide residues (EU EC, 2005). Milk and vegetable oil products can also be contaminated with pesticides. A number of studies have suggested that although the concentrations did not exceed EU legal limits, the organochlorine pesticide 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT) was detected in a high percentage of milk products in the Greek market (97.4%) (Tsakiris et al., 2015) and the organophosphate (OP) pesticides, including fenthion and dimethoate, were detected in more than 80% of olive oil products from the Greek market (Tsatsakis et al., 2003). In Canada, it has been estimated that 68.5% of fruits and vegetables contain detectable residues of one or more pesticides; although most of these pesticide were at low concentrations (<1 mg/kg), there were still 3% of fruits and vegetables with pesticide levels higher than legal maximum residue limits (Ripley et al., 2000). The pesticide residues on food items mainly originate from farming and/or from pesticide applications during food storage and transport (Sanborn et al., 2002).

Occupational pesticide exposures, particularly in agricultural occupations (Ye et al., 2013), have been associated with human respiratory health problems, including self-reported coughing, wheezing, and airway inflammation (O'Malley, 1997; Sanborn et al., 2002), asthma (Beard et al., 2003; Deschamps et al., 1994; Hoppin et al., 2006, 2008, 2009; Senthilselvan et al., 1992), chronic obstructive pulmonary disease (COPD) (Chakraborty et al., 2009; Hoppin et al., 2007; Tual et al., 2013; Valcin et al., 2007), lung cancer (Alavanja et al., 2004; Beane Freeman et al., 2005; Bonner et al., 2005; Hou et al., 2006; Lee et al., 2004; Pesatori et al., 1994; Purdue et al., 2007; Rusiecki et al., 2006; Samanic et al., 2006), and impaired lung function (Chakraborty et al., 2009; Hernandez et al., 2008; Mekonnen and Agonafir, 2004; Peiris-John et al., 2005; Reynolds et al., 2012; Royce et al., 1993; Salameh et al., 2005; Zuskin et al., 2008). However, given that low-dose environmental pesticide exposures are more prevalent than higher-dose occupational exposures (Damalas and Eleftherohorinos, 2011), it would be more important to understand how environmental pesticide exposures impact respiratory health in the general populations.

In this review article, we critically reviewed evidence available to date examining the associations between environmental pesticide exposures and respiratory health, including lung function, respiratory symptoms and diseases, in the general populations. This article also highlights questions arising from the literature, including our recent analysis using the data from the Canadian Health Measures Survey (CHMS), for further research. To review the literature, we searched English-language studies, reports and abstracts between 1980 and May 2016 in MEDLINE® using key words (including synonyms, adjective and plural forms) and combinations of key words, including occupation, non-occupation, environment, pesticide, insecticide, herbicide, respiratory, pulmonary, airway, lung function, infection, asthma, bronchitis, and COPD. Searching strategy also included cross-referencing of research and review papers. Studies of occupational and workplace-related pesticide exposures were excluded.

1. Pesticide exposures and respiratory health in general populations

While association between workplace-related pesticide exposures and respiratory diseases and symptoms are well documented (Ye et al., 2013), a summary of adverse health impact of environmental chemicals, including pesticides, indicates that pesticide exposures from environment or diet may as well cause respiratory diseases and symptoms in the general populations (Sanborn et al., 2002).

1.1. Respiratory symptoms

Respiratory symptoms associated with non-occupational or environmental pesticide exposures include wheezing, coughing, airway irritation, and airway infection in children. A study in Tanzania, showed that habitants in the houses sprayed with lambda-cyhalothrinnose, a pyrethroid (PYR) insecticide, had nose or throat irritation accompanied by sneezing and coughing (Moretto, 1991). A cross-sectional study of children aged 5 to 16 years in Lebanese public schools showed that residential and/or domestic exposures to pesticides, including OPs, PYRs, bipyridyl herbicides and fungicide, were significantly associated with chronic cough with phlegm (residential: Odds Ratio (OR) = 1.59, 95% Confidence Interval (CI): 1.03–2.45; domestic: OR = 1.96, 95% CI: 1.32–2.92) and recurrent wheezing (residential: OR = 2.73, 95% CI: 1.85–4.05; domestic: OR = 1.49, 95% CI: 1.03–2.16) (Salameh et al., 2003).

Although pesticide exposures are not the direct cause of respiratory infection, such as a virus or bacteria (Tracy et al., 2015), organochlorine pesticides have nonetheless been linked to such infections in young children. A population-based study among Canadian Inuit infants suggested that the prenatal exposure of pesticides was associated with at least 1.56 times higher risk of developing upper respiratory tract infection, but not of the lower respiratory tract (Dallaire et al., 2004). A cohort study in Spain linked the recurrent lower respiratory tract infections in infants to the organochlorine pesticide exposures (Relative Risk = 2.40, 95% CI: 1.19–4.83) (Sunyer et al., 2010). The authors in this study suggested that the high prevalence of lower respiratory tract infection was due to the immunologic suppression effect of 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene (DDE) (Sunyer et al., 2010). In addition, the long-term lower respiratory tract infection during childhood may eventually induce chronic inflammatory diseases of airways, such as asthma, in their later lives (Sigurs et al., 2000, 2005).

1.2. Respiratory diseases

Along with other social, environmental factors and life styles, pesticide exposures have been attributed to increased prevalence of asthma in the past three decades (Hernandez et al., 2011; Selgrade et al., 2006). Although most epidemiological evidences on the association between pesticide use and asthma were in the occupational settings (Beard et al., 2003; Deschamps et al., 1994; Faria et al., 2005; Fieten et al., 2009; Hoppin et al., 2002, 2006, 2008, 2009; Senthilselvan et al., 1992; Vandenplas et al., 2000), non-occupational or environmental exposures to pesticides have also been associated with asthma in general populations.

In California, environmental spills of carbamate insecticides led to incidences of irritant-induced asthma among community residents (Cone et al., 1994). In Australia, asthmatic symptoms in subjects with pre-existing asthma and/or a history of chest tightness were linked to acute exposure to household PYR insecticides (Newton and Breslin, 1983).

The impact of pesticide exposures on risk of asthma in children has gained great attention. In a case report, an 11-year-old girl in the U.S. diagnosed with asthma at age of 6 years underwent a "respiratory arrest secondary to acute asthmatic attack" after giving a bathe to her pet dog using an animal shampoo containing pyrethrin and subsequently died (Wagner, 2000). A cross-sectional study of children aged 5–16 years in Lebanon public school showed that residential and domestic exposure to pesticides were significantly associated with risk of asthma (residential: OR = 2.10, 95% CI: 1.01–4.42; domestic: OR = 1.99, 95% CI: 1.00–3.99) (Salameh et al., 2003). The birth cohort studies in Spain suggested that pre-natal and/or early life exposure to ogranochlorine insecticides, such as DDT, was positively associated with childhood asthma (OR = 2.63, 95% CI: 1.19–4.69) (Sunyer et al., 2005, 2006; Sunyer et al., 2005). Another birth cohort study in the UK suggested that the medium-to-high level of postnatal exposure to fungicides, which might have been indirectly (*e.g.*, through breast milk) obtained from maternal occupational exposures, was associated with an increased risk of childhood asthma (OR = 1.47, 95% CI: 1.14–1.88) and wheezing (OR = 1.22, 95% CI: 1.02–2.05) (Tagiyeva et al., 2010). A nested case–control study of the Children's Health Study in Southern California demonstrated that environmental exposures to herbicide and insecticide in the first year of life were significantly associated with risk of developing childhood asthma (herbicides: OR =4.58, 95% CI: 1.36–15.43; pesticides: OR = 2.39, 95% CI: 1.17–4.89) (Salam et al., 2004). A case–control study of asthma patients and non-asthmatic controls in Lebanon hospital suggests that residential exposure to pesticides was significantly associated to asthma incidence (OR = 2.11, 95% CI: 2.11–5.85) (Salameh et al., 2006a).

Although lack of information on specific types of pesticide being exposed in some studies (Salam et al., 2004, Salameh et al., 2006a; S Tagiyeva et al., 2010) and few large population-based studies have been conducted (Karpati et al., 2004; O'Sullivan et al., 2005; Salam et al., 2004), findings from these studies have suggested that non-occupational or environmental pesticide exposures have the potential to induce asthma in the general populations, and children are likely among the most vulnerable groups of subjects.

A couple of studies on the mosquito control program in New York City showed that spraying of malathion (an OP insecticide) and resmethrin (a pyrethrin insecticide) did not increase the visit rate of asthma at the Emergency Department during the season (rate ratio = 0.92, 95% CI: 0.80–1.07) (Karpati et al., 2004; O'Sullivan et al., 2005), indicating that low-dose seasonal exposure to environment pesticides might have limited impact on asthma morbidity, and further studies on this topic are warranted.

In addition to asthma, COPD, sinusitis and bronchitis have also been linked to environmental pesticide exposures in the general population. A case–control study in Lebanon showed a significant positive relationship between residential pesticide exposures and chronic bronchitis (OR = 3.70, 95% CI: 2.05–6.70) (Salameh et al., 2006b). A cross-sectional study in the US suggests that the prevalence of sinusitis and bronchitis was higher among subjects exposed to chlordane termiticide in a residential area than non-exposed controls (Menconi et al., 1988).

1.3. Lung function

There is some evidence suggesting the association of pesticide exposures with impaired lung function in occupational settings, especially in agricultural occupations (Fareed et al.,

2013; Hernandez et al., 2008; Mekonnen and Agonafir, 2004; Peiris-John et al., 2005; Reynolds et al., 2012; Salameh et al., 2005). However, very few studies have investigated the effect of pesticides on lung function in non-occupational settings among general populations. A case study of pre-existing asthmatic patients in Australia showed that lung function reduction in forced expiratory volume in 1 sec (FEV_1) and forced expiratory flow between 25% and 75% ($FEF_{25\%–75\%}$) occurred after acute exposure to PYR insecticides in a household (Newton and Breslin, 1983). A cross-sectional study suggested a potential link between home pesticide use and difficulty in performing PEFR tests in children of grades 2–5 in the US (Schneider et al., 2004). Although these studies suggest the effect of pesticide exposures on lung function, the applicability of these data to the general population is limited given these studies were conducted either among a group of patients with pre-existing respiratory diseases (Newton and Breslin, 1983), or in a specific age group (Schneider et al., 2004).

In summary, the effect of environmental pesticide exposures on respiratory health among general populations was understudied. Respiratory symptoms, including wheezing, coughing, airway irritation, and airway infection in children, have been associated with environmental pesticide exposures (Dallaire et al., 2004; Moretto, 1991; Salameh et al., 2003; Sigurs et al., 2000, 2005; Sunyer et al., 2010). Although there was limited evidence for adult populations, a few studies have demonstrated the impact of environmental pesticide exposures on childhood asthma (Salam et al., 2004; Salameh et al., 2003, 2006a; Sunyer et al., 2005, 2006; Tagiyeva et al., 2010; Wagner, 2000). Few epidemiological studies have investigated the effect of environmental pesticide exposures on lung function among general populations.

2. Findings from the CHMS

The CHMS is a nation-wide population-based survey conducted by Statistics Canada to characterize the baseline health information of Canadians. In addition to questionnaire data collection, "objective measures" such as results of spirometry tests and the biomonitoring concentrations of pesticides were also collected by the CHMS (Statistics Canada, 2011). In this section, we briefly discuss the published results of the effect of pesticides on lung function in the general population using the CHMS-Cycle 1 data, except for the analysis of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), which is reported for the first time in this article.

In CHMS-Cycle 1 (2007–2009), there were 5604 participants recruited from New Brunswick (411), Quebec (1545), Ontario (2092), Alberta (766) and British Columbia (790), considered to be representative of 96.3% of the Canadian general population (Statistics Canada, 2011). The pesticides measured in CHMS Cycle 1 included OP insecticides, PYR insecticides, the organochlorine pesticide DDT, and the phenoxyl herbicide 2,4-D (Statistics Canada, 2011). Using the data from CHMS Cycle 1, the biomonitoring concentrations of pesticides and their associations with lung function, self-reported respiratory symptoms and diseases were examined in a series of studies (Ye et al., 2015a, 2016a, 2016b).

2.1. OP insecticides and respiratory health in the Canadian general population

OP insecticides are acetylcholine esterase (AchE) inhibiting compounds that have been extensively used in agriculture and residential areas (Keifer and Firestone, 2007). Only few studies have investigated the effect of environmental OP exposures on respiratory health, including lung function, in the general population (Salameh et al., 2003).

In a study using the data from the CHMS Cycle 1, urine concentrations of OP common metabolites dialkyl phosphates (DAPs) and their associations with various spirometric measures: forced vital capacity (FVC), FEV_1, FEV_1/FVC ratio and ($FEF_{25\%–75\%}$) of FVC were examined (Ye et al., 2016b). Over 90% of the CHMS participants had at least one of the six DAP metabolites detectable in their urine samples (Ye et al., 2016b). In adult participants (20–79 years), every unit increase at the natural logarithmic scale in urinary concentration of ∑DAP was associated with a 32.6 (95% CI: 8.1–57.2) mL reduction in FVC, a 32.7 (95% CI: 6.3–59.0) mL reduction in FEV_1 after adjusting for age, sex, ethnicity, height, weight and smoking (Ye et al., 2016b). In children aged 6 to 12 years (unpublished data) and adolescents aged 12 to 19 years, no significant associations were observed between urinary DAP concentrations and lung function parameters (Ye et al., 2016b). There were no significant associations between urinary concentrations of DAP metabolites and self-reported respiratory symptoms or diseases, including regularly coughing, night cough, dry cough, cough with phlegm, asthma and chronic bronchitis for all age groups (unpublished data).

2.2. PYR insecticides and respiratory health in the Canadian general population

PYRs are synthetic insecticides widely used in residential areas as well as in large scale agricultural applications (UN FAO, 2006; Reigart and Roberts, 1999). There are very few studies investigating the relationship between PYR exposures and respiratory health (Hoppin et al., 2006; Salameh et al., 2003), either in occupational settings or for a specific age group, and more importantly, none of these results are generalizable to general populations.

In a study using the data from the CHMS Cycle 1, urinary concentrations of total PYR metabolites and their associations with lung function, respiratory symptoms and diseases were examined (Ye et al., 2016a). In this study, almost all of the CHMS participants (99.8%) had at least one type of PYR metabolite detectable in their urine samples, with no significant difference in detection frequency across age groups (Ye et al., 2016a). After adjusting for age, sex, ethnicity, height and weight, one unit increase in log transformed urinary concentration (nmol/g creatinine) of total PYR metabolite (∑PYR) was associated with a 17.4 (95% CI: 0.5–34.2) mL reduction in FEV_1 in children (6–11 years), a 37.1 (95% CI: 0–75.1) mL reduction in FVC (p = 0.05) in adolescents (12–19 years), and a 0.3% (95% CI: 0.09%–0.6%) increase in FEV_1/FVC ratio in adults (20–79 years) (Ye et al., 2016a). There were no significant associations between urinary concentrations of PYRs and respiratory symptoms and diseases, including cough regularly, night cough, dry cough, cough with phlegm, asthma and chronic bronchitis (Ye et al., 2016a).

2.3. DDT and respiratory health in the Canadian general population

DDT, an organochlorine insecticide, was historically widely used in agriculture and for controlling insect-transmitted diseases, such as malaria and typhus. Other than several studies using data from the US Agricultural Health Study (AHS) suggesting associations with adult-onset asthma (Hoppin et al., 2008, 2009) and chronic bronchitis (Hoppin et al., 2007), little is known about the effect of DDT on human respiratory health in the general population (Eskenazi et al., 2009).

In a study using the data from CHMS Cycle 1, plasma concentrations of DDT and DDE, the breakdown product of DDT, were examined for their associations with lung function, respiratory symptoms and diseases in adult participants (20–79 years) (Ye et al., 2015a). Over 99% of the CHMS participants aged 20–79 years had DDT-related compounds in their blood samples with an average *p*,*p*′-DDE concentration of 326.9 ng/g plasma lipid (Ye et al., 2015a). Female participants had higher plasma concentrations of *p*,*p*′-DDE than males. The mean concentration of *p*,*p*′-DDE among participants aged 60 years and above was two times higher than among young adults (20–39 years) (Ye et al., 2015a), suggesting the bioaccumulative nature of these chemicals in humans. After adjusting for age, sex, ethnicity, height, smoking status and daily energy expenditure, participants with detectable *p*,*p*′-DDT had 311 (95% CI: 130–492) mL lower mean FVC and 232 (95% CI: 55–408) mL lower mean FEV_1 than those without DDT; on average, each 100 ng/g lipid increase in plasma *p*,*p*′-DDE was associated with an 18.8 (95% C I: 9–29) mL reduction in FVC and an 11.8 (95% CI: 3–21) mL reduction in FEV_1 (Ye et al., 2015a). No significant differences were observed in FEV_1/FVC ratio and $FEF_{25\%–75\%}$ with exposures to DDT/DDE (Ye et al., 2015a). There were no significant associations between DDT/DDE concentrations and respiratory symptoms and diseases, including cough regularly, night cough, dry cough, cough with phlegm, asthma and chronic bronchitis (unpublished data).

2.4. Herbicide 2,4-D and respiratory health in the Canadian general population

The phenoxyl herbicide 2,4-D is a widely used herbicide to control broadleaf weeds in many settings, including in agriculture, on lawns, highways and railroad rights-of-way. Except for several studies using the data from the US AHS, suggesting adverse effects of occupational exposures including atopic asthma (Hoppin et al., 2008) and rhinitis (Slager et al., 2009, 2010), little is known about the impact of 2,4-D exposure on respiratory health in the general population.

The results of our study examining the association between 2,4-D exposure and lung function using the data from the CHMS Cycle 1 are reported here for the first time. Approximately 41.3% of the CHMS participants aged 6–79 years had 2,4-D detectable in their urine samples, consistent with previously published results using the same survey data (Health Canada, 2013). Although the prevalence of detection was higher in adolescents than in children and adults, there was no significant difference in detection frequency across age groups (41.3% for 6–11 years, 44.3% for 12–19 years and 40.9% for 20–79 years). The percentage of participants with detectable 2,4-D in urine furthermore did not differ significantly by sex, ethnicity or smoking status. No significant differences were observed in lung function (FVC, FEV_1, FEV_1/FVC ratio and $FEF_{25\%–75\%}$) between CHMS participants with and without detectable levels of 2,4-D after adjusting for age, sex, ethnicity, height, weight, smoking status (adolescents and adults), daily energy expenditure (adults) and dwelling type (adults). Because more than 50% of the participants did not have detectable levels of 2,4-D, a subgroup analysis was conducted only among participants who had detectable urinary concentrations of 2,4-D. The subgroup analyses showed no significant associations between 2,4-D concentrations and any measure of lung function. There were also no significant associations between urinary levels of 2,4-D and self-reported respiratory symptoms and diseases, such as regularly coughing, night cough, dry cough, cough with phlegm, asthma and chronic bronchitis.

3. Discussion

3.1. Environmental pesticide exposures and respiratory health in general populations

While very few evidence have suggested the potential impact of environmental/non-occupational pesticide exposures on lung function in the general population (Newton and Breslin, 1983; Schneider et al., 2004), the studies using the CHMS Cycle 1 data demonstrated the associations between exposures to OP, PYR and organocholorine insecticide DDT/DDE and impaired lung function in the Canadian general population (Ye et al., 2015a, 2016a, 2016b). No significant associations were observed between phenoxyl herbicide and lung function.

Lung function parameters are often measured by spirometry tests (Statistics Canada, 2011; Hendrick et al., 2002). The CHMS participants with recent surgery of the chest or abdomen, having acute and/or chronic respiratory conditions, persistent cough, or who were taking medication for tuberculosis were excluded from the spirometry testing (Statistics Canada, 2011). These exclusion criteria minimize the potential confounding effect of respiratory medications on the associations reported in the studies using CHMS data, but they may have led to an underestimate of the true effect for some lung function measures (Ye et al., 2016a). Furthermore, lung function parameters are important indicators of respiratory health and general health status in the general population. Non-age related lung function reduction indicates impaired respiratory health (Parker and Thorslund, 2007) with potentially shorter life expectancy (Schunemann et al., 2000).

There were a few studies investigating the relationships between environmental pesticide exposures and self-reported respiratory symptoms and diseases in adult populations (Menconi et al., 1988; Salameh et al., 2006b) and in children (Salam et al., 2004; Salameh et al., 2003; Sunyer et al., 2005, 2006). However, only several studies were conducted at population-based levels (Karpati et al., 2004; O'Sullivan et al., 2005; Salam et al., 2004). In the population-based studies of the Canadian general population using the data from the CHMS Cycle 1, no significant associations were observed

between pesticide exposures and self-reported respiratory symptoms and diseases, including regularly coughing, night cough, dry cough, cough with phlegm, asthma and chronic bronchitis. These results suggest that the effect of environmental pesticide exposures on lung function observed in the studies of CHMS Cycle 1 (Ye et al., 2015a, 2016a, 2016b) may not be sufficient to change the population prevalence of respiratory symptoms or diseases. However, the impact of pesticide on lung function may be critical for some participants experiencing intensive pesticide exposures in a defined settings, such as those living in areas near farms (Salameh et al., 2003), or for participants with pre-existing respiratory conditions (Newton and Breslin, 1983), or for participants in their early lives (Salam et al., 2004).

3.2. Biomonitoring of pesticide exposures

Many epidemiological studies of pesticide exposure have used questionnaire-based measurements, job titles, or relative distance to pesticide sources as a surrogate of actual levels of pesticide exposures for individual subjects (Ejigu and Mekonnen, 2005; Ye et al., 2013). However, due to variations in the exposure profile, such as exposure duration, routes of exposures and physiological states at the time being exposed, the use of job titles or working hours to quantify pesticide exposures often gives rise to substantial uncertainties.

In the CHMS Cycle 1, concentrations of pesticides or their metabolites in human urine and blood samples were available for estimating the actual physiological burden of pesticides in participants from all sources of exposures (Barr et al., 2006; Kapka-Skrzypczak et al., 2011). For example, the plasma concentrations of DDT/DDE used in the CHMS study were likely to reflect the cumulative level of DDT exposures from all sources, as DDT and DDE are known to have slow elimination rate (US CDC, 2013; Longnecker, 2005). In fact, the biomonitoring concentrations of DDT/DDE are most likely to reflect the historical exposures to DDT, as the use of DDT has been banned for over 30 years in Canada (UN EP, 2010). Historical exposures to DDT also allow to speculate the possible temporal sequence between pesticide exposure and the DDT-associated lung function reduction despite the data in the CHMS being collected in a cross-sectional desgin (Ye et al., 2015a).

For pesticides with shorter metabolic half-lives, such as OPs, PYR insecticides and phenoxyl herbicides (Cocker et al., 2002; Sudakin, 2006), it is difficult to estimate the cumulative or peak exposures using the biomonitoring approach, especially with a cross-sectional design. It is even more challenging for this approach to estimate pesticide exposures at relatively low-doses in the general population. For example, although urinary concentrations of 2,4-D has been used as a valid estimate for 2,4-D exposures in the study of agricultural and farm workers (Curwin et al., 2005), in the CHMS Cycle 1, the majority of participants (58.7%) had a urinary concentration of 2,4-D lower than the limit of detection (LOD) of current gas chromatography–mass spectrometry. For those participants, other than a symbol designated as “less than LOD”, no numeric concentrations of 2,4-D were actually quantified (Statistics Canada, 2011). Unfortunately, using a dichotomized (detectable or not) categorization of 2,4-D levels may compromise the sensitivity of regression models in estimating the real effect of 2,4-D on lung function (Royston et al., 2006). Alternative approach of imputing a large amount of left-truncated data, so as to create a continuous variable, is not optimal either (Succop et al., 2004). In a review of epidemiological studies of the associations between herbicide 2,4-D and chronic diseases, Burn et al. suggested that current studies using the biomonitoring data of 2,4-D did not provide “convincing or consistent evidence for any chronic adverse effect of 2,4-D in humans” (Burns and Swaen, 2012), which might be partially due to the limited ability to accurately measure 2,4-D exposures.

In addition to biomonitoring measurements using urine and blood samples, other biological matrices, such as hair, can also be used for estimating pesticide exposures. For example, hair samples were suitable for measuring DAP concentrations in subjects with acute OP pesticide exposures (Tsatsakis et al., 2012) and occupational OP exposures (Kokkinaki et al., 2014), and the summed DAP concentrations in hair samples were highly correlated ($r = 0.728$, $p < 0.001$) with the summed DAP concentrations measured in urine samples (Kokkinaki et al., 2014). Nevertheless, all these biomonitoring approaches have limitations in estimating cumulative pesticide exposures in cross-sectional study designs. Improved study designs, such as longitudinal study designs with repeated measurement of urinary/blood/hair pesticide concentrations and more sensitive analytical techniques, are warranted for studying low-dose short-half-life pesticide exposures in the general population.

3.3. Future research

In many studies (Fareed et al., 2013; Hernandez et al., 2008; Mekonnen and Agonafir, 2004; Peiris-John et al., 2005; Reynolds et al., 2012; Salameh et al., 2005), including ours using the data from CHMS Cycle 1, the effect of pesticides on lung function was most evident for neurotoxic insecticides, including OP insecticides, PYR insecticides and the organochlorine insecticide DDT (Ye et al., 2015a, 2016a, 2016b), than herbicides. The OP insecticides are AchE inhibitors which lead to post-synaptic accumulation of the neurotransmitter acetylcholine (Ach) and therefore an overstimulated postsynaptic nerve (Fukuto, 1990; Keifer and Firestone, 2007). Both PYR insecticides and DDT can interfere with normal function of voltage-gated sodium/chloride channels in neurons, which results in repeated firing or prolonged depolarizing of neurons (Ray and Fry, 2006). Animal studies have shown that these neurotoxic insecticides can induce the overstimulation of airway neurons and lead to excessive contractile responses of airway smooth muscles (Fryer and Jacoby, 1998; Minette and Barnes, 1988; Souhrada and Souhrada, 1989; Souhrada et al., 1988). Although these results based on animal models have not been confirmed in humans, it is plausible that the neurotoxicity of insecticides accounts for the negative associations between insecticide exposures and lung function observed in the studies of CHMS Cycle 1. In contrast, the phenoxyl herbicide 2,4-D, for which we identified no significant effects, and which has limited neurotoxicity in mammals, is thought to act in target plants by disrupting the function of the plant growth hormone indole acetic acid (IAA) (Grossmann, 2010). Moreover, the dioxin and dioxin-like

impurities in the herbicide 2,4-D can confound the health impacts of 2,4-D reported in humans (Holt et al., 2010). Separate investigations for different types of pesticides and evaluation of the confounding effect of impurities in pesticide formulae are important for future research.

Children are likely to be the most vulnerable population upon the environmental pesticide exposures (Salam et al., 2004; Salameh et al., 2003, 2006a; Sunyer et al., 2005, 2006; Tagiyeva et al., 2010; Wagner, 2000). The studies using the CHMS Cycle 1 data suggested that some effects of insecticides on lung function appeared to be age specific. The effects of OP on lung function were significant among adults (20–79 years) (Ye et al., 2016b), but less evident in children and adolescents despite the fact that children (6–11 years) had the highest mean concentration of total DAPs in all age groups (unpublished data). In contrast, the effect of PYR insecticides on lung function was predominantly seen in children and adolescents (Ye et al., 2016a).

These age-specific effects might be due to age-related lung development. Lungs are not fully developed in children and adolescents and are therefore possibly more susceptible to airway inhaled environmental toxicants (Roy et al., 2012; Schwartz, 1989), including PYR insecticides (Damalas and Eleftherohorinos, 2011). Why the same would not be true for OP pesticides is unclear. Many OP insecticides, such as chlorpyrifos (US EPA, 2006), have been banned and replaced with the 'less toxic' PYR insecticides for gardens and residential areas (UN FAO, 2006), and consequently dietary intake is the likely major source of exposures to OP insecticides in the general population (Reigart and Roberts, 1999; Ye et al., 2015b) despite that they can be absorbed by inhalation as well (Damalas and Eleftherohorinos, 2011). Children and adolescents are therefore likely exposed to OP insecticides in a limited extent through inhalation which may mitigate any potential effect on the lungs. Moreover, the non-cholinergic mechanism of low-dose OP exposures (De Coster and van Larebeke, 2012; Kawashima and Fujii, 2003; Tarkowski et al., 2004) and unknown mechanism of DAP metabolites, with a possibly different toxicity profile from parent OP compounds (Sudakin and Stone, 2011), may lead to the age-specific association observed in the CHMS study (Ye et al., 2016b). To better understand the age-specific effect of OP insecticides on lung function, further studies aiming to separate the effect of parent OP insecticides from their metabolites are warranted.

While the analyses of the CHMS Cycle 1 data have suggested an adverse effect of pesticide exposures on lung function in the Canadian general populations (Ye et al., 2015a, 2016a, 2016b), no significant associations were observed for respiratory symptoms and diseases. One possible reason is that the pesticide-associated loss of lung function in the CHMS participants was not adequate to develop overt respiratory symptoms or diseases, especially when pesticide exposures are often at low-doses in the general population (Damalas and Eleftherohorinos, 2011). Cross-sectional measurement of the biomonitoring levels of pesticide may also have failed to capture important time-related variations in pesticide exposures and their associations with respiratory symptoms and diseases (*i.e.*, the data simply didn't capture the important exposure metric). Future investigations using repeated longitudinal biomonitoring data could help clarify if these were the case.

Lastly, the analysis of the CHMS Cycle 1 data showed that dietary intake of fruits, vegetables, pulses and nuts is the major source of pesticide exposures in the Canadian general population (Ye et al., 2015b). Future population-based interventions aiming to reduce pesticide exposures among the general populations should focus on greater regulation of pesticide use in such food items. Promoting organic farming of fruits, vegetables, pulses and nuts may help to reduce pesticide exposures in the general populations (Curl et al., 2003; Lu et al., 2006).

4. Conclusions

While the associations between occupational pesticide exposures and respiratory health were well documented, there is limited availability of studies on pesticide exposures and respiratory health in the general population. This is an important gap in the literature given that low-dose environmental pesticide exposures are more prevalent than higher-dose occupational exposures. The studies of the CHMS data have provided new population-based evidence for the effect(s) of environmental pesticide exposures on respiratory health in the general population in Canada. Exposures to OP insecticides, PYR insecticides, and the organochlorine pesticide DDT were associated with impaired lung function in the Canadian general population, but no significant associations were observed for the herbicide 2,4-D. The research focusing on how environmental pesticide exposures impact respiratory health in general populations will help to improve the role of current regulatory policies in mitigating pesticide-related health problems in the general public. Future studies with repeated longitudinal data are also critical for assessing temporal variations in pesticide exposures and their health impact.

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