

**Associations of Residential Exposure to Pesticides and Cleaning Agents
with Asthma and Related Symptoms.**

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Associations of Residential Exposure to Pesticides and Cleaning Agents with Asthma and Related Symptoms

Relaties tussen blootstelling aan pesticiden via het milieu en schoonmaakmid-
delen in huis en astma en gerelateerde klachten

(met een samenvatting in het Nederlands)

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Chapter 1: General Introduction

INTRODUCTION

Today's children and adolescents are environmentally exposed to various chemicals including pesticides and cleaning agents. Environmental exposure to pesticides may cause adverse health effects for adults living close to agricultural spraying sites (Ames et al., 1993). The association of residential exposure to pesticides with asthma and related symptoms and diseases in children is not well established. However, the increase in environmental exposure to pesticides has been paralleled by an increase in respiratory diseases and asthma in the general population (Tadevosyan et al., 2021). For instance, there are already some reports of an association between environmental exposure to pesticides and an increased risk of early-onset transient wheezing, respiratory and allergic symptoms in children (Raheison et al., 2019, Salam et al., 2004, Lu et al., 2018).

Cleaning products are among the most widely used consumer products. Indications of an association between the use of cleaning agents and an increase in the risk of asthma and allergic symptoms among professional cleaners and non-professional household cleaners have been convincingly shown in previous studies (Clausen et al., 2020, Dumas et al., 2021, Bedard et al., 2014, Lemire et al., 2020). Although there are few studies on the effects of cleaning agents on children, the findings suggest that children whose mothers made frequent use of chemical-based domestic products during pregnancy are more likely to wheeze persistently throughout early childhood (Sherriff et al., 2005). Also, data from a Canadian birth cohort study suggest that frequent use of household cleaning products in early life is associated with an increased risk for childhood wheezing and asthma at the age of 3 years (Parks et al., 2020).

In the studies described in this thesis, it was hypothesised that environmental exposure to pesticides and household cleaning agents may enhance the prevalence of asthma, other related respiratory symptoms, rhinitis and eczema in adolescents.

The associations of environmental exposure to pesticides and household cleaning agents with the risk of asthma, related respiratory symptoms, rhinitis and eczema in children and adolescents are still unclear.

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study provides information on environmental exposure to pesticides and the presence of asthma, related respiratory symptoms, rhinitis and eczema in adolescents. Also, it provides information on the use of cleaning agents. In this thesis, we used data from standardized asthma outcomes questionnaires that were self-completed by the parents in the Dutch language when the children were 14 years old to investigate the association between household exposure to pesticides and cleaning agents and the prevalence of asthma, rhinitis and eczema in adolescents.

WHAT ARE PESTICIDES AND CLEANING AGENTS?

Pesticides are substances or mixtures of products intended for preventing damage to crops and designed to destroy, repel or mitigate pests. These include herbicides, fungicides, insecticides, nematicides and acaricides that control pests such as fungi, insects, nematodes and mites. Pesticides are toxic by definition and cannot differentiate target from non-target species of plants and animals, and hence should essentially be subject to regulations ensuring safe use by humans.

Cleaning agents are chemicals (liquids, powders, sprays, or granules) used to remove dirt, dust, stains and odours to enhance domestic cleanliness and hygiene. Cleaning agents consist of a wide range of active ingredients (Lynch, 2000, Franzblau and Sahakian, 2003, Deschamps et al., 1994, Gorguner et al., 2004), including detergents, degreasers, abrasives, acids, chlorine bleach and solvents such as ethanol.

HISTORY OF PESTICIDES AND CLEANING AGENTS IN THE WORLD

The use of pesticides in agriculture for pest and disease control started 4500 years ago. At that time, different naturally occurring chemicals were used as pesticides for crop protection; some of these include arsenic, mercury and lead (Unsworth, 2010). Other natural compounds, which were used as pesticides are nicotine sulfate, extracted from tobacco leaves, pyrethrum from chrysanthemums, and rotenone, which occurs naturally in several plant species.

In the nineteenth century, researchers focused on natural techniques involving compounds made with the roots of tropical vegetables and chrysanthemums. In the 20th century, Dichlorodiphenyltrichloroethane (DDT) was discovered, which is an extremely effective pesticide that became rapidly used as the main insecticide in the world. However, due to environmental, biological and human health effects, DDT was banned in many countries in the last several decades of the 20th century. After the ban, DDT was replaced by organophosphate (OP) and carbamate insecticides followed by pyrethroids insecticides. These pesticides are currently used for pest control in agriculture and public health in many parts of the world (King and Aaron, 2015, Orzeł et al., 2022).

Cleaning agents began to evolve slowly in the mid-1900 when modern soap and detergent products began to emerge. Over the past fifty years, cleaning agents especially detergents expanded to automatic dishwasher products, liquid soaps, laundry fabric softeners, enzyme products, cold water detergents, concentrated powders and most recently super-concentrated detergents, gels as well as refills. Their uses have been expanded and today they are routinely used by millions of people worldwide.

BURDEN OF ASTHMA AND ALLERGIC DISEASES

There are different manifestations of allergic diseases such as asthma, rhinitis, atopic eczema and dermatitis (Bousquet et al., 2011). An analysis of birth cohort studies has revealed that eczema, rhinitis and asthma coexist in the same children at 4 and 8 years more often than would be expected by chance (Pinart et al., 2014). In addition, the presence of these multiple diseases at 4 years of age is a strong determinant of the presence of comorbidity at 8 years of age (Pinart et al., 2014). Another study suggested that children with rhinitis at 10 years of age were much more likely to have asthma, atopic eczema, and food allergy than children without rhinitis (Bertelsen et al., 2010). That is why in the studies described in this thesis, asthma, related respiratory symptoms, rhinitis and eczema in adolescents of 14 years of age were considered as health endpoints.

Asthma is a major noncommunicable disease (NCD), affecting both children and adults. Inflammation and narrowing of the small airways in the lungs cause asthma symptoms, which can be any combination of cough, wheeze, shortness of breath and chest tightness. More than 300 million people worldwide are affected by asthma (Rehman et al., 2018, Vos et al., 2020). Asthma often remains both under- diagnosed and untreated, disturbing the activities of the patient for a lifetime and creating a burden on families, societies and countries in general. The prevalence of asthma in the European Union (EU) is 8.2 % in adults and 9.4 % in children (Gibson et al., 2013). The prevalence of asthma increased worldwide in the second half of the last century until the 1990s, but since then, there has been no clear temporal pattern (De Marco et al., 2012).

Asthma is often underdiagnosed and under-treated, particularly in low- and middle-income countries. People with under-treated asthma can suffer sleep disturbance, which can cause tiredness during the day and poor concentration. Asthma patients and their families may miss school and work, with a financial impact on the family and wider community. If symptoms are

severe, people with asthma may need to receive emergency health care and be admitted to the hospital for treatment and monitoring. In the most severe cases, asthma can lead to death. Access to inhalers for the treatment of symptoms is a problem in many countries. For instance, in 2019 only half of the people with asthma had access to a bronchodilator and less than one in five had access to a steroid inhaler in public primary healthcare facilities in low-income countries (World Health Organization, 2021).

A wide variety of mechanisms are associated with allergic diseases and the most frequent underlying trigger is an IgE-mediated reaction (Bousquet et al., 2011, Pinart et al., 2014). Over the past century, there has been a dramatic increase in the population affected by IgE-associated allergic diseases in European countries (Valenta et al., 2012). Also, the prevalence of asthma has increased particularly in low and middle-income countries (Baïz and Annesi-Maesano, 2012) probably due to environmental or/and genetic factors or due to an improvement in asthma diagnostic programs. It has been estimated that there may be an additional 100 million people living with asthma by 2025 (To et al., 2012).

PREVENTION AND INCIDENCE OF ASTHMA AND MITE ALLERGY STUDY

In this thesis, data from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study were used to assess the association between environmental exposure to pesticides and the prevalence of asthma and related respiratory symptoms among the study participants at 14 years of age. Data from the PIAMA study were also used to analyse the association between the use of household cleaning agents and the prevalence of asthma and allergic symptoms among the study participants at the age of 14 years.

The PIAMA study is a prospective birth cohort study among children recruited from the Dutch general population in the northern, middle and southwestern parts of the country. It was

developed in the Netherlands in response to the increase in asthma prevalence in the second half of the last century described earlier.

The objectives of the PIAMA study were to evaluate the effectiveness of the use of mite-impermeable mattress covers for the prevention of asthma and mite allergy in children of allergic mothers and to investigate the natural history of childhood asthma and risk factors for the development of asthma.

The PIAMA study started with the recruitment of pregnant women through 52 prenatal health care clinics in the northern, middle and southwestern parts of the Netherlands in 1996 and 1997. A validated screening questionnaire on maternal allergy was used to ascertain maternal allergic status. A total of 10,232 women completed the screening questionnaire (Lakwijk et al., 1998). Based on this screening 7,862 women (2,779 allergic women and 5,083 non-allergic women) were invited to participate in the study. Approximately 50% of the invited pregnant women agreed to participate and gave written informed consent ($n = 4,146$). Of the baseline population of 4,146 women, 183 were lost before any data on the child had been obtained, so the study started with 3,963 newborn children. All children were followed up annually to the age of 8 years. From age 11 on wards, children and their parents were contacted again every three years (from age 20 onwards the participants only), to complete questionnaires that were sent by mail or more recently provided as online questionnaires.

In this thesis, data obtained from questionnaires which were completed by the parents when the participants were 14 years of age were used to investigate the association between environmental exposure (pesticides and cleaning agents) and the prevalence of asthma and allergic symptoms.

THESIS AIMS AND OUTLINE

This thesis describes the association of environmental exposure to pesticides and cleaning agents with the prevalence of asthma, respiratory and allergic symptoms in adolescents at 14 years of age.

The first aim of this thesis was to estimate residential exposure to pesticides for the participants of the Dutch PIAMA birth cohort study by assessing the proximity of participants' homes to fields likely treated with pesticides as a proxy for exposure to pesticides and combining the acreage of fields with farmer-reported pesticide use. The second aim was to investigate the association between residential pesticide exposure and the prevalence of asthma and related symptoms within the PIAMA birth cohort study. The third aim was to examine the association between the use of household cleaning agents and the prevalence of asthma, rhinitis and eczema in adolescents.

Chapter 2 of this thesis describes the assessment of residential exposure to pesticides using the information on the fields cultivated with selected crops within 50, 100, 500 and 1000 m of the participant's home addresses at the time of the 14-year follow-up as proxies for environmental pesticide exposures. The spatial data on the presence of crops were combined with survey data on pesticide use by farmers to estimate the amount of pesticides used within different distances of the participant's homes for the year 2012.

In **Chapter 3**, we used the data on residential pesticide exposure developed in **Chapter 2** and linked them with the prevalence of asthma and related respiratory symptoms at 14 years of age to investigate the association between residential exposure to pesticides and asthma and related respiratory symptoms among adolescents within the PIAMA birth cohort study. We included all participants who were included in the exposure assessment study and who had information on at least one of the outcomes (asthma and related respiratory symptoms) at the age of 14.

Chapter 4 describes the assessment of the association of cleaning agents use in households and the prevalence of asthma, rhinitis and eczema symptoms in adolescents participating in the PIAMA birth cohort study at the age of 14 years. To the best of our knowledge, there is no evidence of any study that investigated the association between cleaning agents used in a household and respiratory and allergic symptoms in adolescents.

Chapter 5 provides an overview of the current understanding of pesticide use and health implications and future research opportunities in Tanzania. This chapter was added to make a comparison between the results obtained in the Netherlands and the situation in the home country of the author of this thesis.

Finally, in **Chapter 6**, we discuss the results obtained in this thesis and draw lessons that could be applicable in Tanzania. We also address the challenges and opportunities in assessing pesticide exposure for a large population in developing countries including Tanzania and the challenges in communicating scientific or epidemiological findings to decision-makers.

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Chapter 2: Proximity to agricultural fields as proxy for environmental exposure to pesticides among children: The PIAMA birth cohort

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Abstract

Background: Agricultural pesticides are frequently used for crop protection. Residents living in close proximity to treated fields may be exposed to these pesticides. There is some indication that children living near agricultural fields have an increased risk of developing asthma and decreased lung function.

Objectives: The aim of this study was to assess the proximity of participants' homes to fields likely treated with pesticides as proxy for environmental exposure to agricultural pesticides among participants of a Dutch birth cohort study, and to combine acreage of fields with farmer-reported pesticide use.

Methods: Potential pesticide exposure at the home address at the time of the 14-year follow-up was estimated for 2,291 participants of the Dutch PIAMA birth cohort study. We used spatial data on the presence of crops during the year 2012 to calculate the surface area of specific crops relevant for pesticide use in the Netherlands cultivated within 50, 100, 500 and 1,000 m of the study homes. Farmer-reported pesticides use on specific crops from a national survey performed in 2012 was used to estimate the amount of all pesticides and pesticides with known irritant properties for the respiratory system applied within the aforementioned distances of the study homes.

Results: For 3%, 7%, 40%, and 65% of the homes, any relevant crops were present within 50, 100, 500 and 1,000 m, respectively. Among these, the most frequent crops were corn, cereals, and potatoes. For almost the same percentages of homes, it was estimated that pesticides with known irritant properties for the respiratory system were potentially applied within these distances.

Conclusions: We observed that a small proportion of the study participants lived in close proximity (<50 or <100 m) to agricultural fields with crops relevant for pesticide use in the Netherlands. The percentage of study homes within 500 or 1,000 m of agricultural fields with these crops was much larger.

Keywords: Birth cohort, exposure, agricultural pesticides, geographical information system.

1. Introduction

The Netherlands is well known for the production of a variety of crops, such as corn, fruits, vegetables, potatoes, floriculture, and flower bulbs. Pesticides are widely used in agriculture in order to increase production and prevent damage (Van Dijk et al., 1999). Residents living in close proximity to agricultural fields may be exposed to pesticides through primary spray drift or after application, e.g. through volatilization of pesticide residues from crops and soil or wind erosion of soil particles (Deziel et al., 2015; FOCUS Working Group, 2008). This was examined in a study conducted in The Netherlands, which included 12 bulb growers' (farmers') homes and 15 non farmers' houses located approximately 10–400 m from flower bulb fields, and found increased concentrations of pesticides in house dust samples of farmers and non-farmers (Hogenkamp et al., 2003). Similar increases were reported by studies conducted in California and Iowa in homes within 500 m and up to 1,250 m from vegetables, corn and strawberry fields (Gunier et al., 2011; Harnly et al., 2009; Ward et al., 2006). Findings of the US studies may not be directly transferable to the Netherlands because of differences in agricultural pesticide application practices.

While it is true that most of the pesticides applied in modern agriculture are not persistent in the natural environment, they do tend to persist more in houses due to lack of degrading microorganisms, moisture and sunlight. This shows the importance of investigating exposure to agricultural pesticides among children, as pesticide exposure in homes has been associated with respiratory diseases among children (Lewis et al., 1994; Salameh et al., 2003; Schwartz et al., 2015; Xu et al., 2012).

There are several methods of assessing environmental exposure to agricultural pesticides: by collecting house dust samples or biological samples such as blood or urine. Such samples can be analysed for pesticide residues or their metabolites (Bouvier et al., 2005; Chevrier et al., 2014; Lewis et al., 1994). These direct methods of assessing environmental agricultural

pesticides exposure, however, are time consuming and costly and therefore, not suitable for large-scale studies.

Environmental exposure to agricultural pesticides can also be assessed indirectly by combining spatial data on crop cultivation with information on the location of residential homes in a Geographic Information System (GIS). This method is suitable for efficiently assessing environmental exposure to pesticides in large population studies (Booth et al., 2015; Rappazzo et al., 2016). One of the limitations of this method is that it does not provide information about the specific pesticides applied. In the Netherlands, spatial data on annual crop cultivation is available for recent years, but spatially resolved information on pesticide use is lacking. We addressed this problem in the present study by combining geographical information data on the presence of crops with likely pesticide use in the Netherlands with data on farmer-reported pesticide use on specific crops.

The aim of this study was to assess the proximity to fields likely treated with pesticides as proxy for environmental exposure to agricultural pesticides at the home addresses of the participants of the Dutch PIAMA cohort at the time of the 14-year follow-up. A second aim was to estimate average annual pesticide use on these fields using data on farmer-reported pesticide use.

2. Methodology

2.1 Study design and population

The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study is a prospective Dutch birth cohort study. The baseline study population consisted of 3,963 participants from the northern, middle and western parts of The Netherlands. Participants were born in 1996 and 1997 (Wijga et al., 2014). The PIAMA study has been designed to study the influence of life style and environmental factors on the development of asthma and allergies in children. Questionnaires were administered to the parents during pregnancy, at the child's ages of 3 months and 1 year, and then annually until the age of 8 years. When the children were 11, 14, and 17 years old, both parents and children completed questionnaires (again).

Data on the presence of crops ('BRP gewaspercelen', Dutch Ministry of Interior and Kingdom Relations, 2013) and data on self-reported agricultural pesticide use, collected in a national survey among farmers (Statistics Netherlands (CBS), 2012), were available for the year 2012, when the participants were approximately 15 years old. Therefore, the residential address at the time of the 14 - year questionnaire was used to assess participants' environmental agricultural pesticides exposure for the year 2012. A total of 2,291 children, who participated in the 14-year follow-up and had geocoded residential addresses, were included in this study.

2.2 Environmental agricultural pesticide exposure assessment

Environmental exposure to agricultural pesticides was assessed using the participants' home addresses, geographic information system data on the presence of crops and survey data on specific pesticide use (Figure 1). We assessed environmental exposure to agricultural pesticides in three different ways: 1) by the presence of any crops relevant for pesticide use in the Netherlands in circular buffers with radii of 50, 100, 500 and 1,000 m around the children's homes; 2) by the presence of specific crops relevant for pesticide use in the Netherlands within

these distances from the children's homes; 3) by estimating the amount of (specific) agricultural pesticides used within these buffers.

2.3 Presence of (specific) crops around the child's home address

We imported the x-y coordinates of the participants' home addresses at the time of the 14-year follow-up into a geographical information system using ArcGIS and combined them with the location of crop plots ('BRP gewaspercelen') of 2012 (National Georegistry, 2012). The BRP is a national vector data set of 69 different types of crops at an underlying scale of 1:10,000, with annually updated crop information. Next, for each home address, circular buffers with radii of 50, 100, 500 and 1,000 m were created and intersected with the BRP dataset (supplementary Figure 1). These circular buffers were selected based on primary spray drift (likely relevant at 50 and 100 m primarily) and secondary transport processes (500 and 1,000 m) from agricultural fields during and after application (Gunier et al., 2011; Hogenkamp et al., 2003; Simcox et al., 1995). For each of the selected crops (a list of all selected crops is presented in supplementary Table 1), the total surface area within a specific distance around the homes was calculated. Furthermore, the selected crops were grouped into fruit, cereals, vegetables, commercial crops, floriculture/bulbs, corn, and potatoes (supplementary Table 1).

2.4 Amount of agricultural pesticides used around children's homes

We used data from a survey of Statistics Netherlands (CBS) among farmers performed in 2012, which collected information on self-reported agricultural pesticide use for a number of crops (Statistics Netherlands (CBS), 2012). In that survey, farmers provided the amount (in kg) and the area treated, and CBS calculated the average dosage in kg/ha (among farmers who applied pesticides) and the overall average kg/ha (for the total crop area, including those not treated). For this survey, farmers were randomly selected and approximately 3,000 farmers completed

questionnaires on agricultural pesticide use on specific crops. The CBS dataset was then linked to the area of crops extracted from the BRP data as described in supplementary Table 2. There were 191 unique agricultural pesticides listed in the 2012 CBS pesticides survey. We restricted our analysis to the 79 agricultural pesticides (herbicides, fungicides, growth regulators and insecticides), which were reported to be used in more than 50% of the agricultural fields for any of the selected crops that were present within 1,000 m of the study participants' homes. We used the 50% cut point to ensure a reasonable probability of actual pesticide use on fields near participants' homes. For each of these agricultural pesticides, we estimated the total amount (in kg) applied in 2012 within 50, 100, 500 and 1,000 m of the participants' home addresses by multiplying the acreage for a specific crop with the amount of specific agricultural pesticide used on this crop.

Agricultural pesticides that are known to be associated with respiratory endpoints were identified from the pesticides properties database (PPDB) and the pesticides manual (University of Hertfordshire, 2016). The PPDB has four categories: 1. yes, known to cause a problem; 2. no, known not to cause a problem; 3. possibly, status not identified; 4. no data found. We selected agricultural pesticides with known irritant properties for the respiratory system (n=25).

2.5 Statistical analysis

For both the surface area cultivated with relevant crops and the estimated amounts of agricultural pesticides applied, the median, lower and upper quartiles, 90th and 95th percentiles, and maximum were calculated for the 50, 100, 500 and 1,000 m buffers around children's homes. We calculated Spearman correlation coefficients between surface areas of specific crops and estimated amounts of individual agricultural pesticides applied, respectively, within the different buffers around children's homes. Heat maps were created to visualize these correlations.

We also created heat maps of the Spearman correlation coefficients between individual pesticides with known irritant properties for the respiratory system applied within 50, 100, 500 and 1,000 m distance around children's homes and the surface area of specific selected crops present within these distances of the children's homes.

We also categorized areas of crops and estimated amounts of agricultural pesticides used (all pesticides and pesticides with known irritant properties for the respiratory system) and investigated the agreement (weighted kappa) between them for the 50, 100, 500 and 1,000 m buffers around children's homes. We used tertiles of non-zero values and put all zero values in a baseline reference category. The purpose of this analysis was to provide a simplified presentation of our data in addition to the univariate statistics and Spearman correlation coefficients.

Statistical analyses were performed in SAS version 9.4 except for the correlation heat maps, which were produced with R 3.0.2 software package.

3. Results

Supplementary Figure 2 shows a map of the Netherlands with the addresses of all PIAMA participants at the time of the 14-year follow-up. The provinces of Friesland, Groningen, in the north of the country, and the provinces of Zuid-Holland and Utrecht, in the center and west of the country, are highlighted as these are the provinces where most of the study participants lived. Supplementary Figures 3-9 shows parcels of land with cereals, corn, potatoes, vegetables, floriculture/bulbs, fruit trees, and commercial crops for the year 2012 together with the 14-year home addresses of the cohort participants for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland. The maps show that cereals, corn, potatoes, and commercial crops were more common in the provinces of Friesland and Groningen and that vegetables,

floriculture/bulbs and fruit trees were more present in the provinces of Utrecht and Zuid-Holland.

A total of 3%, 7%, 40% and 65% of the children's homes had any of the selected crops within 50, 100, 500 and 1,000 m, respectively (Table 1). Corn, cereals, and potatoes were the most common crop groups found within these distances around the children's homes (Table 1).

Table 2 presents the distribution of the number of square meters for any selected crops and crop groups within 50, 100, 500 and 1,000 m of the children's homes. The 95th percentiles of the cultivated areas were 1,516 m², 214,430 m² and 1,148,806 m² (0.2, 21.4 and 114.8 hectares) for the 100 m, 500 m and 1,000 m buffers, respectively. Corn, potatoes and cereals occupied the largest surface areas within each of the analysed distances from the study homes.

One or more out of a set of 79 pesticides reported in the 2012 survey were estimated to be applied within 50, 100, 500, and 1,000 m of 3%, 7%, 40%, and 64%, of the homes, respectively (supplementary Table 3). These numbers were very similar for the subset of pesticides with known respiratory irritant properties (supplementary Table 3). The small differences in percentages between all 79 pesticides and the 25 pesticides with known irritant properties for the respiratory system are due to the fact that pesticides like florasulam, mancozeb, terbuthylazine, and nicosulfuron, which are respiratory irritants, were applied on the most prevalent crops such as corn, potatoes and cereals.

Chlormequat, diquat dibromide, mancozeb, prosulfocarb, and terbuthylazine were the pesticides, estimated to be applied in the largest amounts within all buffers (supplementary Table 3).

Heat maps of Spearman correlation coefficients of crop group-specific surface areas within 50, 100, 500 and 1,000 m of the children's homes are shown in Supplementary Figures 10-13. Correlations were high between cereals, potatoes, and commercial crops. We observed low to moderate correlations ($r_s < 0.7$) between the surface areas cultivated with vegetables and cereals,

potatoes and commercial crops, and corn and cereals within 50, 100, 500 and 1,000 m buffers (supplementary Figures 10-13).

Heat maps of Spearman correlation coefficients between the estimated amounts of all individual agricultural pesticides that were applied on the selected crops within 50, 100, 500, and 1,000 m of the children's homes (56 and 72 different pesticides for the 50 and 100 m buffers, 79 different pesticides for the 500 and 1,000 m buffers) are presented in supplementary figures 14-17. Heat maps of Spearman correlations between the estimated amounts of individual agricultural pesticides with known irritant properties for the respiratory system applied on the selected crops are shown in supplementary Figures 18-21 for the 50, 100, 500, and 1,000 m buffers (16 and 22 different pesticides applied within the 50 and 100 m buffer, respectively, 25 different pesticides applied within the 500 and 1,000 m buffers). We observed moderate to high correlations ($r_s > 0.5$) between some of the individual agricultural pesticides with known irritant properties for the respiratory system. Most correlations, however, were weak. The moderate to high correlations ($r_s > 0.5$) include those between iodosulfuron methyl sodium and methosulfuron methyl, chlormequat and iodosulfuron methyl sodium, chlormequat and mesosulfuron methyl, terbuthylazine and florasulam, nicosulfuron and florasulam, lambda-cyhalothrin and maneb, lambda-cyhalothrin and asulam, kresoxim-methyl and lambda-cyhalothrin, kresoxim-methyl and maneb, maneb and asulam, kresoxim-methyl and asulam and nicosulfuron and terbuthylazine.

When we categorised surface areas cultivated with the selected crops and total estimated amounts of agricultural pesticides used, the agreement between crop surface area and amounts of pesticides was high (weighted kappa 0.8 - 0.9) for all specified distances from children's homes (Table 3 for pesticides with known irritant properties for the respiratory system and supplementary Table 4 for all selected pesticides).

Figure 1: Assessment of residential proximity to crop fields likely treated with agricultural pesticides as proxy for environmental exposure to pesticides - flow chart.

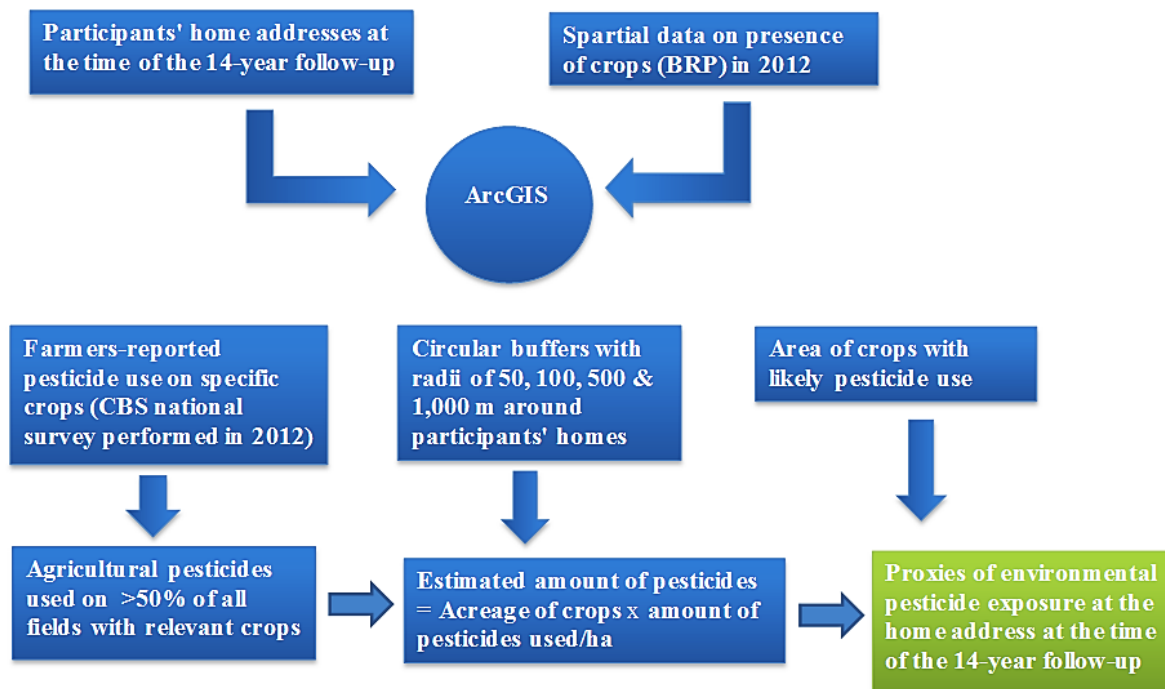


Table 1: Presence of crops (grouped) relevant for pesticide use in the Netherlands within of 50, 100, 500 and 1,000 m of the home addresses of the PIAMA participants at the time of the 14-year follow up (N = 2,291).

	Radius of circular buffer			
	50 m	100 m	500 m	1,000 m
	N [%]	N [%]	N [%]	N [%]
Any crops	70 [3.0]	170 [7.4]	926 [40.4]	1,480 [64.6]
Orchard	2 [0.1]	5 [0.2]	57 [2.5]	118 [5.2]
Cereals	20 [0.9]	52 [2.3]	380 [16.6]	750 [32.7]
Vegetables	0 [0]	6 [0.3]	93 [4.1]	249 [10.9]
Commercial crops	6 [0.3]	17 [0.7]	206 [9]	468 [20.4]
Floriculture/bulbs	4 [0.2]	7 [0.3]	130 [5.7]	361 [15.8]
Corn	27 [1.2]	75 [3.3]	662 [28.9]	1248 [54.5]
Potatoes	21 [0.9]	48 [2.1]	298 [13]	563 [24.6]

Table 2: Distribution of the area (m²) of crops with likely pesticide use within 50, 100, 500 and 1,000 m of the PIAMA participants' home addresses at the time of the 14-year follow up (N= 2,291).

Radius of circular buffer		Any of the selected crops	Orchard	Cereals	Vegetables	Commercial crops	Floriculture	Corn	Potatoes
50 m	P95	0	0	0	0	0	0	0	0
	Max	7,439	853	6,200	0	1,359	2,129	1,765	3,139
	P90	0	0	0	0	0	0	0	0
100 m	P95	1,516	0	0	0	0	0	0	0
	Max	30,480	8,215	20,414	2,656	7,419	8,609	15,332	15,508
	P50	0	0	0	0	0	0	0	0
500 m	P75	28,324	0	0	0	0	0	5,053	0
	P90	126,144	0	20,192	0	0	0	48,617	9,639
	P95	214,430	0	65,966	0	25,965	1,387	82,895	57,385
1,000 m	Max	657,875	216,594	338,345	190,317	182,389	245,071	274,360	389,635
	P25	0	0	0	0	0	0	0	0
	P50	50,030	0	0	0	0	0	11,539	0
	P75	273,513	0	23,530	0	0	0	118,951	0
	P90	723,067	0	196,987	1,909	70,715	5,931	251,724	173,713
	P95	1,148,806	560	412,372	41,566	149,787	15,060	353,419	374,792
	Max	2,648,566	659,363	1,325,338	606,518	631,099	1,701,590	870,207	1,240,584

Table 3: Associations between categorized surface area of crops cultivated and amount of agricultural pesticides with known irritant properties for the respiratory system used within 50, 100, 500 and 1,000 m of the PIAMA participants' homes (N= 2,291).

Radius of circular buffer	Agricultural pesticides	Area of crops (m ²)				Total	Weighted kappa
50 m	Amount agricultural pesticides associated with respiratory outcomes (g)(n=16)	0	>0 - 437	≥437 - 1,074	≥1,074		0.81
	0	2,221	3	3	3	2,230	
	>0 - 26	0	13	7	1	21	
	≥26 - 106	0	4	10	6	20	
	≥106	0	4	3	13	20	
	Total	2,221	24	23	23	2,291	
100 m	Amount agricultural pesticides associated with respiratory outcomes (g)(n=22)	0	>0 - 1696	≥1,696 - 5230	≥5,230		0.84
	0	2,121	8	5	5	2,139	
	>0 - 95	0	37	12	2	51	
	≥95 - 511	0	8	24	18	50	
	≥511	0	4	15	32	51	
	Total	2,121	57	56	57	2,291	

Table 3: (continued).

Radius of circular buffer	Agricultural pesticides		Area of crops (m ²)				Total	Weighted kappa
500 m	Amount associated with respiratory outcomes (g)(n=25)	agricultural pesticides	0	>0 – 22,247	≥22,247 – 93,484	≥ 93,484		0.88
	0		1,365	28	11	0	1,404	
	>0 – 1,039		0	238	55	0	293	
	≥1,039 – 6,010		0	31	182	80	293	
	≥6,010		0	9	58	234	301	
	Total		1,365	306	306	314	2,291	
1,000 m	Amount associated with respiratory outcomes (g)(n=25)	agricultural pesticides	0	>0 – 92,598	≥92,598 – 317,994	≥317,994		0.87
	0		811	42	1	0	854	
	>0 – 4,259		0	401	74	0	475	
	≥4,259 – 23,217		0	39	324	111	474	
	≥23,217		0	7	89	392	488	
	Total		811	489	488	503	2,291	

4. Discussion

We assessed environmental exposure to pesticides at the residential addresses for participants of a Dutch birth cohort study using spatial data on the presence of crops and survey data on agricultural pesticides use by farmers from existing sources. We used this information to estimate the crop surface area cultivated with selected, relevant crops and the amount of agricultural pesticides used within different distances of the participants' homes for the year 2012. Distances represent different exposure pathways including direct pesticide drift over short distances (50 and 100m) and secondary transport processes over larger distances (500 and 1,000m) (Gunier et al., 2011; Hogenkamp et al., 2003; Simcox et al., 1995). We observed that a small proportion of the study participants lived in close proximity (<50 or <100m) to agricultural fields with selected crops relevant for pesticide use in the Netherlands. The percentage of study homes within 500 or 1,000 m from agricultural fields was much larger.

More than 10% of the study homes had cereals, vegetables, commercial crops, floriculture/bulbs, corn and/or potatoes within 500 and 1,000 m distances. Crops mapped in proximity to homes using GIS have been used as a tool for estimating environmental exposure to agricultural pesticides before, e.g. (Brouwer et al., 2017; Nuckols et al., 2007; Rull et al., 2009). Studies from the United States (Gunier et al., 2011; Ward et al., 2006) have shown that the presence of vegetables, corn and strawberry agricultural fields within 500, 750 and even 1,250 m distance of homes is associated with increased pesticide concentrations in homes. The findings of the US studies, however, likely do not directly apply to our study due to different application methods in the Netherlands and in the US, where aerial pesticide spraying is more common.

In our study, we considered the presence of agricultural fields within distances of up to 1,000 m around children's homes as relevant for environmental exposure to agricultural pesticides. This assumption is supported by a previous study from The Netherlands, using a similar

methodology as ours, which found that measured pesticide concentrations in air and rainfall were correlated with modelled pesticides at distances of up to 1 km (Brouwer et al., 2017). Our analysis showed that the surface areas cultivated with crops relevant for pesticide use in the Netherlands within 50 and 100 m distance from participants' homes were relative small. However, we found that relatively large areas within 500 and 1,000 m distance from study homes were cultivated with corn, cereals, and potatoes. The surface area cultivated with corn around homes has been used as a surrogate for environmental exposure to pesticides and associated with birth defects in a study from the United States (Ochoa-Acuña and Carbajo, 2009). We recognize, however, that the relevance of the surface area cultivated with specific crops for environmental exposure to pesticides apart from the size of the fields depends on factors such as the amount of agricultural pesticides applied and crop rotation.

Physical and chemical properties of agricultural pesticides are important predictors of pesticide concentrations in the environment as they influence how agricultural pesticides behave after application. Agricultural pesticides can be transferred from agricultural fields to homes by drift during the application or, subsequently, through volatilization from the soil, plants or wind erosion depending on physical-chemical properties (Van Dijk and Guicherit, 1999).

In this study, we estimated the amount of agricultural pesticides applied within distances of 50, 100, 500 and 1,000 m of the children's homes and estimated that relatively large quantities of chlormequat, diquat dibromide, mancozeb, pencycuron, pendimethalin, prosulfocarb, terbuthylazine and sulphur were applied within these buffers. As their vapour pressure at 25° C ranges from 4.1×10^{-04} to 1.94, some of these pesticides are considered to be compounds with low volatility (University of Hertfordshire, 2016) but other pesticides like pendimethalin and terbuthylazine were still detected in air and precipitation in Europe (Van Dijk and Guicherit, 1999). Also, it has been shown that up to 90% of the amount of these pesticides applied on agricultural fields can be volatilized into the atmosphere (Bedos et al., 2002b;

Unsworth et al., 1999). A study conducted in France has shown that even pesticides with low volatility were detected in particles in outdoor air (Bedos et al., 2002a). These studies support our assumption of agricultural pesticides being detectable within smaller (<100 m) and larger (500 and 1,000 m) distances from agricultural fields.

Take-home pesticide exposure by farmers, in addition to proximity to treated fields, is another source of children's exposure to pesticides that is not accounted for in the present exposure assessment. However, the percentage of children living on a farm is low in the current study sample: 2% lived on a farm during the first year of life and at the age of 5 years. Nevertheless, this needs to be taken into account in future epidemiological analyses.

We found a strong association between the total area of cropland and the estimated total amounts of pesticides applied on those crops (Table 3 and supplementary Table 4). However, correlations between amounts of individual pesticides and between areas cultivated with individual groups of crops were often low to moderate ($r_s < 0.5$). This opens the possibility to investigate associations between crop group specific surface areas or estimated amounts of specific pesticides used and health outcomes in future applications of our exposure assessment methodology.

Our study has several limitations. We currently do not know how relevant the estimated crop areas and amounts of agricultural pesticides used are for long term exposure studies as this depends on crop rotation, changes in pesticide use over time as well as changing application practices.

Another limitation of this study is that we did not have actual measurements of pesticide concentrations in house dust or biological samples to compare with the estimated amount of pesticides applied within the buffers surrounding children's homes. We, therefore, have no direct information on the validity of our exposure estimates although the previously mentioned study from the Netherlands suggested reasonable agreement with measured concentrations of

selected pesticides in air and in rainfall (Brouwer et al., 2017). Finally, there are no data on pesticides used on specific fields. Consequently, we are unable to estimate pesticide exposure other than assuming that the average amounts of pesticides applied to specific crops in the Netherlands (self-reported use data by farmers, collected in the agricultural census) apply to each agricultural field where the crop is cultivated.

5. Conclusions

We observed that a small proportion of the study participants lived in close proximity (<50 or <100m) to agricultural fields with crops based on pesticide use. The percentage of study homes within 500 or 1,000 m from agricultural fields was much larger. We also observed large amounts of individual pesticides associated with respiratory irritation were applied within 500 and 1,000 m buffers. This means, in future work, we will use these data to investigate associations with respiratory disease endpoints.

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Conflict of interest statement

None of the authors declares an actual or potential conflict of interest.

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SUPPLEMENTARY TABLES AND FIGURES

Table S1: Categorization of crops relevant for pesticide use in the Netherlands and present within 1,000 m of 2,291 the study homes and crop codes from the BRP dataset.

Crop category	Crop codes	Radius of circular buffer			
		50 m	100 m	500 m	1,000 m
		n [%]	n [%]	n [%]	n [%]
Orchard crops					
Fruit	212	2 [0.1]	5 [0.2]	57 [2.5]	118 [5.2]
Cereals					
Winter wheat	233	9 [0.4]	22 [1.0]	185 [8.1]	381 [16.6]
Summer wheat	234	3 [0.1]	10 [0.4]	117 [5.1]	324 [14.1]
Winter barley	235	0	0	10 [0.4]	30 [1.3]
Summer barley	236	9 [0.4]	23 [1.0]	183 [8.0]	412 [18.0]
Rye (not for animal feeding)	237	0	0	29 [1.3]	133 [5.8]
Oats	238	0	2 [0.1]	11 [0.5]	57 [2.5]
Triticale	314	0	0	12 [0.5]	38 [1.7]
Cereals, other	2652	0	0	4 [0.2]	21 [0.9]
Vegetables					
Field peas	241	0	0	2 [0.1]	3 [0.1]
Brown beans	242	0	0	2 [0.1]	5 [0.2]

Table S1: (continued)

Crop category	Crop name	Crop codes	Radius of circular buffer			
			50 m	100 m	500 m	1,000 m
			n [%]	n [%]	n [%]	n [%]
Vegetables						
Field beans (dry harvesting)		243	0	0	0	2 [0.1]
	Green/yellow peas (green harvesting)	244	0	0	0	14 [0.6]
	Onions, from seeds	262	0	2 [0.1]	41 [1.8]	110 [4.8]
	Open land vegetables (including vegetable seeds)	672	0	3 [0.1]	55 [2.4]	183 [8.0]
	Broad beans (dry harvesting, not for consumption)	853	0	0	4 [0.2]	16 [0.7]
Broad beans (green harvesting)		854	0	0	2 [0.1]	12 [0.5]
	Onions, from seeds and sets (incl. Shallots)	1931	0	2 [0.1]	13 [0.6]	41 [1.8]
	(Field) peas (dry harvesting)	2650	0	0	2 [0.1]	3 [0.1]
Commercial Crops						
Sugar beet		256	4 [0.2]	14 [0.6]	184 [8.0]	416 [18.2]
	Cichorium	511	0	0	0	16 [0.7]
Hemp (fiber)		944	0	0	10 [0.4]	37 [1.6]
	Winter rapeseed	1922	0	0	3 [0.1]	14 [0.6]
Summer rapeseed		1923	0	0	0	4 [0.2]

Table S1: (continued)

Crop category	Crop name	Crop codes	Radius of circular buffer			
			50 m	100 m	500 m	1,000 m
			n [%]	n [%]	n [%]	n [%]
Commercial Crops						
Fodder beets (including topinambour)		2651	0	0	6 [0.3]	15 [0.7]
	Grass seeds (including clover seed)	2653	0	2 [0.1]	21 [0.9]	98 [4.3]
	Flax	3736	0	0	0	5 [0.2]
Floriculture/bulbs						
Floriculture crops (including flower seeds)		175	0	0	29 [1.3]	68 [3.0]
	Flower bulbs and tubers	176	0	0	16 [0.7]	46 [2.0]
	Nursery stock and perennials	229	4 [0.2]	6 [0.3]	95 [4.2]	283 [12.4]
Corn						
Corn for animal feeding		259	26 [1.1]	72 [3.1]	652 [28.5]	1236 [54.0]
	Grain Corn	316	0	3 [0.1]	37 [1.6]	95 [4.2]
	Corn-cob-mix	317	0	0	7 [0.3]	26 [1.1]
Sweet corn		814	0	0	2 [0.1]	15 [0.7]
	Corn for energy production	2032	0	0	3 [0.1]	9 [0.4]

Table S1: (continued)

Crop category	Crop name	Crop codes	Radius of circular buffer			
			50 m	100 m	500 m	1,000 m
			n [%]	n [%]	n [%]	n [%]
Potatoes						
Potatoes as control measure AM		2025	0	0	0	4 [0.2]
Consumption potatoes, clay/loess soil		2951	3 [0.1]	8 [0.4]	99 [4.3]	203 [8.9]
Seed potatoes, clay/loess soil		3730	2 [0.1]	2 [0.1]	19 [0.8]	79 [3.5]
Seed potatoes, sand/peat		3731	2 [0.1]	3 [0.1]	34 [1.5]	97 [4.2]
Starch potatoes		3732	15 [0.7]	36 [1.6]	171 [7.5]	270 [11.8]
Consumption potatoes, sand/peat		3792	0	0	26 [1.1]	111 [4.9]

Table S2: Linkage of crop codes from BRP dataset with crops in CBS pesticide survey dataset*.

BRP Crop code	BRP Crop name	CBS Crop name
212	Fruit	Fruit ¹
233	Winter wheat	Winter wheat
234	Summer wheat	Summer wheat
235	Winter barley	Summer barley
236	Summer barley	Summer barley
242	Brown beans	Brown beans
243	Field beans (dry harvesting)	Snap bean
853	Broad beans (dry harvesting) (not consumption)	Snap bean
854	Broad beans (green harvesting)	Snap bean
244	Peas green/yellow, harvest green	Green peas
2650	Peas including shock cherry (harvesting dry)	Green peas
262	Onion sowing	Onion sowing
1931	Onions , seed and plant (incl. Shallots)	Onion seedlings
1922	Rapeseed, winter (also seed butter)	Rapeseed
1923	Rapeseed, summer (also seed butter)	Rapeseed
256	Beets , sugar	Sugar beet
2651	Fodder beets(including topinambour)	Sugar beet
3736	Flax	Flax
2653	Grass seeds (including clover seed)	Grass seed
511	chicory	Chicory
175	Floricultural crops (including seeds)	Floriculture open field
176	Flower bulbs and - tubers	Flower bulbs ²)
229	Nursery stock and perennials	Nursery stock ³
259	Corn , cutting	Maize
2032	Corn , energy	Maize
316	Corn , grain	Maize
317	Corn , corncob mix	Maize
814	Corn , sugar	Maize

Table S2: (continued)

BRP Crop code	BRP Crop name	CBS Crop name
2951	Potatoes, consumption clay / loess soil	Consumption potatoes
3792	Potatoes, consumption sand / peat	Consumption potatoes
3730	Potatoes , seed on clay / loess soil	Seed potatoes
3731	Potatoes, seed on sand / peat	Seed potatoes
3732	Starch potatoes	Starch potatoes

¹-weighted average of apples and pears based on weighting was done by total acreage in 2012.

²-weighted average of Hyacinths (bulbs), Lilies (bulbs), Tulips (bulbs), Daffodils (bulbs), Gladiolus and Irises based on weighting was done by total acreage in 2012.

³weighted average of Perennials open field, Ornamental conifers, Fruit trees nursery, Forest and shrubbery, Rose bushes open field and Avenue and park trees based on weighting was done by total acreage in 2012.

*The table is limited to crops relevant for pesticide use in the Netherlands and present within 1,000m of the study homes.

Table S3: Distribution of the amount of agricultural pesticides (g) applied in 2012 for the 50, 100, 500 and 1,000 m buffers (N= 2,291).
Radius of circular buffer

Agricultural pesticides	50 m			100 m			500 m			1,000 m			
	N [%] >0	P95	N [%] >0	P95	N [%] >0	P75	P90	P95	N [%] >0	P50	P75	P90	P95
Any pesticide ¹	69 [3]	0	167 [7]	237	917 [40]	4,117	36,731	89,861	1,476 [64]	6,363	45,878	277,769	560,005
Any pesticide known to be a respiratory irritant ²	61 [3]	0	152 [7]	45	887 [39]	1,293	14,882	48,331	1,437 [63]	2,071	15,957	13,238	339,883
Abamectine	2 [0]	0	5 [0]	0	57 [1]	0	0	0	118 [5]	0	0	0	0
Acetamiprid	4 [0]	0	6 [0]	0	95 [4]	0	0	0	283 [12]	0	0	4	22
Amitrole	2 [0]	0	5 [0]	0	57 [2]	0	0	0	118 [12]	0	0	0	20
Asulam*	0 [0]	0	1 [0]	0	17 [1]	0	0	0	61 [3]	0	0	0	0
Bentazon	0 [0]	0	0 [0]	0	11 [0]	0	0	0	51 [2]	0	0	0	0
Bifenox	1 [0]	0	2 [0]	0	21 [1]	0	0	0	98 [4]	0	0	0	0
Bixafen	20 [1]	0	51 [2]	0	354 [15]	0	62	224	677 [30]	0	47	645	1,360
Boscalid	3 [0]	0	10 [0]	0	136 [6]	0	0	17	332 [14]	0	0	160	653
Bupirimate	6 [0]	0	11 [0]	0	145 [6]	0	0	7	373 [16]	0	0	24	173
Captan	6 [0]	0	11 [0]	0	145 [6]	0	0	343	373 [16]	0	0	1115	12,205
Carbetamide	0 [0]	0	0 [0]	0	1 [0]	0	0	0	16 [1]	0	0	0	0
Carfentrazone-ethyl	4 [0]	0	5 [0]	0	53 [2]	0	0	0	174 [8]	0	0	0	87

Table S3: (continued)

Radius of circular buffer																			
50 m					100 m					500 m					1,000 m				
Agricultural pesticides	N [%] >0	P95	N [%] >0	P95	N [%]>0	P75	P90	P95	N [%]>0	P75	P90	P95	N [%]>0	P50	P75	P90	P95		
Chlormequat*	9 [0]	0	22 [1]	0	185 [8]	0	0	1,815	381 [17]	0	0	4,090	14,316						
Chlorpropham	0 [0]	0	4 [0]	0	63 [3]	0	0	0	165 [7]	0	0	0	1,270						
Chlorothalonil*	4 [0]	0	6 [0]	0	95 [4]	0	0	0	283 [12]	0	0	13	66						
Chloridazon	0 [0]	0	4 [0]	0	62 [3]	0	0	0	154 [7]	0	0	0	1,407						
Clomazone	0 [0]	0	0 [0]	0	10 [0]	0	0	0	47 [2]	0	0	0	0						
Cyazofamide	3 [0]	0	9 [0]	0	125 [5]	0	0	21	314 [14]	0	0	574	2475						
Cycloxydim	0 [0]	0	1 [0]	0	16 [0]	0	0	0	46 [2]	0	0	0	0						
Cyprodinil*	0 [0]	0	0 [0]	0	6 [0]	0	0	0	28 [1]	0	0	0	0						
Deltamethrin	4 [0]	0	6 [0]	0	95 [4]	0	0	0	283 [12]	0	0	1	4						
Dimethenamid -P	27 [1]	0	75 [3]	0	662 [29]	254	2,445	4,170	1,248 [54]	580	5,983	12,662	17,777						
Diquatdibromide*	7 [0]	0	14 [1]	0	166 [7]	0	0	393	411 [18]	0	0	2,674	7,234						
Dithianon	2 [0]	0	5 [0]	0	57 [2]	0	0	0	118 [5]	0	0	0	51						
Esfenvalerate	4 [0]	0	6 [0]	0	66 [3]	0	0	0	198 [9]	0	0	0	54						

Table S3: (continued)

Radius of circular buffer															
50 m				100 m				500 m				1,000 m			
Agricultural pesticides	N [%]	P95 >0	P95	N [%]	P95 >0	P95	N [%]	P95 >0	P95	N [%]	P95 >0	P95	N [%]	P95 >0	P95
Metamitron	4 [0]	0	0	15 [1]	0	198 [9]	0	0	3,745	432 [19]	0	0	9,353	21,091	
Metazachlor	4 [0]	0	0	6 [0]	0	97 [4]	0	0	0	297 [13]	0	0	123	531	
Metribuzin	3 [0]	0	0	9 [0]	0	125 [5]	0	0	15	314 [14]	0	0	412	1,777	
Metsulfuron-methyl*	3 [0]	0	0	10 [0]	0	117 [5]	0	0	0	324 [14]	0	0	9	23	
mineral Oil	0 [0]	0	0	1 [0]	0	16 [1]	0	0	0	46 [2]	0	0	0	0	
Nicosulfuron*	27 [1]	0	0	75 [3]	0	662 [29]	11	110	187	1,248 [54]	26	268	568	797	
Pencycuron*	4 [0]	0	0	5 [0]	0	53 [2]	0	0	0	174 [8]	0	0	0	1065	
Pendimethalin*	0 [0]	0	0	4 [0]	0	62 [3]	0	0	0	154 [7]	0	0	0	2,082	
Prochloraz	0 [0]	0	0	1 [0]	0	16 [1]	0	0	0	46 [2]	0	0	0	0	
Prohexadione-Calcium*	2 [0]	0	0	5 [0]	0	57 [2]	0	0	0	118 [5]	0	0	0	2	
Propamocarb	7 [0]	0	0	14 [1]	0	166 [7]	0	0	1,232	411 [18]	0	0	8,273	24,646	
Propyzamide	4 [0]	0	0	6 [0]	0	96 [4]	0	0	0	292 [13]	0	0	7	37	
Prosulfocarb*	3 [0]	0	0	9 [0]	0	125 [5]	0	0	163	314 [14]	0	0	4,452	19,201	
Prothioconazole	20 [1]	0	0	53 [2]	0	361 [16]	0	164	592	685 [30]	0	119	1,681	3,561	
Pyraclostrobin	3 [0]	0	0	9 [0]	0	125 [5]	0	0	1	314 [14]	0	0	37	161	

Table S3: (continued)

Radius of circular buffer														
50 m			100 m			500 m			1,000 m					
Agricultural pesticides	N [%] >0	P95	N [%] >0	P95	N [%] >0	P75	P90	P95	N [%] >0	P50	P75	P90	P95	P95
Ethofumesate	4 [0]	0	14 [1]	0	187 [8]	0	0	1,672	419 [18]	0	0	4,216	9,976	
Phenmedipham	4 [0]	0	15 [1]	0	198 [9]	0	0	908	432 [19]	0	0	2,290	5,428	
Flonicamid	6 [0]	0	11 [0]	0	145 [6]	0	0	2	373 [16]	0	0	8	37	
Florasulam*	28 [1]	0	77 [3]	0	673 [29]	0	3	4	1,265 [55]	1	6	14	20	
Fluazinam	0 [0]	0	2 [0]	0	56 [2]	0	0	0	147 [6]	0	0	0	503	
Fludioxonil	0 [0]	0	0 [0]	0	6 [0]	0	0	0	28 [1]	0	0	0	0	
Fluopicolide	7 [0]	0	14 [1]	0	166 [7]	0	0	147	411 [18]	0	0	985	2,933	
Fluoxastrobin	0 [0]	0	2 [0]	0	41 [2]	0	0	0	110 [5]	0	0	0	0	
Fluroxypyr-meptyl	39 [2]	0	104 [5]	0	765 [33]	95	527	861	1,356 [59]	202	1,209	2,681	4,019	
Folpet	0 [0]	0	1 [0]	0	16 [1]	0	0	0	46 [2]	0	0	0	0	
Gibberellin A4 + A7	2 [0]	0	5 [0]	0	57 [2]	0	0	0	118 [5]	0	0	0	0	
Glufosinate-ammonium	4 [0]	0	7 [0]	0	106 [5]	0	0	0	312 [14]	0	0	88	369	
Glyphosate	6 [0]	0	13 [1]	0	214 [9]	0	0	732	513 [22]	0	0	1,787	7,114	
Ioxyniloctanoate	0 [0]	0	2 [0]	0	42 [2]	0	0	0	114 [5]	0	0	0	0	

Table S3: (continued)

Radius of circular buffer														
50 m					100 m					500 m				
Agricultural pesticides	N [%]	P95	N [%]	P95	N [%]	P95	N [%]	P95	N [%]	P95	N [%]	P95	N [%]	P95
	>0		>0		>0		>0		>0		>0		>0	
Iprodione*	0 [0]	0	0 [0]	0	0 [0]	0	8 [0]	0	0	0	32 [1]	0	0	0
Iodosulfuron - methyl- sodium*	9 [0]	0	22 [1]	0	185 [8]	0	0	0	8	381 [17]	0	0	19	65
Kresoxim-methyl*	0 [0]	0	1 [0]	0	16 [1]	0	0	0	0	46 [2]	0	0	0	0
Lambda-cyhalothrin*	0 [0]	0	1 [0]	0	16 [1]	0	0	0	0	46 [2]	0	0	0	0
Linuron	25 [1]	0	55 [2]	0	380 [17]	0	655	2,768	731 [32]	0	501	8,315	17,357	
Maleic hydrazide*	0 [0]	0	2 [0]	0	41 [2]	0	0	0	0	110 [5]	0	0	0	0
Mancozeb*	21 [1]	0	51 [2]	0	351 [15]	0	3,719	36,673	680 [30]	0	63	83,679	247,341	
Mandipropamid	3 [0]	0	9 [0]	0	125 [5]	0	0	42	314 [14]	0	0	1,150	4,961	
Maneb*	0 [0]	0	1 [0]	0	16 [1]	0	0	0	46 [2]	0	0	0	0	0
MCPA	16 [1]	0	38 [1]	0	323 [14]	0	226	1,896	735 [32]	0	134	5,048	12,839	
Mecoprop-P*	5 [0]	0	8 [0]	0	115 [5]	0	0	0	351 [15]	0	0	10	74	
Mesosulfuron-methyl*	9 [0]	0	22 [1]	0	185 [8]	0	0	21	381 [17]	0	0	47	163	
Mesotrione	27 [1]	0	75 [3]	0	662 [29]	24	233	397	1,248 [54]	55	570	1,206	1,693	
Metalaxyl-M	4 [0]	0	8 [0]	0	108 [5]	0	0	0	310 [14]	0	0	2	6	

Table S3: (continued)

Radius of circular buffer													
50 m			100 m			500 m			1,000 m				
Agricultural pesticides	N [%] >0	P95	N [%] >0	P95	N [%] >0	P75	P90	P95	N [%] >0	P50	P75	P90	P95
Pyrimethanil	2 [0]	0	5 [0]	0	57 [2]	0	0	0	118 [5]	0	0	0	10
S-metolachlor	0 [0]	0	4 [0]	0	64 [3]	0	0	0	174 [8]	0	0	0	1,785
Spirotetramat	4 [0]	0	6 [0]	0	95 [4]	0	0	0	283 [12]	0	0	1	4
Tebuconazole	14 [1]	0	32 [1]	0	287 [13]	0	11	73	662 [29]	0	16	262	710
Terbuthylazine*	30 [1]	0	75 [3]	0	662 [29]	163	1,572	2,681	1,248 [54]	373	3,847	8,141	11,430
Thiacloprid	4 [0]	0	7 [0]	0	106 [5]	0	0	0	312 [14]	0	0	1	5
Thiamethoxam	4 [0]	0	5 [0]	0	53 [2]	0	0	0	174 [8]	0	0	0	27
Triadimenol*	7 [0]	0	13 [1]	0	164 [7]	0	0	6	437 [19]	0	0	30	197
Trifloxystrobin	4 [0]	0	7 [0]	0	106 [5]	0	0	0	312 [14]	0	0	13	39
Triflusalufuron-methyl*	0 [0]	0	0 [0]	0	1 [0]	0	0	0	16 [1]	0	0	0	0
Sulphur*	4 [0]	0	6 [0]	0	95 [4]	0	0	0	283 [12]	0	0	345	1,706

¹A total of 56 and 72 individual pesticides have been estimated to be applied within the 50 and 100 m buffers; a total of 79 individual pesticides have been estimated to be applied within 500 and 1,000m buffers.

² A total of 16 and 22 individual pesticides known to be a respiratory irritant have been estimated to be applied within the 50 and 100 m buffers; a total of 25 individual pesticides known to be a respiratory irritant have been estimated to be applied within 500 and 1,000m buffers.

* Agricultural pesticides known to be a respiratory irritant applied within 50, 100, 500 and 1000 m buffers.

Table S4: Associations between categorized surface area of crops cultivated and amount of all agricultural pesticides used within 50, 100, 500 and 1,000 m of the PIAMA participants' homes (N = 2,291).

Radius of circular buffer	Agricultural pesticides	Area of crops (m ²)				Total	Weighted kappa
50 m	Amount of all agricultural pesticides(g)(n=56)	0	>0 - 437	≥437 - 1,074	≥1,074		
	0	2,221	1	0	0	2,222	0.87
	>0 - 69	0	14	8	1	23	
	≥69 - 168	0	5	11	7	23	
	≥ 168	0	4	4	15	23	
	Total	2,221	24	23	23	2,291	
100 m	Amount of all agricultural pesticides (g) (n=72)	0	>0 - 1,696	≥1,696 - 5,230	≥ 5,230		
	0	2,121	1	1	1	2,124	0.89
	>0 - 261	0	45	11	0	56	
	≥261 - 946	0	7	28	20	55	
	≥ 946	0	4	16	36	56	
	Total	2,121	57	56	57	2,291	

Table S4: (continued)

Radius of circular buffer	Agricultural pesticides	Area of crops (m ²)				Total	Weighted kappa
500 m	Amount of all agricultural pesticides (g) (n=79)	0	>0 - 22,247	≥22,247 - 93,484	≥ 93,484		0.90
	0	1,365	8	1	0	1,374	
	>0 - 2974	0	260	45	0	305	
	≥2974 - 17262	0	34	191	76	301	
	≥17262	0	4	69	238	311	
	Total	1,365	306	306	314	2,291	
1,000 m	Amount of all agricultural pesticides (g) (n=79)	0	>0 - 92,598	≥92,598 - 317,994	≥317,994		0.89
	0	811	4	0	0	815	
	>0 - 11193	0	429	59	0	488	
	≥11193 - 58804	0	54	326	107	487	
	≥58804	0	2	103	396	501	
	Total	811	489	488	503	2,291	

Figure S1. Illustration of the land-use dataset (BRP gewaspercelen 2012) used with a fictive address and buffers with radii of 50, 100, 500, and 1,000 m for that address.

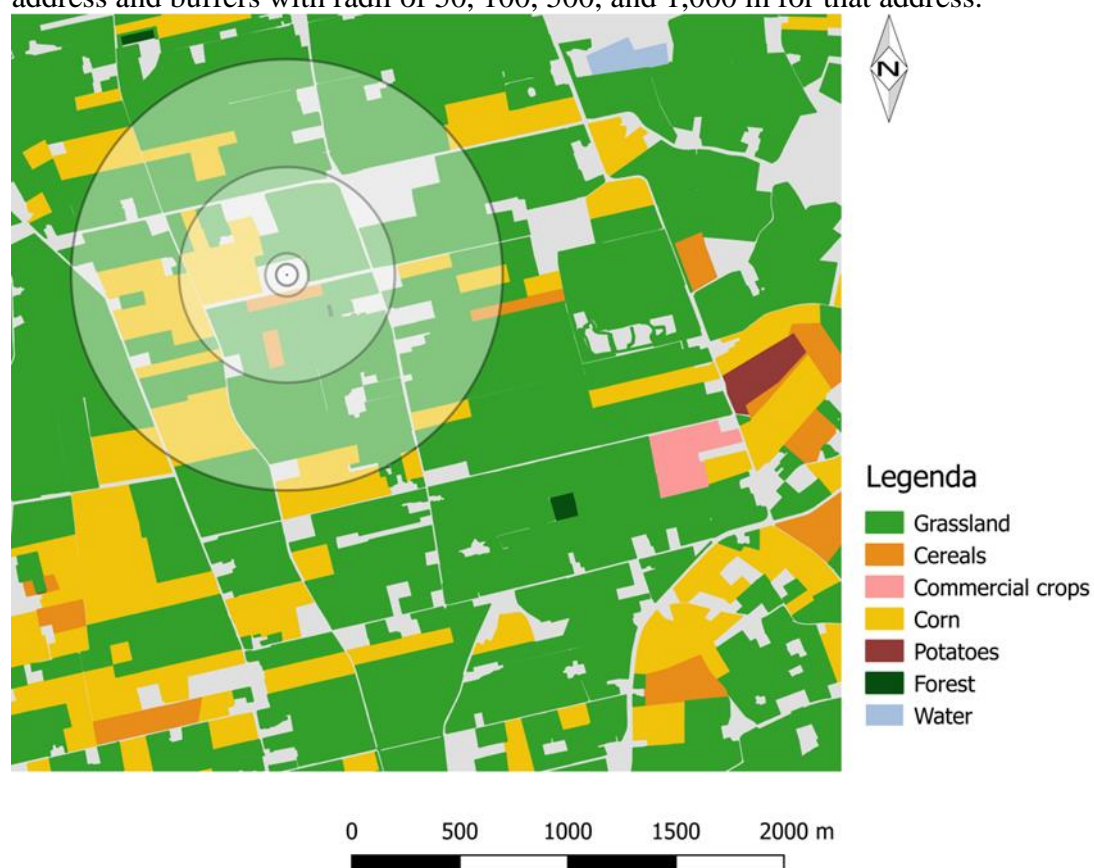


Figure S2: Map of the Netherlands with the 14-year addresses of the PIAMA participants. Provinces of Friesland and Groningen, Zuid-Holland and Utrecht are highlighted

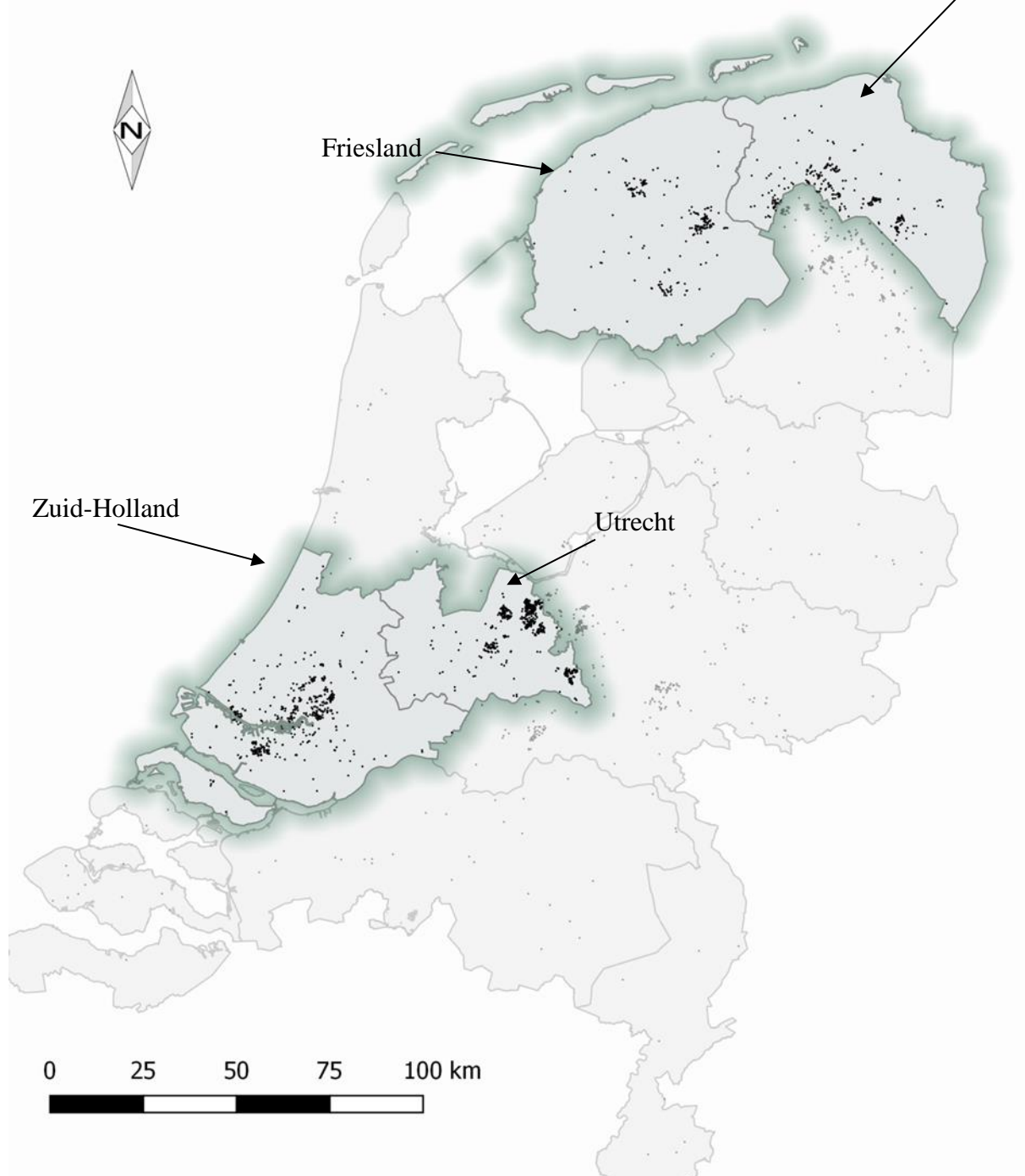


Figure S3: Parcels of land with cereals (yellow polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.

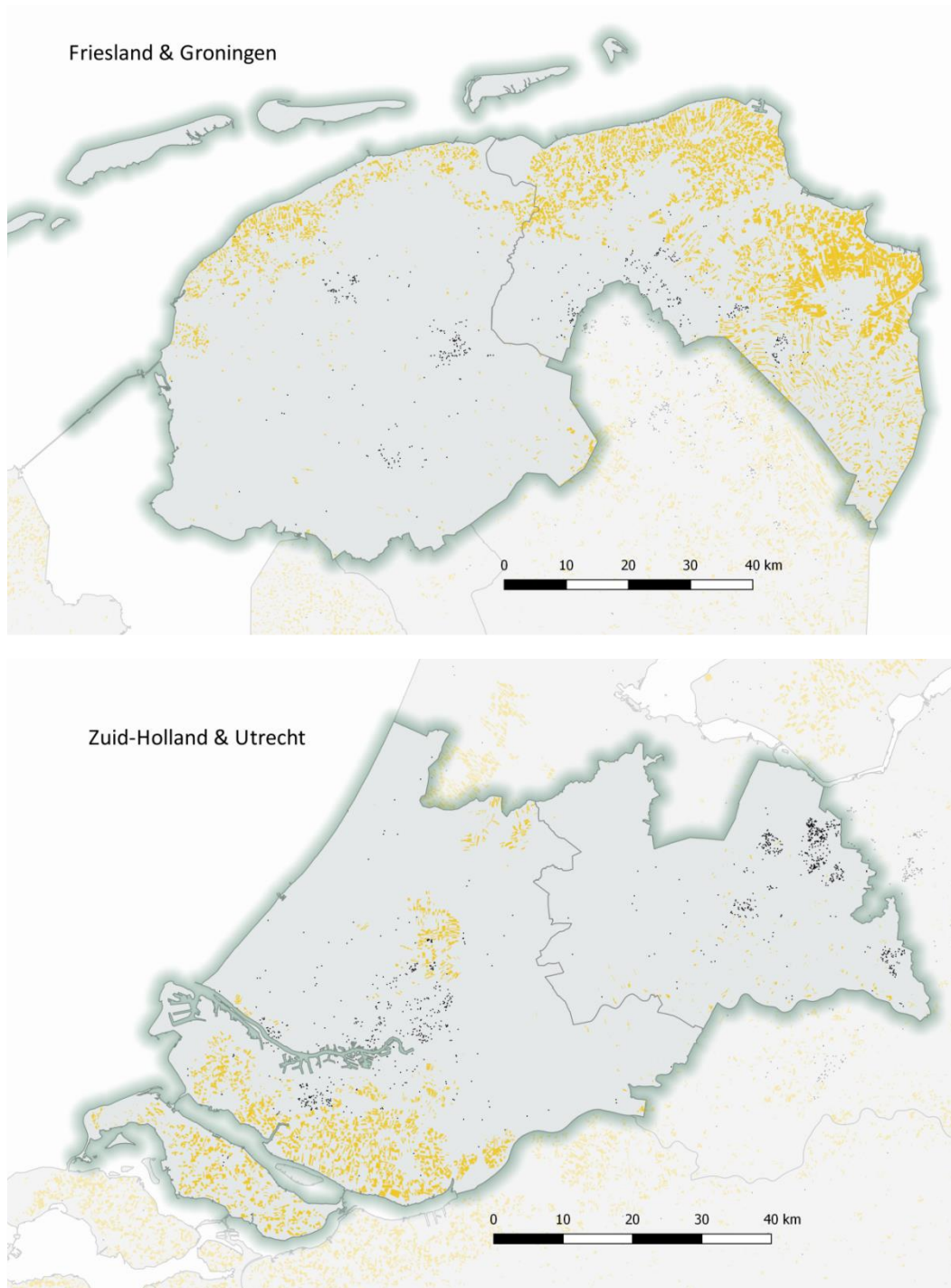


Figure S4: Parcels of land with corn (yellow polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.

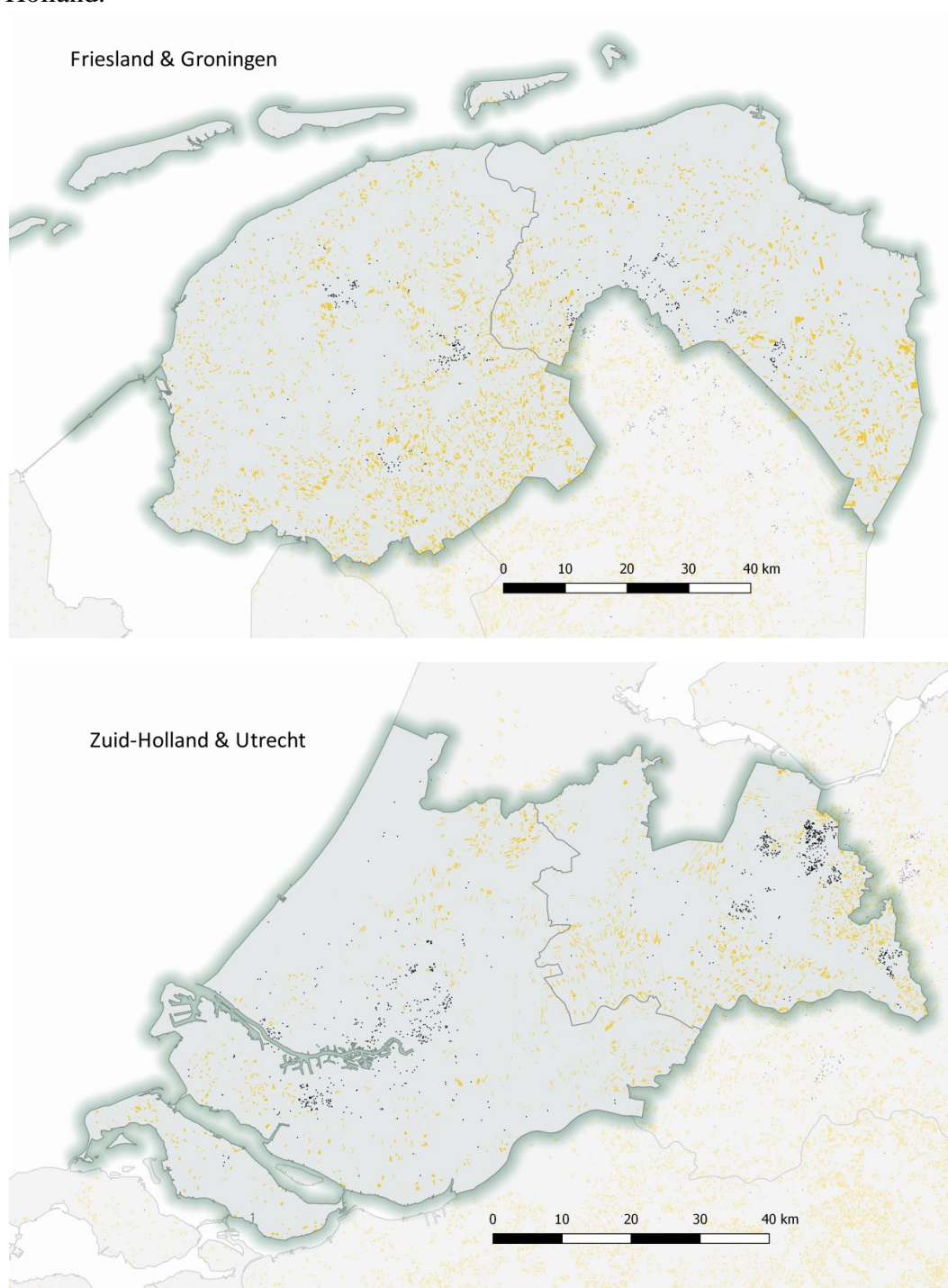


Figure S5: Parcels of land with potatoes (brown polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.

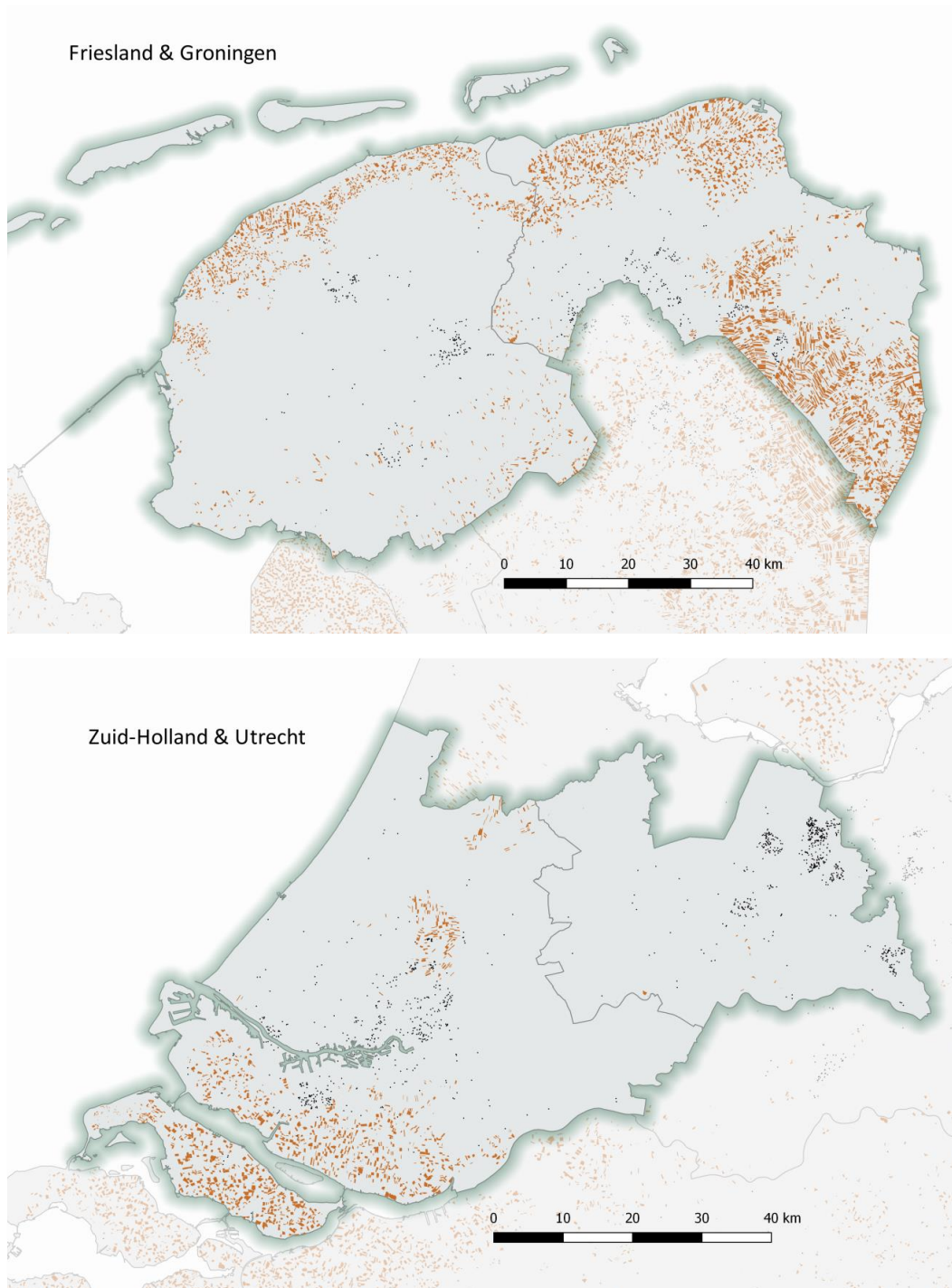


Figure S6: Parcels of land with vegetables (purple polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.



Figure S7: Parcels of land with floriculture/bulbs (green polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.

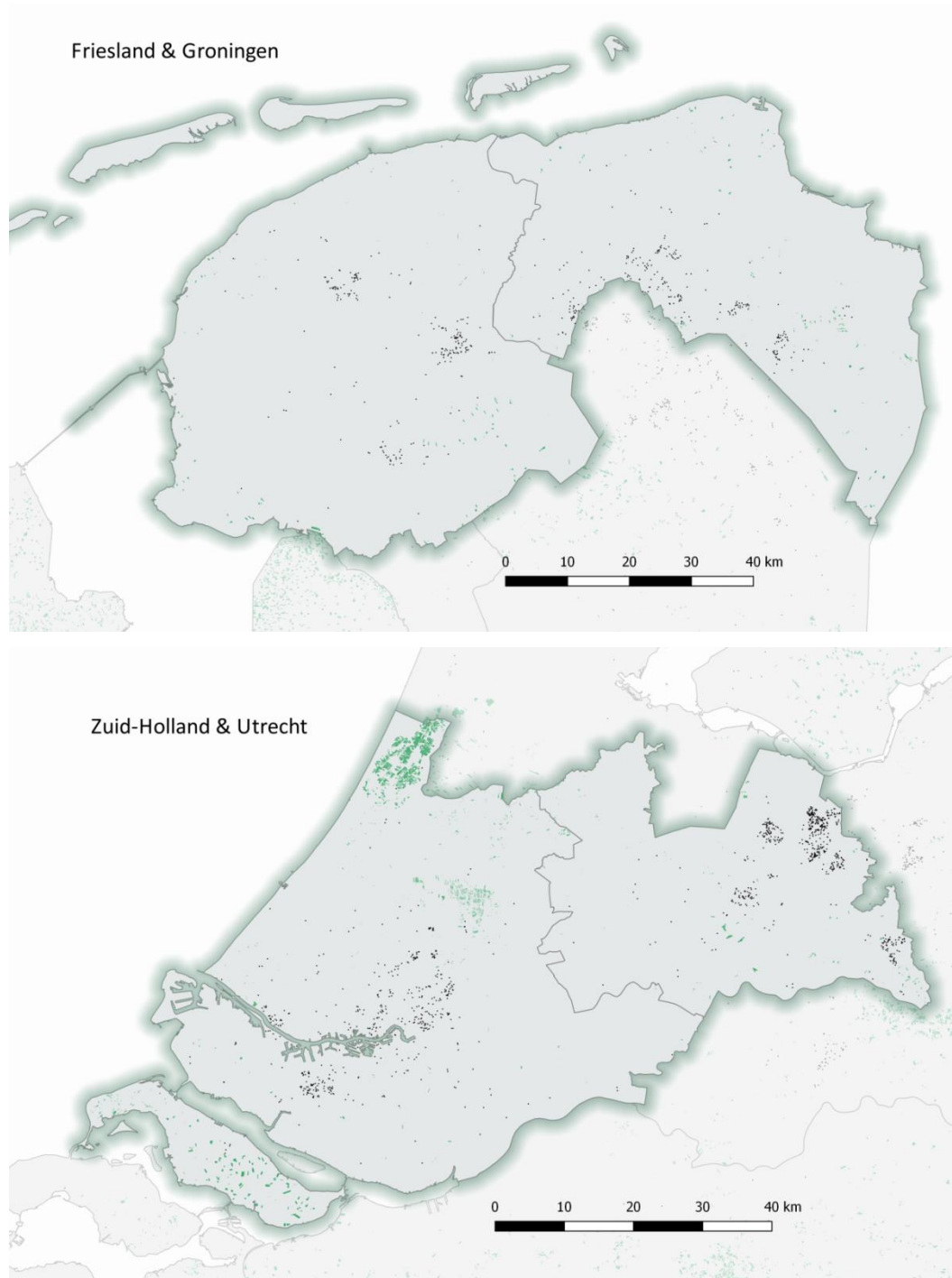


Figure S8: Parcels of land with fruit trees (green polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.

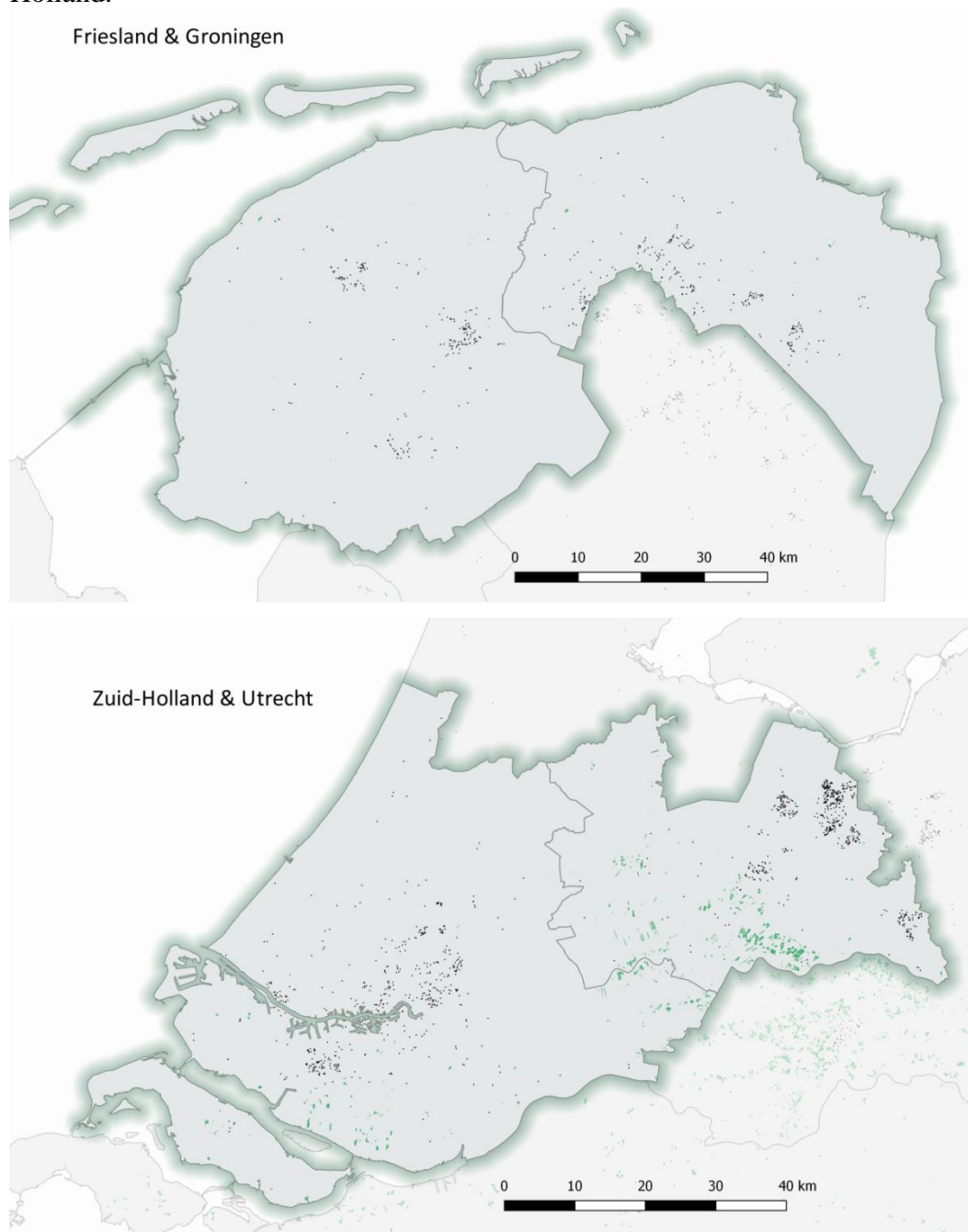


Figure S9: Parcels of land with commercial crops (blue polygons) and 14-year addresses of cohort participants (black dots) for the provinces of Friesland, Groningen, Utrecht, and Zuid-Holland.

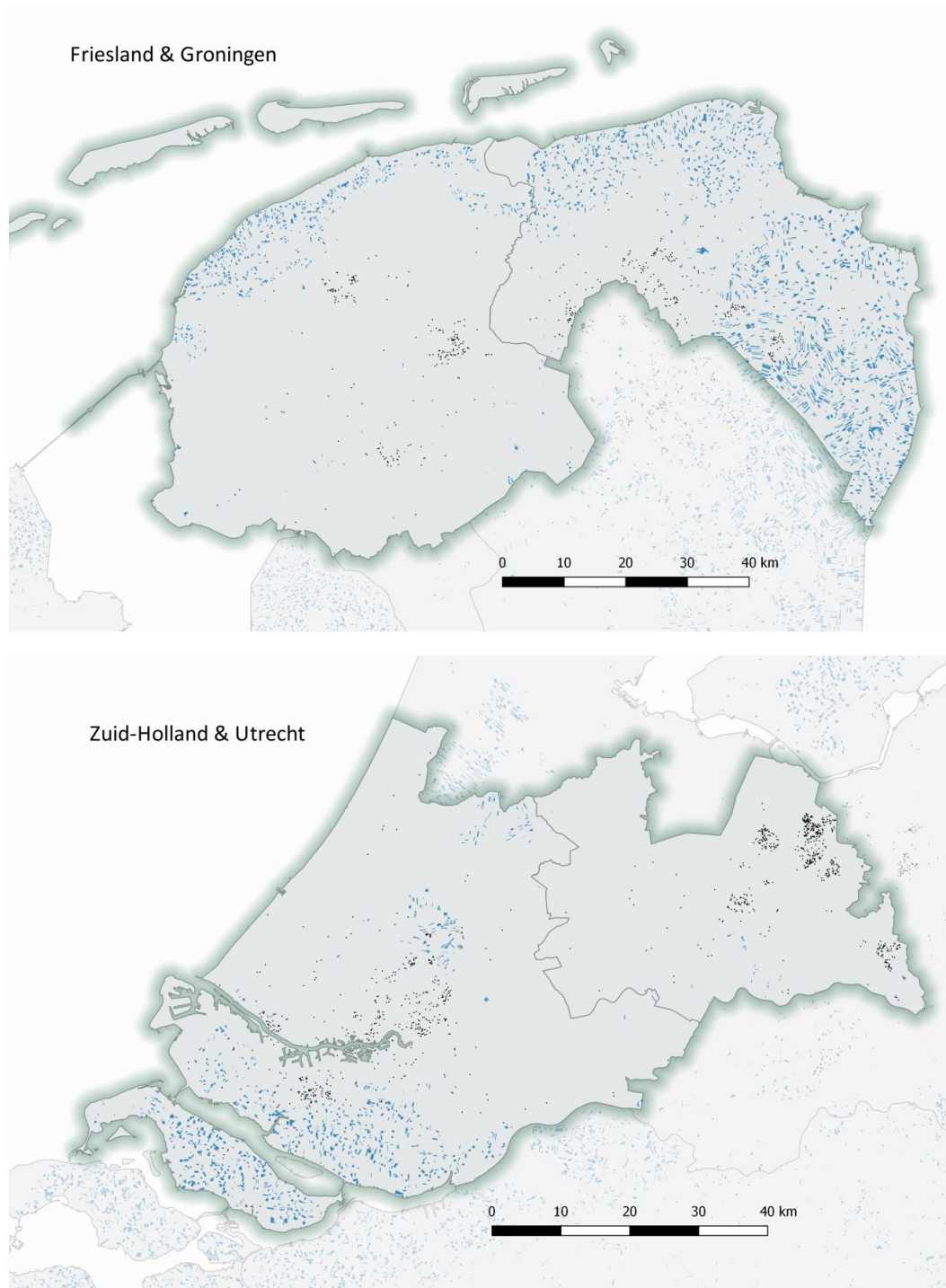


Figure S10: Heat map showing correlation between crop group-specific surface areas within a 50-meter distance around children’s homes.

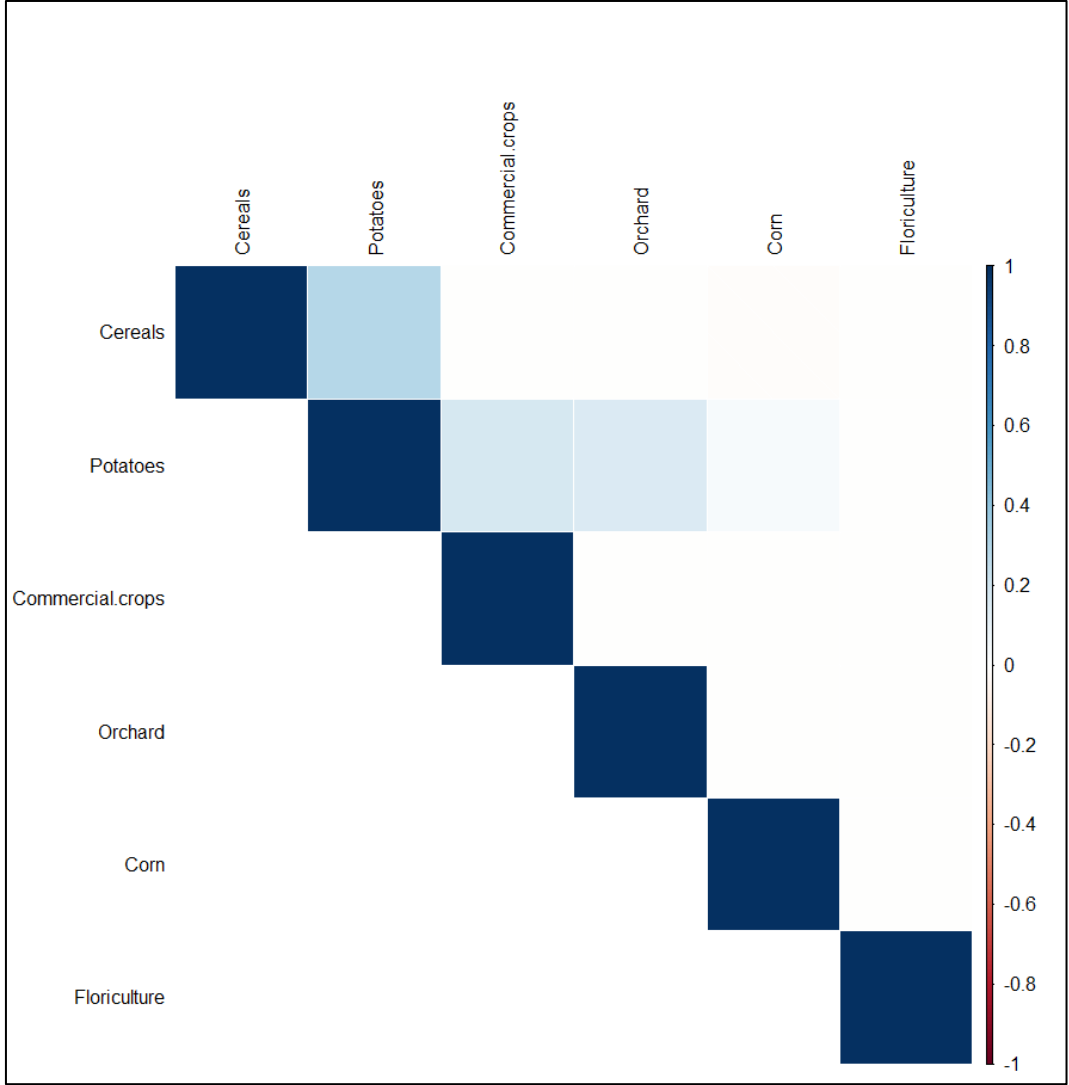


Figure S11: Heat map showing correlation between crop group-specific surface areas within a 100-meter distance around children’s homes.

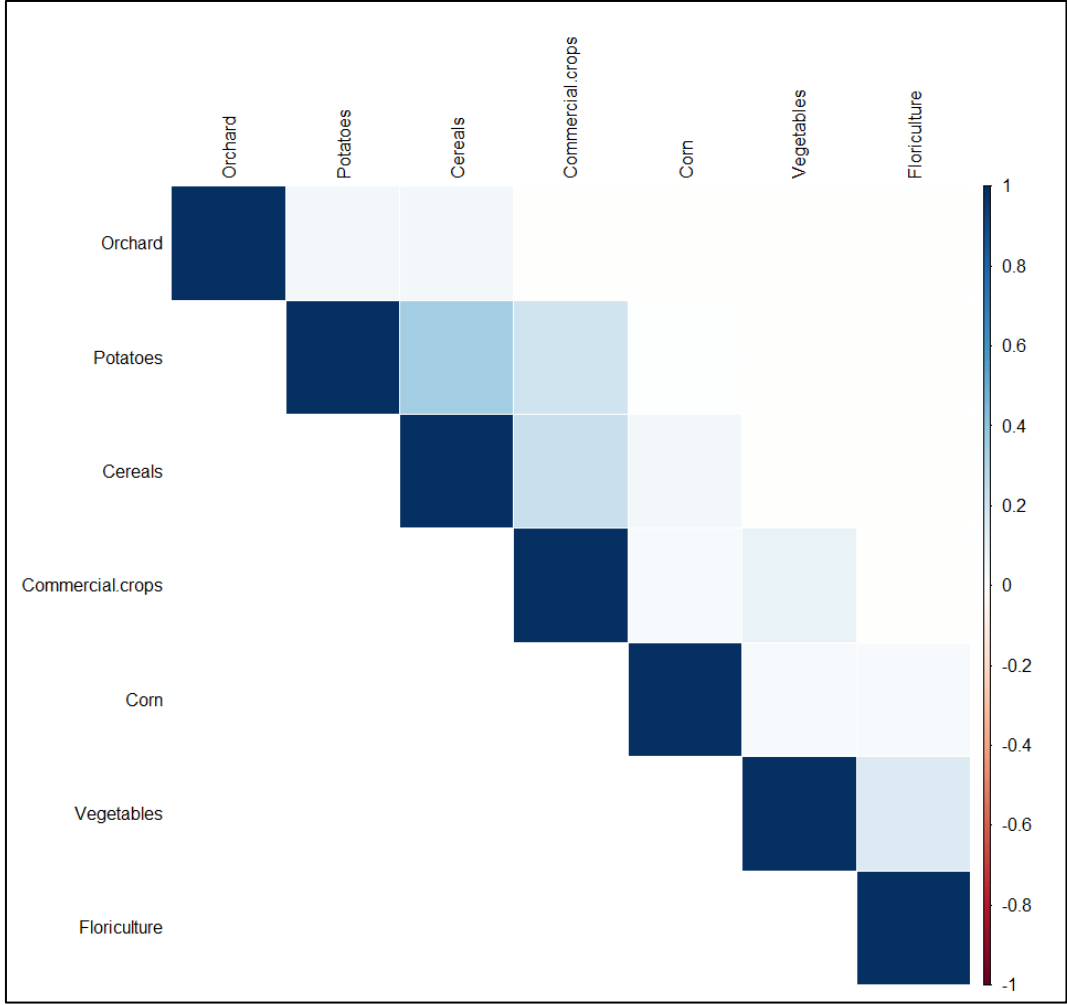


Figure S12: Heat map showing correlation between crop group-specific surface areas within a 500-meter distance around children’s homes.

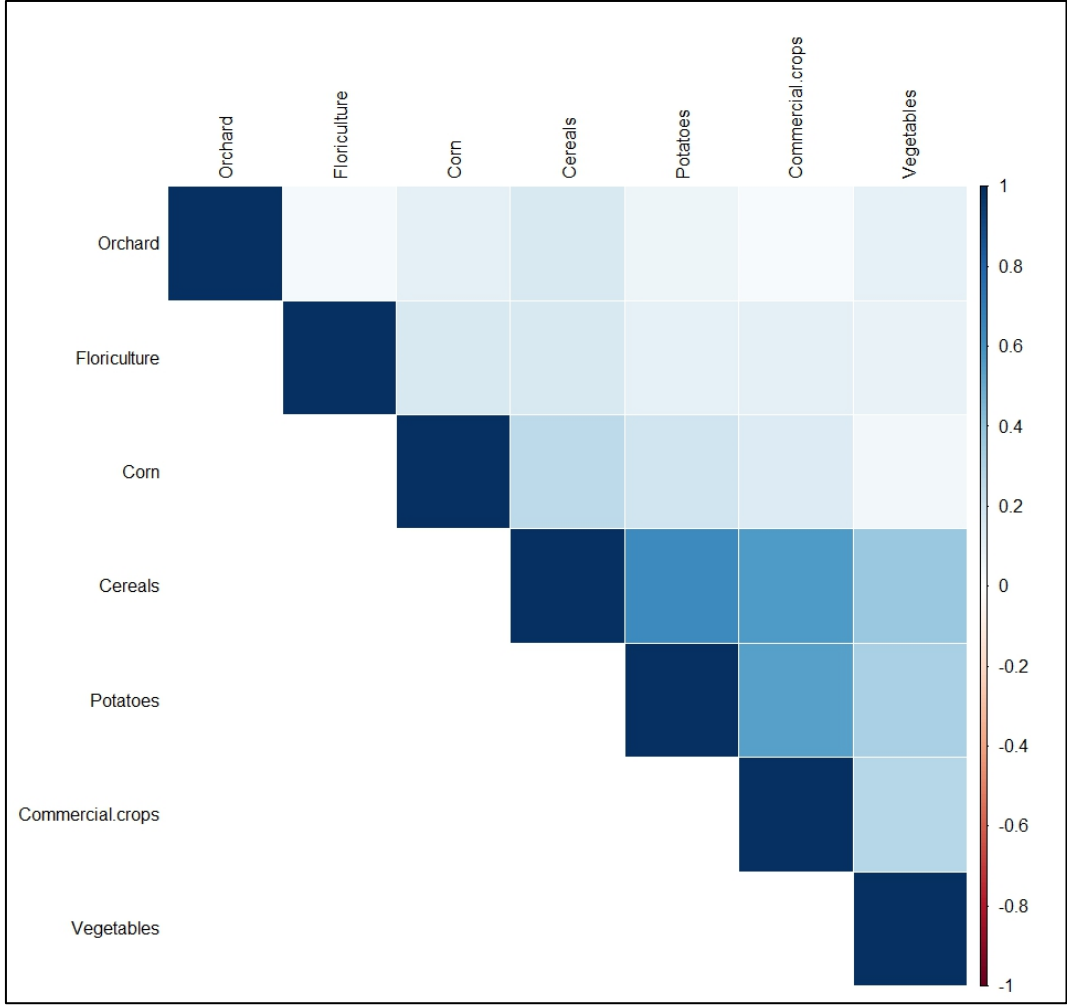


Figure S13: Heat map showing correlation between crop group-specific surface areas within a 1,000-meter distance around children’s homes.

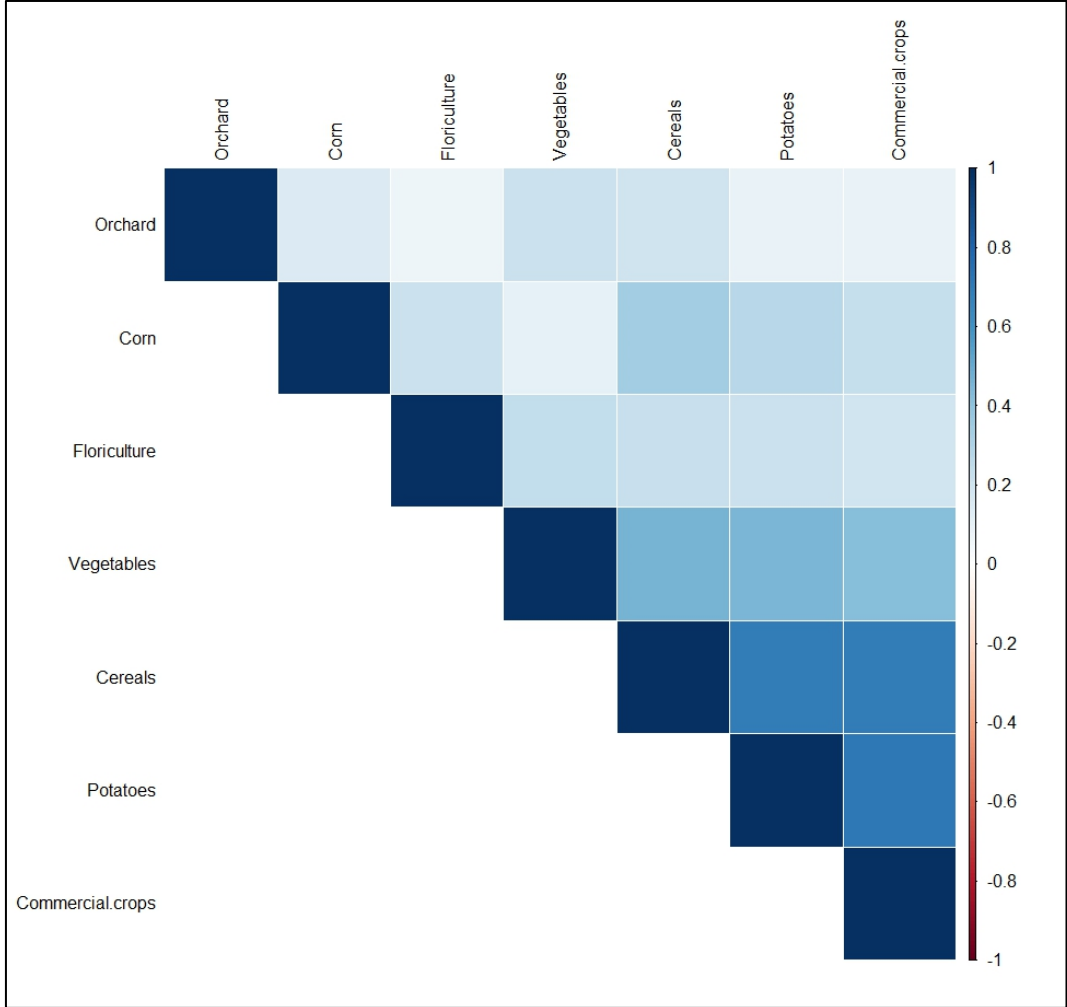
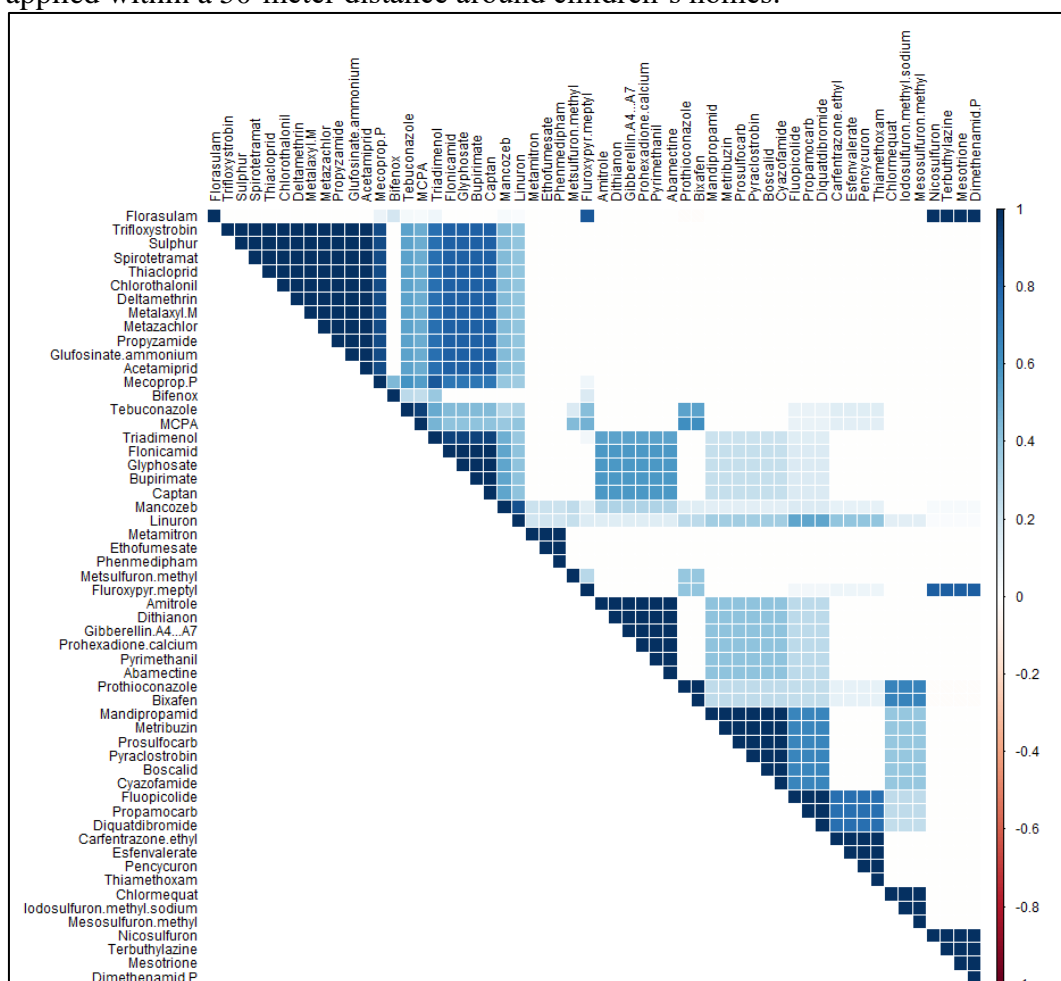


Figure S14: Heat map showing correlation between amounts of all individual agricultural applied within a 50-meter distance around children's homes.



Heatmap showing the correlation of 100 pesticides (rows) with 100 plant species (columns). The color scale ranges from -1 (dark blue) to 1 (dark red). The pesticides listed on the y-axis are: Asulam, Cycloxydim, Foprop, Kresoxim methyl, Lambda cyhalothrin, Mineral Oil, Prochloraz, Oxynil octanoate, Maleic hydrazide, Flupoxystrobin, Chloridazon, Pendimethalin, S-metolachlor, Chlorpropham, Esfenvalerate, Metamitron, Phenmedipham, Bifenox, Boscalid, Ethofumesate, Prothioconazole, Penoxycuron, Carfentrazone ethyl, Thiamethoxam, Fluoroxpyr methyl, Diquat dibromide, Propamocarb, Fluogicoide, Bixafen, Metsulfuron methyl, Florasulam, Tebuconazole, Iodosulfuron methyl sodium, Mesosulfuron methyl, Chlormequat, Mancozeb, Linuron, Metribuzin, Mandipropamid, Prochloropirid, Cyazoflamide, Trisulfocarb, Thiacloprid, Trifloxystrobin, Glufosinate ammonium, Glyphosate, MCPA, Mecoprop P, Metalaxyl M, Tridimenol, Mesotrione, Terbutylazine, Nicosulfuron, Dimethenamid P, Propyzamide, Metazachlor, Sulphur, Chlorothalonil, Deltamethrin, Spirotetramat, Acetamiprid, Flonicamid, Bupirimate, Captan, Prohexadione Calcium, Gibberellin A4, A7, Pyrimethanil, Diflufenican, Abamectin, and Amitrole. The plant species listed on the x-axis are: Asulam, Cycloxydim, Foprop, Kresoxim methyl, Lambda cyhalothrin, Mineral Oil, Prochloraz, Oxynil octanoate, Maleic hydrazide, Flupoxystrobin, Chloridazon, Pendimethalin, S-metolachlor, Chlorpropham, Esfenvalerate, Metamitron, Phenmedipham, Bifenox, Boscalid, Ethofumesate, Prothioconazole, Penoxycuron, Carfentrazone ethyl, Thiamethoxam, Fluoroxpyr methyl, Diquat dibromide, Propamocarb, Fluogicoide, Bixafen, Metsulfuron methyl, Florasulam, Tebuconazole, Iodosulfuron methyl sodium, Mesosulfuron methyl, Chlormequat, Mancozeb, Linuron, Metribuzin, Mandipropamid, Prochloropirid, Cyazoflamide, Trisulfocarb, Thiacloprid, Trifloxystrobin, Glufosinate ammonium, Glyphosate, MCPA, Mecoprop P, Metalaxyl M, Tridimenol, Mesotrione, Terbutylazine, Nicosulfuron, Dimethenamid P, Propyzamide, Metazachlor, Sulphur, Chlorothalonil, Deltamethrin, Spirotetramat, Acetamiprid, Flonicamid, Bupirimate, Captan, Prohexadione Calcium, Gibberellin A4, A7, Pyrimethanil, Diflufenican, Abamectin, and Amitrole.

Figure S16: Heat map showing correlation between amounts of all individual agricultural pesticides applied within a 500-meter distance around children's homes.

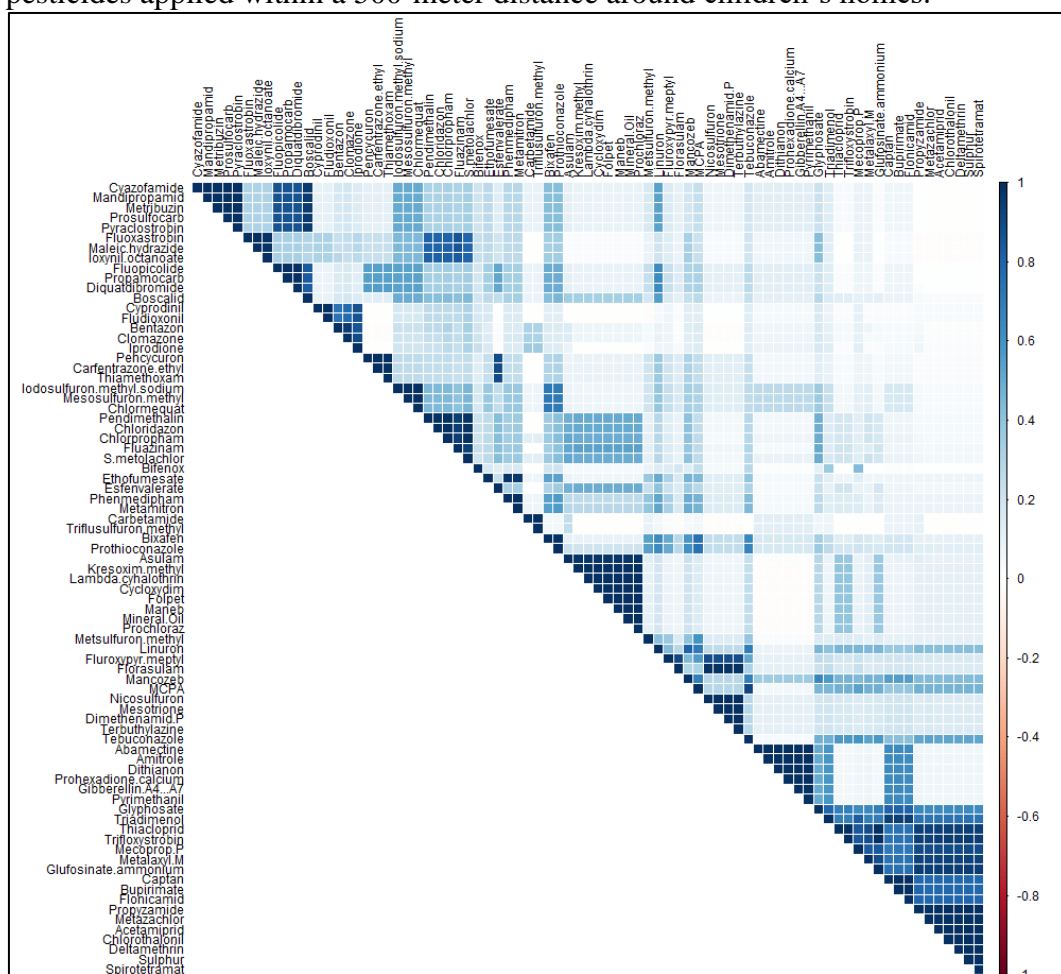


Figure S18: Heat map of Spearman correlations between estimated amounts of individual agricultural pesticides with known respiratory irritant properties applied within 50 meter of the children’s homes.

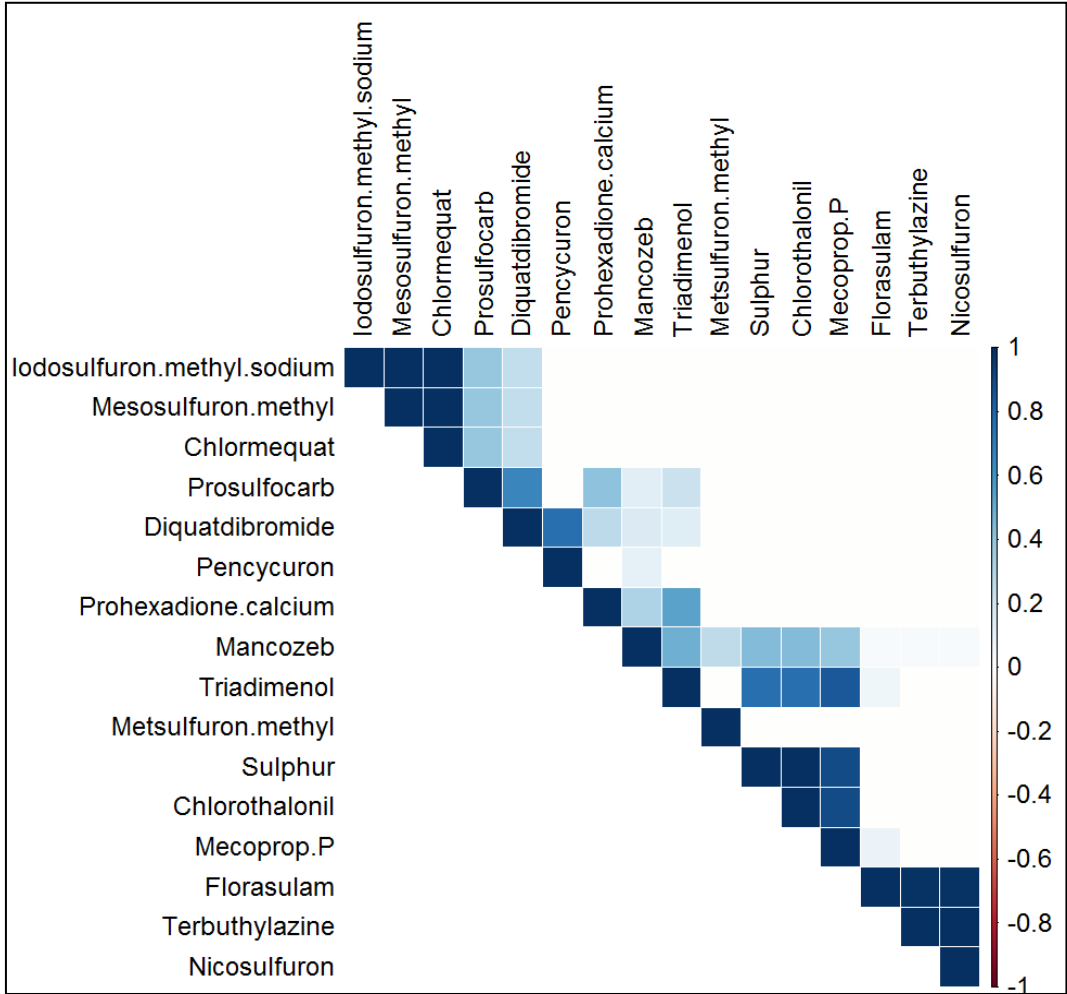


Figure S19: Heat map of Spearman correlations between estimated amounts of individual agricultural pesticides with known respiratory irritant properties applied within 100 meter of the children’s homes.

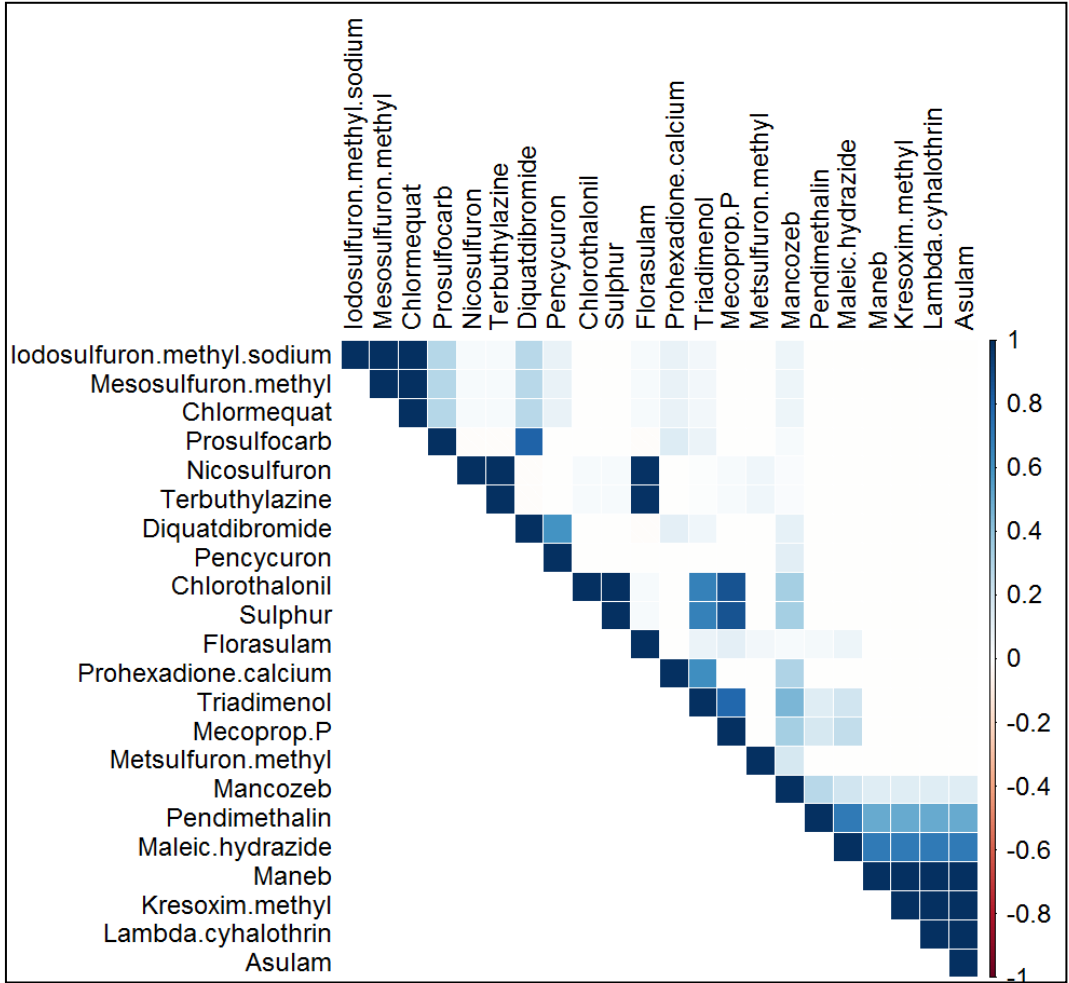


Figure S20: Heat map of Spearman correlations between amounts of individual agricultural pesticides with known respiratory irritant properties within a 500-meter distance around children’s homes.

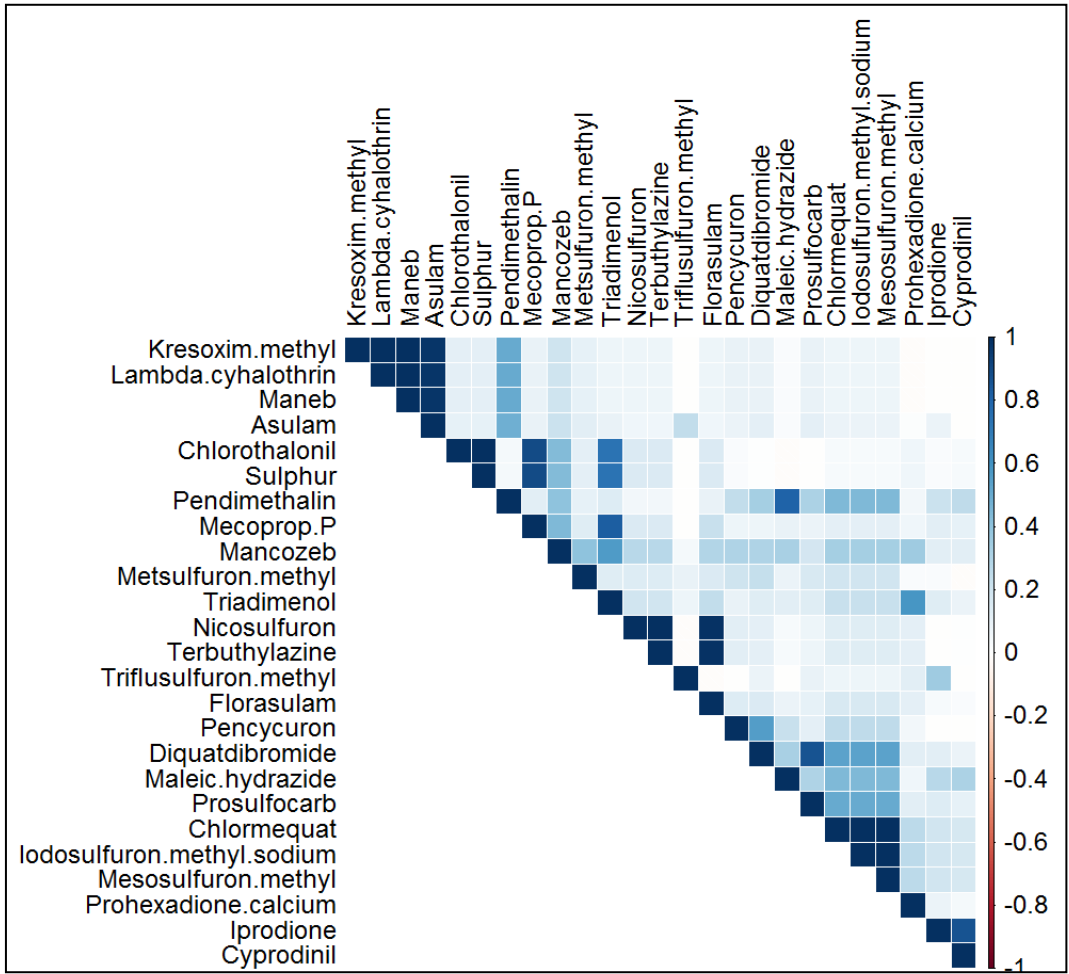
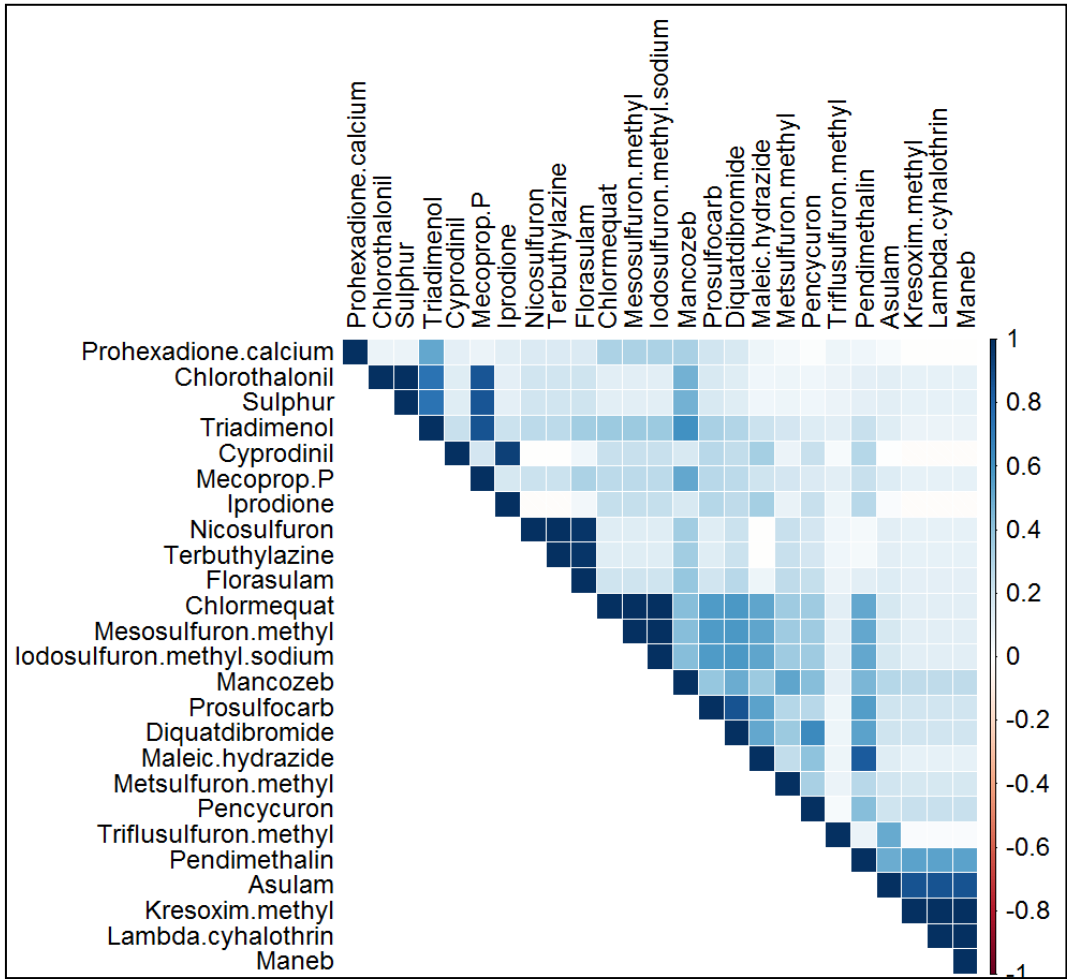


Figure S21: Heat map of Spearman correlations between amounts of individual agricultural pesticides with known respiratory irritant properties within a 1000-meter distance around children’s homes.



Chapter 3: Associations of residential exposure to agricultural pesticides with asthma prevalence in adolescence: the PIAMA birth cohort

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Abstract

Background: It has been suggested that children who are exposed to agricultural pesticides have an increased risk of asthma, but evidence for associations of residential pesticide exposure with childhood asthma is inconsistent.

Objectives: To investigate the associations of residential pesticide exposure with the prevalence of asthma and related symptoms within a Dutch birth cohort study.

Methods: In this cross-sectional analysis, we included participants of the PIAMA birth cohort study with data on residential pesticide exposure and asthma from parent-completed questionnaires at age 14, collected in 2012 (N= 1,473). We used spatial data on the presence of individual crops (cereals, open-field vegetables, commercial crops, open-field floriculture/bulbs, corn and potatoes) and pesticide application on these crops to estimate residential exposure to pesticides with known irritant properties for the respiratory system within distances of 100, 500, 1,000 m of the participants' homes. Logistic regression was used to estimate associations between exposure and outcomes, adjusting for potential confounders.

Results: No associations were found between living within 100, 500 and 1,000 m of agricultural fields likely treated with pesticides and symptoms of asthma. For instance, for participants living within 100 m of fields with any crops likely treated with pesticides, the adjusted odds ratios (95% confidence interval) for the prevalence of asthma, shortness of breath and dry night cough at age 14 were 0.31 (0.07, 1.32), 0.61 (0.23, 1.57) and 1.26 (0.56, 2.80), respectively. No associations were found between exposure to pesticides with known irritant properties for the respiratory system and asthma or related symptoms.

Conclusions: There was no association between living near agricultural fields likely treated with pesticides and asthma and related respiratory symptoms, among our study participants.

Keywords: Agricultural pesticides, Respiratory outcomes, Asthma, Birth cohort, Adolescents.

1. Introduction

Asthma is one of most common chronic diseases among children (World Health Organization, 2017). Many factors have been associated with an increased risk of asthma including genetic and environmental factors.

Agricultural pesticides are frequently used to fight pests and to improve plant growth and increase agricultural production. When these pesticides are applied to agricultural fields, they can transfer through the air to nearby homes and may be harmful to health (Coronado et al., 2011, Lu et al., 2000, Deziel et al., 2017). Previous studies have suggested that children living close to agricultural treated fields may have an increased risk of asthma possibly due to the transfer of pesticides to their homes (Schwartz et al., 2015, Salameh et al., 2003).

Pesticides with respiratory irritant properties may lead to asthma through interaction with functional irritant receptors in the airways (Hernandez et al., 2011). This process may promote neurogenic inflammation. In addition, cross-talk between airway nerves and inflammatory cells can help to maintain chronic inflammation that eventually damages the bronchial epithelium (Hernandez et al., 2011). This has been hypothesised to increase the risk of developing asthma, exacerbate an existing asthmatic condition or trigger asthma attacks by increasing bronchial hyper-responsiveness. In addition, exposures to agricultural pesticides have been linked with an increased level of Th2 cytokines in children (Duramad et al., 2006). Th2 cytokines play an important role in the development of allergic diseases, including asthma and related respiratory symptoms (Holgate, 1999).

At present, epidemiological evidence for associations of residential pesticide exposure with childhood asthma is inconsistent (Gascon et al., 2014a, Gascon et al., 2014b, Karmaus et al., 2003, Karmaus et al., 2001, Liu et al., 2012, Mamane et al., 2015, Merchant et al., 2005, Perla et al., 2015, Reardon et al., 2009, Salam et al., 2004, Salameh et al., 2003, Sunyer et al., 2005, Sunyer et al., 2006, Tagiyeva et al., 2010, Weselak et al., 2007). As these studies were based

on different designs, sample sizes, exposure and outcome definitions, it is not possible to conclude, which of these factors contributed most to the heterogeneity of the study findings. For example, in these studies, residential exposure to agricultural pesticides has been assessed in different ways, namely using (self-reported) distances from treated agricultural fields as a proxy (Salameh et al., 2003), biomonitoring (Coronado et al., 2011, Bouvier et al., 2005) as well as measurements of pesticides contaminants in house dust samples (Ward et al., 2006) and indoor air (Garron et al., 2009).

We tested our hypothesis of an association between residential exposure to pesticides and asthma and related respiratory symptoms among adolescents within our Dutch PIAMA birth cohort study. Our study is based on a very well-defined cohort and uses extensively documented methods of exposure (Bukalasa et al., 2017) and outcome (Pinart et al., 2014) assessment, which improves the transparency of the findings and comparability with other studies.

2. Methodology

2.1 Study design and population

The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study is a prospective Dutch birth cohort study. The baseline study population consisted of 3,963 participants from the northern, middle and western parts of The Netherlands, who were born in 1996 and 1997 (Wijga et al., 2014). The PIAMA study was designed to examine the influence of lifestyle and environmental factors on the development of asthma and allergies in children. Questionnaires were administered to parents during pregnancy, at the child's ages of 3 months and 1 year, and then annually until the age of 8 years. When the children were 11, 14 and 17 years, questionnaires were completed by both parents and children.

The present study is a cross-sectional analysis within the prospective PIAMA birth cohort study using data collected when the participants were about 14 years old. This study builds on our previous work on the assessment of pesticide exposure using proximity to agricultural fields with crops relevant for pesticide use and surface areas of these crops as a proxy for exposure among PIAMA participants (Bukalasa et al., 2017). We included all participants who were included in the exposure assessment study and who had information on at least one of the outcomes of interest, i.e. asthma and related respiratory symptoms at the age of 14. We restricted the current study population to participants with questionnaires completed in 2012, i.e. the year for which we had data on exposure, to assure that exposure preceded health outcomes (N=1,473, Figure S1).

2.2 *Health outcomes*

We used data from standardized asthma outcomes questionnaires that were self-completed by the parents in the Dutch language when the children were 14 years old to define asthma and related symptoms at age 14. Asthma was defined as at least two positive answers to the following three questions: (1) has a doctor ever diagnosed asthma in your child, (2) has your child had wheezing or whistling in the chest in the last 12 months, (3) has your child been prescribed asthma medication during the last 12 months. This definition was developed by a panel of experts within the MeDALL consortium (Pinart et al., 2014). Additional outcomes of interest were shortness of breath during the past 12 months and dry night cough during the past 12 months.

2.3 *Agricultural Pesticides exposure assessment*

An assessment of environmental pesticide exposure within the PIAMA birth cohort study has been described elsewhere (Bukalasa et al., 2017). In brief, we used areas of selected crops extracted from the Basic Registration of Crops (BRP, vector dataset with 1:10,000 underlying resolution) of 2012 (Dutch Ministry of Interior and Kingdom Relations, 2013) within 50, 100, 500 and 1,000 m of the participants' home addresses at the time of the 14-year follow-up as proxies for environmental pesticide exposures. We used data for the same year for all participants. Since the 14-year questionnaires were completed by the parents between October 2011 and August 2013 we used data for 2012 (which is well within that period) to assess residential exposure to pesticides. In the present study, our assessment focused on 100, 500 and 1,000 m buffers around the participants' homes to investigate exposure at short distances only (100 m buffer) and exposure at shorter and larger distances (500 and 1,000 m buffers).

In addition, we assigned likely used pesticides (in a gram of active ingredient per year) in the aforementioned buffers based on a 2012 farmer survey by Statistics Netherlands (CBS) in combination with the acreage of specific crops around the participants' homes as described previously (Bukalasa et al., 2017). We included in the present analysis pesticides with known irritant properties for the respiratory system identified through the pesticides properties database (PPD) and the pesticides manual (University of Hertfordshire, 2016).

For the assessment of associations with the presence of specific crops, we selected cereals, open-field vegetables, commercial crops (sugar beet, cichorium, hemp (fiber), winter rapeseed, summer rapeseed, fodder beets (including topinambour), grass seeds (including clover seeds and flax), open field floriculture/bulbs, corn and potatoes within 500 and 1,000 m of the homes. We selected these crops as it is likely that they have been treated with pesticides and because they were present for at least 10% of the study participants in the respective buffers resulting in sufficient numbers of exposed children (Table 1). None of the crops met the 10% criterion

with the 100 m buffer because we had only a few participants living within a short distance of agricultural fields. Like for the specific crops, we restricted our analysis of associations with amounts of pesticides used to pesticides that were likely applied around at least 10% of the participants' homes. These included chlormequat, chlorothalonil, diquat dibromide, florasulam, iodosulfuron-methyl-sodium, mancozeb, mecoprop-P, mesosulfuron-methyl, metsulfuron-methyl, nicosulfuron, prosulfocarb, terbuthylazine, triadimenol and sulphur (Table S2). We restricted our study to residential exposure and did not include exposure at the school addresses because children spend most of their time at home. Also, the focus of this study was to investigate environmental agricultural pesticide exposure at the residential addresses. Therefore, household pesticides exposure, which was assessed by one single, very broad question, was not taken into account.

2.4 Covariates

Covariates have been identified from previous studies (Liu et al., 2012, Perla et al., 2015, Salameh et al., 2003) as determinants of the outcomes of interest (asthma and related respiratory symptoms). These covariates included the sex of the adolescent, smoking in the adolescent's home at the time of the outcome assessment, BMI z-score of the child at the time of outcome assessment, parental education (defined as the maximum of the mother's and the father's educational level and categorized as low (primary school, lower vocational, or lower secondary education), intermediate (intermediate vocational education or intermediate/higher secondary education), and high (higher vocational education and university)), presence of furry pets (cat, dog, and/or rodent) at home at the time of outcome assessment, maternal and paternal allergy (defined as asthma ever, hay fever, and/or allergy to house dust mite and/or pets), child's ethnicity, and estimated traffic-related air pollution. Several metrics of air pollution were available: an annual average of nitrogen oxides, particulate matter and 'soot' at the

participant's home address at the time of the outcome assessment, estimated by a land-use regression model developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Beelen et al., 2013). As these metrics were highly correlated, we only adjusted for nitrogen dioxide (NO₂) as a marker of traffic-related air pollution, which has been found to be associated with asthma in earlier analyses (Gehring et al., 2015). We did not take into account the active smoking of the adolescent participants because the number of participants who reported being active smokers at the time of the 14-year follow-up was very small (n=72).

2.5 *Statistical analysis*

We performed descriptive statistical analyses of the demographic variables at age 14 years. We used logistic regression to assess associations of the outcomes of interest with environmental pesticide exposure defined as the area of crops likely treated with pesticides and the estimated amount of agricultural pesticide used around the participant's homes at the time of the 14 years follow-up.

Our exposure variables were used as categorical variables. As few participants lived within 100 m of fields with relevant crops, the areas of crops and estimated amounts of pesticides within the 100 m buffer were dichotomized (zero vs non-zero) and included as binary variables.

For the selected individual crops and the selected pesticides with known irritant properties for the respiratory system applied within 500 and 1,000 m, we defined zero as the reference category and divided non-zero values into three categories using tertiles of non-zero values as cut-offs.

An analysis were performed with and without adjustment for the potential confounding factors described above and the impact of the potential confounders on our association estimates was assessed by comparing adjusted and unadjusted estimates. Crude association estimates were calculated for the full population and the sub-population with complete confounder data to

assess whether differences between crude and adjusted estimates are due to confounding or due to selection. We first adjusted for all potential confounding factors except BMI, which has a larger number of missing values than the other confounders (13 %) and then assessed potential confounding by BMI separately by adding it as another covariate to the model. Since association estimates with and without adjustment for BMI were basically the same (data not shown), the model without adjustment for BMI is presented in tables.

Associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs); the Wald test was used to determine the statistical significance of the relationship for categorical exposure variables. We tested for a linear trend across categories using Wald-Chi-squared tests in standard logistic regression by assigning numeric values (0,1,2,3) to the categories and using this numeric variable as a continuous exposure variable. Statistical analyses were conducted using SAS version 9.4.

3. Results

Table 1 shows the prevalence of (specific groups of) crops within 100, 500, and 1,000 m of the participant' homes. Distributions of the amount of individual pesticides with known irritant properties for the respiratory tract applied within 100, 500 and 1,000 m are presented in Table S1.

Distributions of demographic characteristics of the study population (n=1,473) and respiratory symptoms at age 14 are given in Table 2. Approximately half of the adolescents were male, the mean age for the study participants at the time of questionnaire completion was 14.8 years, 12% of the parents reported smoking in the child's home, approximately 60% of the parents were highly educated, and about 30% of the mothers and fathers were atopic. The majority of the participants' parents were both born in the Netherlands (Table 2). The prevalence of asthma was 7%; 9% and 7% of the adolescents had shortness of breath and dry night cough,

respectively (Table 2). The annual average NO₂ levels at the participants' home addresses were generally below the WHO Air Quality Guideline of 40 µ/m³, which is identical to the European Air Quality Limit Value for this substance (European Commission 2013).

The distributions of the prevalence of asthma, shortness of breath and dry night coughing in relation to the area of crops and estimated amounts of individual pesticides are shown in Tables S2 and S3.

Crude (full population and participants with complete confounder data) and adjusted associations of respiratory symptoms with the presence of any crops, as well as the estimated amount of any pesticides applied within 100 m indicated no increased risk of asthma or related symptoms in relation to pesticide exposure (Table 3). Similarly, no associations were found between the prevalence of asthma, shortness of breath and dry night cough on the one hand and the presence of any crops within 500 and 1,000 m of the participants' homes on the other hand (Table 4, Tables S4).

For estimated amounts of individual pesticides applied within 500 and 1,000 m buffers, no associations were observed with the prevalence of asthma, shortness of breath and dry night cough among our study participants (Table 5, Tables S5). The Odds ratios for tertiles of chlorothalonil and sulphur exposure are identical as these two agricultural pesticides were used on exactly the same crops, namely open-field floriculture/bulbs, which means that their associations with respiratory health cannot be disentangled (Table 5).

Table 1: Number and percentage of participants with relevant crops cultivated within 100, 500 and 1,000 m of their home addresses at the time of the 14-year follow-up (N = 1,473).

	Radius of circular buffer		
	100 m	500 m	1,000 m
	N [%]	N [%]	N [%]
Any crops	100 [6.8]	588 [39.9]	945 [64.2]
Cereals	29 [2.0]	236 [16.0]	459 [31.2]
Open field vegetables	5 [0.3]	51 [3.5]	145 [9.8]
Commercial crops	13 [0.9]	115 [7.8]	277 [18.8]
Open field floriculture/bulbs	4 [0.3]	81 [5.5]	222 [15.1]
Corn	41 [2.8]	412 [28.0]	790 [53.6]
Potatoes	30 [2.0]	188 [12.8]	336 [22.8]

Table 2: Characteristics of the study population (N=1,473).

Characteristic	n/N	[%]
Male sex	742/1,473	[50]
Smoking in the child's home	173/1,473	[12]
Pets at home (cat, dog and/or rodent)	884/1,469	[59]
Parental education		
Low	146/1,471	[10]
Intermediate	507/1,471	[34]
High	818/1,471	[56]
Maternal and paternal allergy		
Allergy father	445/1,473	[30]
Allergy mother	397/1,473	[27]
Both parents Dutch nationality	1315/1,443	[91]
Asthma	97/1,470	[7]
Shortness of breath	132/1471	[9]
Dry night cough	100/1,467	[7]
	N	Mean (SD)
Age at questionnaire completion [years]	1,473	14.80 [0.36]
Body mass index [kg/m ²]	1,278	-0.01 [1.10]
Traffic-related air pollution (NO ₂) [µg/m ³]	1,473	22.71[6.62]

Table 3: Associations of the presence of any of any selected crops and estimated amount of pesticide applied within 100 m of the participants' homes with prevalence of asthma and related symptoms at age 14.

Exposure variable	Asthma			Shortness of breath			Dry night cough		
	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
N = 1, 470	N = 1, 434	N = 1, 434	N = 1, 434	N = 1, 471	N = 1, 435	N = 1, 435	N = 1, 467	N = 1, 431	N = 1, 431
Area of crops (m ²):	0.27	0.28	0.31	0.52	0.52	0.61	1.21	1.23	1.26
>0 vs 0	[0.07, 1.13]	[0.07, 1.15]	[0.07, 1.32]	[0.21, 1.29]	[0.21, 1.29]	[0.23, 1.57]	[0.57, 2.56]	[0.58, 2.61]	[0.56, 2.80]
Amount of pesticides (g of active ingredient/year)	0.31	0.31	0.36	0.58	0.58	0.71	1.36	1.39	1.45
>0 vs 0	[0.08, 1.27]	[0.08, 1.29]	[0.09, 1.55]	[0.23, 1.46]	[0.23, 1.46]	[0.27, 1.85]	[0.64, 2.90]	[0.65, 2.97]	[0.65, 3.22]

^a Crude estimates for the full population.

^b Crude estimates for the population with complete confounder data.

^c Adjusted for sex of the child, smoking in the child's home at age 14, SES (parental education i.e. combination of mother or father), pets at home at age 14 year follow-up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnicity group of mother and father, and traffic-related air pollution (NO₂) at age 14-year follow-up in multiple logistic regression models.

* P < 0.05.

Table 4: Associations of the presence of the selected crops within 1,000 m of the participants' homes with prevalence of asthma symptoms at age 14.

	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m²)	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Any crop	0.78 [0.51, 1.19]	0.77 [0.50, 1.17]	0.88 [0.54, 1.44]	0.94 [0.65, 1.36]	0.94 [0.65, 1.37]	1.13 [0.73, 1.74]	1.00 [0.65, 1.52]	0.99 [0.64, 1.51]	1.08 [0.66, 1.76]
>0 vs 0									
Cereals	p = 0.912 ^d 0.45 [0.18, 1.14]	p = 0.872 ^d 0.47 [0.18, 1.17]	p = 0.760 ^d 0.52 [0.20, 1.33]	p = 0.606 ^d 0.47 [0.22, 1.04]	p = 0.683 ^d 0.48 [0.22, 1.05]	p = 0.341 ^d 0.54 [0.24, 1.21]	p = 0.465 ^d 1.64 [0.91, 2.95]	p = 0.429 ^d 1.56 [0.85, 2.86]	p = 0.418 ^d 1.63 [0.87, 3.06]
>0 -37,040 vs 0									
>37,040 - 173,093	1.10 [0.57, 2.14]	1.03 [0.52, 2.05]	1.10 [0.53, 2.30]	1.06 [0.59, 1.91]	0.99 [0.54, 1.81]	1.08 [0.57, 2.05]	1.25 [0.64, 2.44]	1.30 [0.67, 2.54]	1.36 [0.68, 2.73]
vs 0									
>73,093 vs 0	0.99 [0.51, 1.91]	1.00 [0.52, 1.94]	1.16 [0.57, 2.38]	1.24 [0.73, 2.12]	1.24 [0.73, 2.12]	1.44 [0.80, 2.59]	1.11 [0.57, 2.16]	1.13 [0.58, 2.20]	1.16 [0.57, 2.37]

Table 4: (continued)

	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m²)	N = 1, 470	N = 1, 434	N = 1, 434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Open field vegetables	p = 0.730 ^d	p = 0.790 ^d	p = 0.885 ^d	p = 0.781 ^d	p = 0.747 ^d	p = 0.692 ^d	p = 0.591 ^d	p = 0.528 ^d	p = 0.588 ^d
>0 – 14,798 vs 0	0.29 [0.04, 2.14]	0.29 [0.04, 2.16]	0.31 [0.04, 2.32]	0.44 [0.11, 1.82]	0.43 [0.10, 1.81]	0.43 [0.10, 1.87]	1.63 [0.63, 4.22]	1.65 [0.64, 4.27]	1.74 [0.67, 4.56]
>14,798 – 80,865 vs 0	0.58 [0.14, 2.44]	0.59 [0.14, 2.47]	0.60 [0.14, 2.60]	0.89 [0.32, 2.53]	0.88 [0.31, 2.50]	0.88 [0.30, 2.58]	0.94 [0.29, 3.07]	0.94 [0.29, 3.10]	0.93 [0.28, 3.09]
>80,865 vs 0	1.25 [0.44, 3.55]	1.32 [0.46, 3.76]	1.38 [0.47, 4.05]	1.44 [0.60, 3.45]	1.49 [0.62, 3.59]	1.54 [0.63, 3.80]	1.28 [0.45, 3.63]	1.35 [0.47, 3.85]	1.27 [0.44, 3.67]
Commercial crops	p = 0.762 ^d	p = 0.706 ^d	p = 0.543 ^d	p = 0.549 ^d	p = 0.548 ^d	p = 0.407 ^d	p = 0.646 ^d	p = 0.692 ^d	p = 0.545 ^d
>0 – 37,762 vs 0	1.64 [0.82, 3.28]	1.66 [0.83, 3.33]	2.14 [1.03, 4.44]	1.72 [0.95, 3.14]	1.71 [0.94, 3.11]	2.00 [1.07, 3.74]	0.84 [0.36, 1.98]	0.85 [0.36, 2.00]	0.90 [0.38, 2.13]
>37,762 – 115,504 vs 0	1.51 [0.70, 3.24]	1.55 [0.72, 3.33]	1.46 [0.64, 3.31]	1.57 [0.81, 3.04]	1.57 [0.81, 3.06]	1.53 [0.75, 3.10]	0.99 [0.42, 2.33]	1.01 [0.43, 2.39]	0.90 [0.37, 2.20]
>115,504 vs 0	0.71 [0.25, 1.99]	0.73 [0.26, 2.04]	0.85 [0.29, 2.52]	0.79 [0.34, 1.86]	0.79 [0.34, 1.87]	0.90 [0.37, 2.23]	0.80 [0.32, 2.04]	0.82 [0.32, 2.08]	0.75 [0.28, 1.99]

Table 4: (continued)

	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m²)	N = 1, 470	N = 1, 434	N = 1, 434	N = 1, 471	N = 1, 435	N = 1, 435	N = 1, 467	N = 1, 431	N = 1, 431
Open field floriculture	p = 0.336 ^d	p = 0.290 ^d	p = 0.252 ^d	p = 0.612 ^d	p = 0.633 ^d	p = 0.682 ^d	p = 0.167 ^d	p = 0.139 ^d	p = 0.092 ^d
>0 – 5,088 vs 0	1.03 [0.40, 2.62]	1.07 [0.42, 2.73]	1.02 [0.39, 2.68]	1.34 [0.65, 2.77]	1.37 [0.67, 2.83]	1.35 [0.64, 2.85]	1.23 [0.52, 2.92]	1.28 [0.54, 3.05]	1.39 [0.58, 3.33]
>5,088 – 14,330 vs 0	1.79 [0.83, 3.87]	1.85 [0.86, 3.99]	1.83 [0.82, 4.12]	1.06 [0.48, 2.37]	1.07 [0.48, 2.38]	1.06 [0.46, 2.41]	1.77 [0.82, 3.81]	1.82 [0.84, 3.92]	1.96 [0.89, 4.30]
>14,330 vs 0	1.12 [0.44, 2.86]	1.15 [0.45, 2.95]	1.28 [0.48, 3.38]	0.61 [0.22, 1.69]	0.610 [0.22, 1.71]	0.64 [0.22, 1.83]	1.37 [0.57, 3.25]	1.41 [0.59, 3.35]	1.51 [0.62, 3.68]
Corn	p = 0.619 ^d	p = 0.609 ^d	p = 0.788 ^d	p = 0.116 ^d	p = 0.148 ^d	p = 0.489 ^d	p = 0.556 ^d	p = 0.433 ^d	p = 0.590 ^d
>0 – 53,686 vs 0	0.96 [0.55, 1.69]	1.00 [0.57, 1.77]	1.14 [0.62, 2.08]	1.15 [0.73, 1.83]	1.19 [0.75, 1.89]	1.33 [0.81, 2.18]	1.24 [0.73, 2.11]	1.27 [0.75, 2.15]	1.38 [0.80, 2.41]
>53,686 - 164,363 vs 0	0.64 [0.34, 1.23]	0.68 [0.35, 1.30]	0.81 [0.40, 1.63]	0.70 [0.41, 1.20]	0.73 [0.42, 1.25]	0.82 [0.46, 1.47]	0.78 [0.42, 1.44]	0.74 [0.39, 1.39]	0.76 [0.39, 1.49]
>164,363 vs 0	1.01 [0.58, 1.74]	0.98 [0.56, 1.72]	1.22 [0.64, 2.32]	0.71 [0.42, 1.21]	0.73 [0.43, 1.24]	0.87 [0.48, 1.57]	0.91 [0.52, 1.62]	0.87 [0.48, 1.56]	0.93 [0.48, 1.78]

Table 4: (continued)

	Asthma		Shortness of breath				Dry night cough	
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m²)	N = 1, 470	N = 1, 434	N = 1, 434	N = 1, 471	N = 1, 435	N = 1, 435	N = 1, 467	N = 1, 431
Potatoes	p = 0.840 ^d	p = 0.773 ^d	p = 0.288 ^d	p = 0.881 ^d	p = 0.877 ^d	p = 0.382 ^d	p = 0.408 ^d	p = 0.372 ^d
>0 - 56,848 vs 0	0.57 [0.20, 1.59]	0.59 [0.21, 1.65]	0.73 [0.26, 2.10]	0.63 [0.27, 1.47]	0.63 [0.27, 1.48]	0.75 [0.31, 1.79]	0.60 [0.22, 1.69]	0.62 [0.22, 1.77]
>56,848 -	1.47	1.50	1.94	1.49	1.49	1.81	2.35	2.39
227,078 vs 0	[0.76, 2.85]	[0.77, 2.92]	[0.95, 3.98]	[0.84, 2.66]	[0.83, 2.66]	[0.97, 3.37]	[1.31, 4.19]	[1.29, 4.43]
>227,078 vs 0	0.91	0.93	1.17	0.85	0.85	1.03	0.80	0.80
	[0.41, 2.02]	[0.42, 2.07]	[0.49, 2.79]	[0.42, 1.73]	[0.42, 1.73]	[0.48, 2.21]	[0.34, 1.88]	[0.32, 1.99]

^a Crude estimates for the full population.

^b Crude estimates for the population with complete confounder data.

^c Adjusted for sex of the child, smoking in the child's home at age 14, SES (parental education i.e. combination of mother or father), pets at home at age 14 year follow up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnicity group of mother and father, and traffic-related air pollution (NO₂) at age 14 year follow up in multiple logistic regression models.

^d p-value trend test.

Table 5: Associations of the estimated amounts of individual pesticides applied within 1,000 m of the participants' homes with prevalence of and asthma and related symptoms at age 14.

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Any pesticides ^b	0.77 [0.51, 1.16]	0.75 [0.49, 1.15]	0.86 [0.52, 1.40]	0.85 [0.59, 1.22]	0.85 [0.59, 1.23]	0.99 [0.65, 1.52]	1.03 [0.67, 1.56]	1.02 [0.66, 1.56]	1.12 [0.69, 1.81]
>0 vs 0									
Chlormequat	p = 0.459 ^d 1.64 [0.76, 3.53]	p = 0.535 ^d 1.69 [0.78, 3.63]	p = 0.665 ^d 1.75 [0.78, 3.90]	p = 0.710 ^d 1.21 [0.57, 2.58]	p = 0.651 ^d 1.22 [0.57, 2.61]	p = 0.538 ^d 1.28 [0.58, 2.79]	p = 0.740 ^d 1.66 [0.77, 3.57]	p = 0.737 ^d 1.45 [0.65, 3.27]	p = 0.798 ^d 1.49 [0.66, 3.39]
>0 - 2,806 vs 0									
>2,806 - 11,611	0.19 [0.03, 1.41]	0.21 [0.03, 1.52]	0.28 [0.04, 2.10]	0.76 [0.30, 1.92]	0.80 [0.31, 2.03]	1.02 [0.39, 2.64]	0.84 [0.30, 2.37]	0.90 [0.32, 2.52]	0.93 [0.33, 2.67]
>11,611 vs 0	0.92 [0.36, 2.33]	0.94 [0.37, 2.39]	0.90 [0.34, 2.37]	1.29 [0.63, 2.64]	1.30 [0.63, 2.66]	1.25 [0.59, 2.64]	1.13 [0.48, 2.67]	1.14 [0.48, 2.71]	1.08 [0.45, 2.58]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
	N = 1, 470	N = 1, 434	N = 1, 434	N = 1, 471	N = 1, 435	N = 1, 435	N = 1, 467	N = 1, 431	N = 1, 431
Chlorothalonil	p = 0.671 ^d	p = 0.720 ^d	p = 0.655 ^d	p = 0.360 ^d	p = 0.368 ^d	p = 0.340 ^d	p = 0.951 ^d	p = 0.894 ^d	p = 0.804 ^d
> 0 - 30 vs 0	1.52 [0.64, 3.64]	1.54 [0.64, 3.68]	1.33 [0.53, 3.31]	1.07 [0.45, 2.53]	1.06 [0.45, 2.51]	0.95 [0.39, 2.30]	1.20 [0.47, 3.07]	1.21 [0.47, 3.10]	1.26 [0.49, 3.26]
>30 - 80 vs 0	1.05 [0.37, 2.98]	1.08 [0.38, 3.07]	0.97 [0.33, 2.84]	1.15 [0.48, 2.74]	1.16 [0.49, 2.76]	1.10 [0.45, 2.68]	0.49 [0.12, 2.03]	0.50 [0.12, 2.09]	0.51 [0.12, 2.13]
>80 vs 0	0.53 [0.13, 2.20]	0.54 [0.13, 2.26]	0.57 [0.13, 2.46]	0.37 [0.09, 1.54]	0.37 [0.09, 1.55]	0.38 [0.09, 1.62]	1.34 [0.52, 3.44]	1.38 [0.54, 3.55]	1.46 [0.56, 3.83]
Diquatdibromide	p = 0.326 ^d	p = 0.286 ^d	p = 0.155 ^d	p = 0.265 ^d	p = 0.258 ^d	p = 0.144 ^d	p = 0.177 ^d	p = 0.150 ^d	p = 0.172 ^d
> 0 - 1,377 vs 0	1.66 [0.77, 3.57]	1.71 [0.79, 3.68]	2.03 [0.89, 4.61]	0.84 [0.36, 1.99]	0.85 [0.36, 2.00]	0.97 [0.40, 2.35]	0.76 [0.27, 2.14]	0.78 [0.28, 2.20]	0.77 [0.27, 2.20]
>1,377 - 5,192 vs 0	0.18 [0.03, 1.34]	0.19 [0.03, 1.38]	0.26 [0.04, 1.88]	0.40 [0.12, 1.27]	0.40 [0.12, 1.28]	0.50 [0.15, 1.64]	1.59 [0.74, 3.42]	1.63 [0.76, 3.51]	1.62 [0.73, 3.55]
>5,192 vs 0	2.02 [1.00, 4.06]	2.07 [1.03, 4.18]	2.17 [1.04, 4.55]	2.08 [1.14, 3.82]	2.09 [1.14, 3.85]	2.13 [1.13, 4.03]	1.53 [0.71, 3.28]	1.57 [0.73, 3.37]	1.55 [0.71, 3.37]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
	N = 1, 470	N = 1, 434	N = 1, 434	N = 1,471	N = 1, 435	N = 1,435	N = 1,467	N = 1, 431	N = 1,431
Florasulam	p = 0.523 ^d 0.88 [0.50, 1.56]	p = 0.517 ^d 0.92 [0.52, 1.63]	p = 0.936 ^d 1.03 [0.56, 1.90]	p = 0.102 ^d 1.14 [0.72, 1.81]	p = 0.132 ^d 1.17 [0.73, 1.86]	p = 0.413 ^d 1.30 [0.79, 2.14]	p = 0.466 ^d 1.30 [0.77, 2.19]	p = 0.357 ^d 1.32 [0.78, 2.23]	p = 0.454 ^d 1.44 [0.83, 2.50]
>0 – 3 vs 0									
>3 – 9 vs 0	0.76 [0.42, 1.38]	0.80 [0.44, 1.46]	0.89 [0.46, 1.71]	0.78 [0.47, 1.31]	0.82 [0.49, 1.37]	0.88 [0.50, 1.54]	0.86 [0.48, 1.54]	0.83 [0.45, 1.51]	0.85 [0.45, 1.61]
>9 vs 0	0.90 [0.51, 1.60]	0.88 [0.49, 1.58]	1.10 [0.56, 2.14]	0.65 [0.37, 1.13]	0.66 [0.38, 1.16]	0.80 [0.43, 1.48]	0.83 [0.46, 1.51]	0.78 [0.42, 1.45]	0.82 [0.41, 1.62]
Iodosulfuron, Methyl, Sodium	p = 0.459 ^d 1.64 [0.76, 3.53]	p = 0.535 ^d 1.69 [0.78, 3.63]	p = 0.665 ^d 1.75 [0.78, 3.90]	p = 0.710 ^d 1.21 [0.57, 2.58]	p = 0.651 ^d 1.22 [0.57, 2.61]	p = 0.538 ^d 1.28 [0.58, 2.79]	p = 0.740 ^d 1.66 [0.77, 3.57]	p = 0.737 ^d 1.45 [0.65, 3.27]	p = 0.798 ^d 1.49 [0.66, 3.39]
>0 - 13 vs 0									
>13 - 53 vs 0	0.19 [0.03, 1.41]	0.21 [0.03, 1.52]	0.28 [0.04, 2.10]	0.76 [0.30, 1.92]	0.80 [0.31, 2.03]	1.02 [0.39, 2.64]	0.84 [0.30, 2.37]	0.90 [0.32, 2.52]	0.93 [0.33, 2.67]
>53 vs 0	0.92 [0.36, 2.33]	0.94 [0.37, 2.39]	0.90 [0.34, 2.37]	1.29 [0.63, 2.64]	1.30 [0.63, 2.66]	1.25 [0.59, 2.64]	1.13 [0.48, 2.67]	1.14 [0.48, 2.71]	1.08 [0.45, 2.58]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a N = 1, 470	Crude OR [95% CI] ^b N = 1, 434	Adjusted OR [95% CI] ^c N = 1, 434	Crude OR [95% CI] ^a N = 1, 471	Crude OR [95% CI] ^b N = 1, 435	Adjusted OR [95% CI] ^c N = 1, 435	Crude OR [95% CI] ^a N = 1, 467	Crude OR [95% CI] ^b N = 1, 431	Adjusted OR [95% CI] ^c N = 1, 431
Mancozeb	p = 0.562 ^d 0.81 [0.38, 1.71]	p = 0.652 ^d 0.84 [0.39, 1.78]	p = 0.905 ^d 0.76 [0.35, 1.66]	p = 0.889 ^d 0.68 [0.33, 1.38]	p = 0.927 ^d 0.69 [0.34, 1.40]	p = 0.627 ^d 0.66 [0.32, 1.36]	p = 0.909 ^d 0.69 [0.31, 1.53]	p = 0.847 ^d 0.71 [0.32, 1.56]	p = 0.819 ^d 0.73 [0.32, 1.63]
>0 - 2,917 vs 0									
>2,917 - 83,323 vs 0	0.62 [0.26, 1.45]	0.65 [0.28, 1.52]	0.76 [0.31, 1.86]	1.33 [0.76, 2.33]	1.36 [0.78, 2.40]	1.55 [0.85, 2.83]	0.84 [0.39, 1.78]	0.75 [0.34, 1.67]	0.74 [0.32, 1.69]
>83,323 vs 0	1.01 [0.51, 2.00]	1.03 [0.52, 2.05]	1.28 [0.59, 2.78]	0.83 [0.43, 1.59]	0.83 [0.43, 1.59]	1.01 [0.49, 2.07]	1.10 [0.57, 2.12]	1.11 [0.57, 2.14]	1.09 [0.52, 2.28]
Mecoprop,P	p = 0.621 ^d 1.40 [0.62, 3.13]	p = 0.546 ^d 1.41 [0.63, 3.17]	p = 0.771 ^d 1.23 [0.53, 2.86]	p = 0.798 ^d 1.29 [0.63, 2.65]	p = 0.833 ^d 1.28 [0.62, 2.62]	p = 0.622 ^d 1.17 [0.56, 2.46]	p = 0.716 ^d 0.92 [0.36, 2.33]	p = 0.639 ^d 0.93 [0.37, 2.36]	p = 0.641 ^d 0.98 [0.38, 2.52]
>0 - 9 vs 0									
>9 - 73 vs 0	0.91 [0.32, 2.56]	0.94 [0.33, 2.64]	0.85 [0.29, 2.48]	0.81 [0.32, 2.05]	0.81 [0.32, 2.06]	0.76 [0.29, 1.96]	1.09 [0.43, 2.79]	1.12 [0.44, 2.87]	1.12 [0.43, 2.89]
>73 vs 0	1.28 [0.50, 3.27]	1.34 [0.52, 3.44]	1.24 [0.46, 3.31]	0.89 [0.35, 2.27]	0.92 [0.36, 2.33]	0.83 [0.31, 2.17]	1.21 [0.47, 3.10]	1.27 [0.49, 3.25]	1.25 [0.48, 3.28]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Mesosulfuron-Methyl	p = 0.459 ^d	p = 0.535 ^d	p = 0.665 ^d	p = 0.710 ^d	p = 0.651 ^d	p = 0.538 ^d	p = 0.740 ^d	p = 0.737 ^d	p = 0.798 ^d
>0 - 32 vs 0	1.64 [0.76, 3.53]	1.69 [0.78, 3.63]	1.75 [0.78, 3.90]	1.21 [0.57, 2.58]	1.22 [0.57, 2.61]	1.28 [0.58, 2.79]	1.66 [0.77, 3.57]	1.45 [0.65, 3.27]	1.49 [0.66, 3.39]
>32 - 132 vs 0	0.19 [0.03, 1.41]	0.21 [0.03, 1.52]	0.28 [0.04, 2.10]	0.76 [0.30, 1.92]	0.80 [0.31, 2.03]	1.02 [0.39, 2.64]	0.84 [0.30, 2.37]	0.90 [0.32, 2.52]	0.93 [0.33, 2.67]
>132 vs 0	0.92 [0.36, 2.33]	0.94 [0.37, 2.39]	0.90 [0.34, 2.37]	1.29 [0.63, 2.64]	1.30 [0.63, 2.66]	1.25 [0.59, 2.64]	1.13 [0.48, 2.67]	1.14 [0.48, 2.71]	1.08 [0.45, 2.58]
Metsulfuron-Methyl	p = 0.518 ^d	p = 0.547 ^d	p = 0.387 ^d	p = 0.533 ^d	p = 0.590 ^d	p = 0.407 ^d	p = 0.483 ^d	p = 0.534 ^d	p = 0.490 ^d
>0 - 9 vs 0	1.62 [0.72, 3.66]	1.41 [0.59, 3.37]	1.31 [0.53, 3.26]	1.14 [0.51, 2.55]	0.98 [0.41, 2.31]	0.91 [0.37, 2.21]	1.74 [0.81, 3.75]	1.82 [0.84, 3.93]	1.78 [0.81, 3.95]
>9 - 23 vs 0	1.54 [0.64, 3.67]	1.56 [0.65, 3.74]	1.52 [0.61, 3.78]	1.49 [0.69, 3.21]	1.49 [0.69, 3.21]	1.50 [0.67, 3.34]	0.92 [0.33, 2.58]	0.94 [0.33, 2.65]	0.90 [0.31, 2.59]
>23 vs 0	0.94 [0.34, 2.66]	0.96 [0.34, 2.70]	1.24 [0.41, 3.75]	1.03 [0.43, 2.43]	1.03 [0.43, 2.43]	1.25 [0.50, 3.14]	0.43 [0.10, 1.78]	0.44 [0.11, 1.83]	0.43 [0.10, 1.86]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR	Crude OR	Adjusted OR	Crude OR	Crude OR	Adjusted OR	Crude OR	Crude OR	Adjusted OR
	[95% CI] ^a N = 1, 470	[95% CI] ^b N = 1, 434	[95% CI] ^c N = 1, 434	[95% CI] ^a N = 1, 471	[95% CI] ^b N = 1, 435	[95% CI] ^c N = 1, 435	[95% CI] ^a N = 1, 467	[95% CI] ^b N = 1, 431	[95% CI] ^c N = 1, 431
Nicosulfuron	p = 0.619 ^d 0.96	p = 0.609 ^d 1.00	p = 0.788 ^d 1.14	p = 0.116 ^d 1.15	p = 0.148 ^d 1.19	p = 0.489 ^d 1.33	p = 0.556 ^d 1.24	p = 0.433 ^d 1.27	p = 0.590 ^d 1.38
>0 - 121 vs 0	[0.55, 1.69]	[0.57, 1.77]	[0.62, 2.08]	[0.73, 1.83]	[0.75, 1.89]	[0.81, 2.18]	[0.73, 2.11]	[0.75, 2.15]	[0.80, 2.41]
>21 - 371 vs 0	0.64	0.68	0.81	0.70	0.73	0.82	0.78	0.77	0.76
	[0.34, 1.23]	[0.35, 1.30]	[0.40, 1.63]	[0.41, 1.20]	[0.42, 1.25]	[0.46, 1.47]	[0.42, 1.44]	[0.39, 1.39]	[0.39, 1.49]
>371 vs 0	1.01	0.98	1.22	0.71	0.73	0.87	0.91	0.87	0.93
	[0.58, 1.74]	[0.56, 1.72]	[0.64, 2.32]	[0.42, 1.21]	[0.43, 1.24]	[0.48, 1.57]	[0.52, 1.62]	[0.48, 1.56]	[0.48, 1.78]
Prosulfocarb	p = 0.235 ^d 1.39	p = 0.200 ^d 1.43	p = 0.157 ^d 1.58	p = 0.1560 ^d 0.77	p = 0.147 ^d 0.78	p = 0.121 ^d 0.83	p = 0.281 ^d 0.77	p = 0.243 ^d 0.79	p = 0.290 ^d 0.74
>0 - 5,945 vs 0	[0.54, 3.56]	[0.56, 3.68]	[0.58, 4.27]	[0.27, 2.16]	[0.28, 2.19]	[0.29, 2.40]	[0.24, 2.51]	[0.24, 2.59]	[0.22, 2.46]
>5,945 - 20,630 vs 0	0.49	0.50	0.63	0.72	0.723	0.87	1.54	1.58	1.56
	[0.12, 2.04]	[0.12, 2.10]	[0.15, 2.65]	[0.26, 2.01]	[0.26, 2.03]	[0.30, 2.47]	[0.64, 3.68]	[0.66, 3.79]	[0.64, 3.76]
>20,630 vs 0	2.10	2.16	2.12	2.16	2.18	2.09	1.46	1.50	1.45
	[0.97, 4.55]	[1.00, 4.70]	[0.94, 4.75]	[1.10, 4.25]	[1.11, 4.30]	[1.04, 4.23]	[0.61, 3.48]	[0.63, 3.58]	[0.60, 3.50]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Terbutylazine	p = 0.619 ^d	p = 0.609 ^d	p = 0.788 ^d	p = 0.116 ^d	p = 0.148 ^d	p = 0.489 ^d	p = 0.556 ^d	p = 0.433 ^d	p = 0.590 ^d
> 0 - 1,736 vs 0	0.96 [0.55, 1.69]	1.00 [0.57, 1.77]	1.14 [0.62, 2.08]	1.15 [0.73, 1.83]	1.19 [0.75, 1.89]	1.34 [0.81, 2.18]	1.24 [0.73, 2.11]	1.27 [0.75, 2.15]	1.38 [0.80, 2.41]
> 1,736 - 53,16 vs 0	0.64 [0.34, 1.23]	0.68 [0.35, 1.30]	0.81 [0.40, 1.63]	0.70 [0.41, 1.20]	0.72 [0.42, 1.25]	0.82 [0.46, 1.47]	0.78 [0.42, 1.44]	0.74 [0.39, 1.39]	0.76 [0.39, 1.49]
> 5,316 vs 0	1.01 [0.58, 1.74]	0.98 [0.56, 1.72]	1.22 [0.64, 2.32]	0.71 [0.42, 1.21]	0.73 [0.43, 1.24]	0.87 [0.48, 1.57]	0.91 [0.52, 1.62]	0.87 [0.48, 1.56]	0.93 [0.48, 1.78]
Triadimenol	p = 0.460 ^d	p = 0.559 ^d	p = 0.520 ^d	p = 0.626 ^d	p = 0.709 ^d	p = 0.647 ^d	p = 0.818 ^d	p = 0.658 ^d	p = 0.654 ^d
> 0 - 14 vs 0	1.11 [0.50, 2.48]	1.13 [0.51, 2.52]	0.95 [0.41, 2.21]	1.06 [0.52, 2.17]	1.06 [0.52, 2.16]	0.96 [0.46, 2.01]	0.76 [0.30, 1.91]	0.76 [0.30, 1.91]	0.80 [0.31, 2.04]
> 14 - 90 vs 0	0.81 [0.32, 2.06]	0.87 [0.34, 2.20]	0.80 [0.31, 2.10]	0.98 [0.46, 2.08]	1.02 [0.48, 2.17]	0.93 [0.43, 2.02]	1.13 [0.51, 2.53]	1.19 [0.53, 2.67]	1.21 [0.53, 2.74]
> 90 vs 0	0.68 [0.24, 1.91]	0.72 [0.26, 2.02]	0.76 [0.26, 2.20]	0.76 [0.33, 1.79]	0.79 [0.34, 1.85]	0.82 [0.34, 1.98]	0.85 [0.34, 2.16]	0.70 [0.25, 1.96]	0.68 [0.24, 1.92]

Table 5: (continued).

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Sulphur	N = 1, 470 p = 0.671 ^d	N = 1, 434 p = 0.720 ^d	N = 1, 434 p = 0.655 ^d	N = 1,471 p = 0.360 ^d	N = 1, 435 p = 0.368 ^d	N = 1,435 p = 0.340 ^d	N = 1,467 p = 0.951 ^d	N = 1, 431 p = 0.894 ^d	N = 1,431 p = 0.804 ^d
> 0 - 777 vs 0	1.52 [0.64, 3.64]	1.54 [0.64, 3.68]	1.33 [0.53, 3.31]	1.07 [0.45, 2.53]	1.06 [0.45, 2.51]	0.95 [0.39, 2.30]	1.20 [0.47, 3.07]	1.21 [0.47, 3.10]	1.26 [0.49, 3.26]
> 777 - 1,977 vs 0	1.05 [0.37, 2.98]	1.08 [0.38, 3.07]	0.97 [0.33, 2.84]	1.15 [0.48, 2.74]	1.16 [0.49, 2.76]	1.10 [0.45, 2.68]	0.49 [0.12, 2.03]	0.50 [0.12, 2.09]	0.51 [0.12, 2.13]
> 1,977 vs0	0.53 [0.13, 2.20]	0.54 [0.13, 2.26]	0.57 [0.13, .46]	0.37 [0.09, 1.54]	0.37 [0.09, 1.55]	0.38 [0.09, 1.62]	1.34 [0.52, 3.44]	1.38 [0.54, 3.55]	1.46 [0.56, 3.83]

^a Crude estimates for the full population.

^b Crude estimates for the population with complete confounder data.

^a Adjusted for sex of the child, smoking in the child's home at age 14, SES (parental education i.e. combination of mother or father), pets at home at age 14 year follow up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnicity group of mother and father, and traffic-related air pollution (NO₂) at age 14 year follow up in multiple logistic regression models.

^d p-value trend test.

* P < 0.05.

4. Discussion

This study did not find associations between living close to agricultural fields with likely pesticide use and the prevalence of asthma, shortness of breath and dry night cough at age 14.

4.1 Residential exposure to agricultural pesticides and asthma

The association of environmental exposure to pesticides with asthma and related symptoms in children has been assessed in several cross-sectional and longitudinal studies and findings of the epidemiological studies that have been performed so far in children are mixed (see Table S6). Some studies reported significant associations of exposure to pesticides with childhood asthma (Karmaus et al., 2001, Salam et al., 2004, Salameh et al., 2003, Sunyer et al., 2006, Tagiyeva et al., 2010) or wheezing (Gascon et al., 2014b, Salameh et al., 2003, Sunyer et al., 2005, Sunyer et al., 2006, Tagiyeva et al., 2010, Gascon et al., 2014a). However, others did not find associations of exposure to pesticides with asthma (Weselak et al., 2007, Perla et al., 2015, Merchant et al., 2005, Karmaus et al., 2003) and wheeze (Perla et al., 2015, Merchant et al., 2005, Gascon et al., 2014b, Gascon et al., 2014a) in children. The inconsistency in published epidemiological findings could at least partially be due to differences in the pesticide exposure assessment (although self-reported exposures and biomonitoring were used in both, studies showing and not showing an association with asthma) as well as the age of the study participants, the exposure period studied and the study design used.

We acknowledge that comparability of our findings with the findings of the published epidemiological studies of the association between residential pesticide exposures is limited for similar reasons. Only one other study assessed associations of asthma with postnatal exposure to pesticides similar to those assessed in our study. The findings of that study were in line with our findings, i.e. no associations were found between exposure to dialkyl phosphate

(DAP) metabolites of organophosphate and risk of asthma ever, current asthma and current wheeze in children aged 6-15 years (Perla et al., 2015). Also, our findings are consistent with those of other studies showing no association between prenatal exposure to recently used agricultural pesticides (piperonyl butoxide, pyrethroids, chlorpyrifos and other organophosphate pesticides) and the risks of asthma (Liu et al., 2012), any respiratory symptoms (Raanan et al., 2015) and cough without a cold (Reardon et al., 2009) in children. However, as acknowledged previously, findings of studies using biomarkers of exposure (Gascon et al., 2014a, Gascon et al., 2014b, Karmaus et al., 2003, Karmaus et al., 2001, Sunyer et al., 2006, Sunyer et al., 2005) and studies assessing the relevance of prenatal exposure (Liu et al., 2012, Raanan et al., 2015, Reardon et al., 2009) rather than postnatal exposure, are not directly comparable with ours relying on postnatal exposure estimated using proximity to fields.

4.2 Residential exposure to agricultural pesticides

Since exposure assessment by biomonitoring or environmental monitoring is often not feasible in large population studies, we rely on indirect methods like some of the previous studies. However, we do not rely on distance only, but we used areas of (specific) crops extracted from a basic registration of crops and amounts of pesticides used within selected distances from participants' home at age 14-year as proxies for residential pesticide exposures as previously described (Bukalasa et al., 2017).

We observed that only a small proportion of our study participants lived within short distances (<100m) of agricultural fields. Larger percentages of study homes, however, were within 500 and 1,000 m of agricultural fields (Bukalasa et al., 2017). Area of (treated) crops and estimated amounts of pesticides used in the vicinity of the residence have been used to estimate

environmental/ ambient exposure to pesticides in other studies (Brouwer et al., 2018, Nuckols et al., 2007, Rull et al., 2009), none of them assessing associations with childhood asthma. While we do not have direct information on the validity of our exposure estimates in terms of measured internal or external dose, one previous study conducted in the Netherlands found a moderate to high correlation between pesticide measurements in air and precipitation at (fixed) monitoring stations and pesticide concentration estimates based on crop cultivation within 500 and 1,000 m buffer around these stations (Brouwer et al., 2018). In addition, a recent meta-analysis of published data from the United States showed that pesticides were detected in house dust samples at a distance of 1,000 m from treated agricultural fields. However, the concentrations of pesticides in house dust samples decreased sharply with increasing distance from the fields and the magnitude of the decrease varied by pesticide type (Deziel et al., 2017). Moreover, the findings from the United States, where aerial spraying is common, may not be directly transferable to the Dutch situation, where no aerial spraying is used. However, to the best of our knowledge, no study like this has been conducted in the Netherlands or elsewhere in European countries.

4.3 Generalizability of study findings

The present study was conducted in the Netherlands within the Dutch PIAMA birth cohort study. For the PIAMA study, participants were recruited from the general population as described previously (Wijga et al., 2014), to represent, within the selected cohort, the general Dutch population of all children living in the Netherlands. However, children of highly educated parents were over-represented and children of parents from non-western countries were underrepresented. Since there is currently no evidence for an increased or decreased susceptibility of children of highly educated parents or children of parents from non-western

countries, this most likely did not affect the generalizability of our findings to the general population of all adolescents living in the Netherlands.

Pesticide application techniques within the European Union are subject to a degree of EU regulation (European Commission, 2017). However, our findings may not be generalizable to all European countries because of differences in allowed pesticides, application techniques and farming-scale. In addition, climate and plant disease pressure can be very different across Europe. Extrapolation of our findings to countries outside the European Union is likely limited, too, given differences in pesticide application techniques. For instance, they would likely not apply in countries such as the United States, Israel and Canada, where aerial spraying of agricultural fields is still permitted (Pearce et al., 2002, Gordon and Richter, 1991, Kahn et al., 1992, Weppner et al., 2006).

4.4 Strengths and limitations

We consider the availability of data on the presence of specific crops together with data on the use of pesticide on these crops from a survey among farmers are strengths of the present study.

A limitation of our study is that we had no information regarding exposure to pesticides in the earlier years of life among our study participants. If this had been available, it would have helped us to understand the role of pesticides exposure over a longer time period. We likewise lacked information on personal pesticides exposure in the homes of our study participants, to assess associations with respiratory outcomes. We did not have to take into account crop rotation as the analysis was restricted to children with health information collected in the year 2012. Statistical power was limited for the smaller buffers (<100 m), where exposures are expected to be highest. However, analyses with exposures within 100 m buffers generally did not suggest an adverse effect.

In this study, we performed many comparisons tests and we acknowledge this may increase the probability of committing a type I error (false positive). As no positive associations were observed, no false positive associations were present either.

5. Conclusion

There was no evidence found for an association between living near agricultural fields likely treated with pesticides and the prevalence of asthma and related respiratory symptoms at age 14 among our study participants. Further research is recommended on quantitative exposure assessment methods using measurements of pesticides in environmental and/or biological samples, and on methods to develop exposure models usable in large-scale epidemiological studies.

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Conflict of interest statement

Professor Gerard H. Koppelman reports grants from the Lung Foundation Netherlands, TEVA Netherlands, Glaxo Smith Kline, the UBBO EMMIUS Foundation, and the TETRI Foundation outside the submitted work.

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SUPPLEMENTARY TABLES AND FIGURES

Figure S1: Flow chart showing availability of information on pesticides exposure and data on asthma and related symptoms at age 14- years.

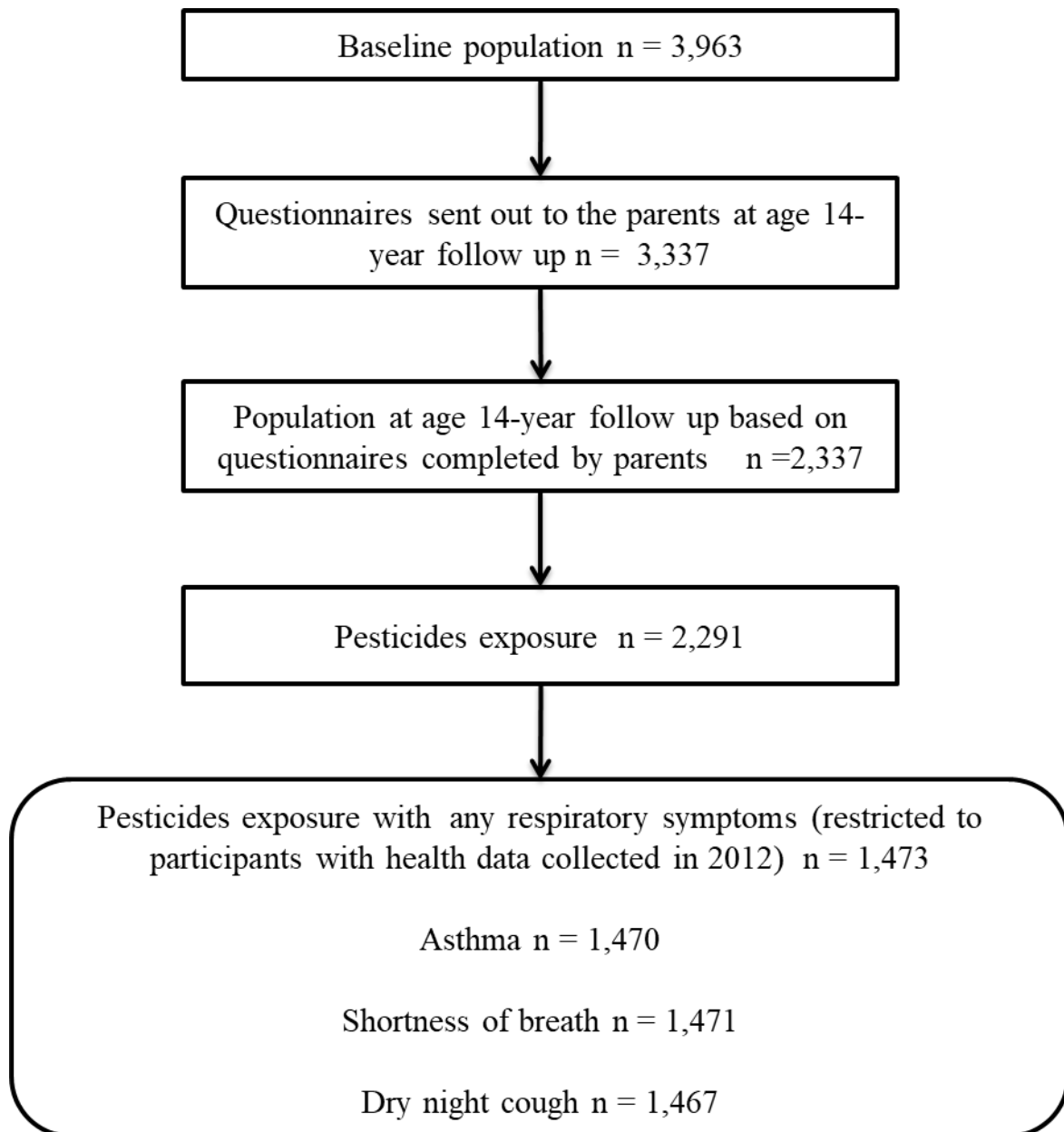


Table S1: Distribution of the amounts of agricultural pesticides (g of active ingredient/year) with known irritant properties for the respiratory system applied in 2012 for the 100, 500 and 1,000 m buffers [N= 1,473].

Agricultural pesticides	Radius of circular buffer											
	100 m				500 m				1,000 m			
	N [%] >0	P95 ^a	N [%] >0	P50 ^a	P75 ^a	P90 ^a	P95 ^a	N [%] >0	P50 ^a	P75 ^a	P90 ^a	P95 ^a
Any pesticide known to be a respiratory irritant	90 [6]	16	563 [38]	0	1,110	11,273	47,898	921 [63]	1,689	13,492	11,982	326,250
Chlormequat	15 [1]	0	118 [8]	0	0	0	1,613	250 [16]	0	0	4,009	14,277
Chlorothalonil	3 [0]	0	63 [4]	0	0	0	0	176 [12]	0	0	13	59
Diquatdibromide	12 [1]	0	109 [7]	0	0	0	537	243 [17]	0	0	2,006	6,042
Florasulam	42 [3]	0	417 [28]	0	0	2	4	799 [54]	1	6	13	18
Iodosulfuron - methyl- sodium	15 [1]	0	118 [8]	0	0	0	7	230 [16]	0	0	18	65
Mancozeb	30 [2]	0	220 [15]	0	0	2,344	32,307	420 [29]	0	41	79,961	233,871
Mecoprop-P	4 [0]	0	70 [5]	0	0	0	0	210 [14]	0	0	7	33
Mesosulfuron-methyl	15 [1]	0	118 [8]	0	0	0	18	230 [16]	0	0	46	163
Metsulfuron-methyl	5 [0]	0	68 [5]	0	0	0	0	202 [14]	0	0	8	21
Nicosulfuron	41 [3]	0	412 [29]	0	6	107	183	790 [54]	18	266	557	740
Prosulfocarb	7 [0]	0	78 [5]	0	0	0	80	184 [12]	0	0	2,251	18,365
Terbuthylazine	41 [3]	0	412 [28]	0	93	1,530	2,627	790 [54]	252	3,814	7,991	10,602
Triadimenol	8 [1]	0	103 [7]	0	0	0	5	269 [18]	0	0	21	170
Sulphur	3 [0]	0	63 [4]	0	0	0	0	176 [12]	0	0	345	1,515

P50 is the median and P75, P90 and P95 are the 75th, 90th, and 95th percentiles

^a P50 is the median and P75, P90 and P95 are the 75th, 90th, and 95th percentiles

Table S2: Cross tabulations of respiratory health outcomes at age 14 by the area of crops, restricted to those participants with health data collected in 2012.

Buffer	Area of crops (m ²)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
100 m	Any crops			
	0	95/1,370 [7]	127/1,371 [9]	92/1,367 [7]
	>0	2/100 [2]	5/95 [5]	8/100 [8]
500 m	Any crops			
	0	61/883 [7]	79/883 [9]	60/883 [7]
	>0	36/587 [6]	53/588 [9]	40/584 [7]
	Cereals			
	0	81/1,234 [7]	108/1,235 [9]	82/1,233 [7]
	>0 – 16,372	7/78 [9]	7/78 [9]	6/76 [8]
	>16,372 – 59,862	6/79 [8]	11/79 [14]	8/79 [10]
	>59,862	3/79 [4]	6/79 [8]	4/79 [5]
	Corn			
	0	71/1,058 [7]	100/1,059 [9]	74/1,057 [7]
	>0 – 15,003	7/144 [5]	12/144 [8]	7/143 [5]
	>15,003– 49,092	11/131 [8]	12/131 [9]	10/130 [8]
	>49,092	8/137 [6]	8/137 [6]	9/137 [7]
	Potatoes			
	0	83/1,282 [6]	113/1,283 [8]	87/1,280 [7]
	>0 – 18,536	6/65 [9]	9/65 [14]	4/64 [6]
	>18,536 – 69,699	6/59 [10]	6/59 [10]	4/59 [7]
	> 69,699	2/64 [3]	4/64 [6]	5/64 [8]

Table S2: (continued)

Buffer	Area of crops (m ²)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
1,000 m	Any crops			
	0	40/526 [8]	49/526 [9]	36/527 [7]
	>0	57/944 [6]	83/945 [9]	64/940 [7]
	Cereals			
	0	70/1,011 [7]	93/1,012 [9]	63/1,011 [6]
	>0 – 37,040	5/153 [6]	7/153 [5]	15/153 [10]
	> 7,040 – 173,093	11/145 [8]	14/145 [10]	11/143 [8]
	>173,093	11/161 [7]	18/161 [11]	11/160 [7]
	Open field vegetables	90/1,325 [7]	120/1,326 [9]	88/1,323 [7]
	0	1/48 [2]	2/48 [4]	5/48 [10]
	>0 – 14,798	2/49 [4]	4/49 [8]	3/48 [6]
	> 14,798 – 80,865	4/48 [8]	6/48 [13]	4/48 [8]
	> 80,865			
	Commercial crops			
	0	75/1,194 [6]	101/1,194 [8]	83/1,191 [7]
	>0 – 37,762	10/101 [10]	14/102 [14]	6/101 [6]
	>37,762 – 115,504	8/87 [9]	11/87 [13]	6/87 [7]
	>115,504	4/88 [5]	6/88 [7]	5/88 [6]
	open field floriculture/bulbs			
	0	79/1,248 [6]	112/1,249 [9]	80/1,246 [7]
	>0 – 5,088	5/77 [6]	9/77 [12]	6/77 [8]
	>5,088 – 14,330	8/74 [11]	7/74 [9]	8/74 [11]
	>14,330	5/71 [7]	4/71 [6]	6/70 [9]

Table S2: (continued)

Buffer	Area of crops (m ²)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
1,000m	Corn			
	0	48/680 [7]	66/681 [10]	47/681 [7]
	>0 – 53,686	18/264 [7]	29/264 [11]	22/261 [8]
	>53,686 – 164,363	12/258 [5]	18/258 [7]	14/257 [5]
	>164,363	19/268 [7]	19/268 [7]	17/268 [6]
	Potatoes			
	0	75/1,134 [7]	102/1,135 [9]	74/1,133 [7]
	>0 – 56,848	4/103 [4]	6/103 [6]	4/102 [4]
	>56,848 – 227,078	11/117 [9]	15/117 [13]	16/116 [14]
	>227,078	7/116 [6]	9/116 [8]	6/116 [5]

Table S3: Cross tabulations of respiratory health outcomes at age 14 by estimated amount of pesticides, restricted to those participants with health data collected in 2012.

Buffer	Amount of pesticides (g of active ingredient/year)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
100 m	Any pesticide			
	0	95/1380 [7]	127/1,381 [9]	92/1,377 [7]
	>0	2/90 [2]	5/90 [6]	8/90 [9]
500 m	Any pesticide			
	0	63/907 [7]	85/908 [9]	62/908 [7]
	>0	34/563 [6]	47/563 [8]	38/559 [7]
	Florasulam			
	0	71/1053 [7]	100/1054 [9]	74/1052 [7]
	> 0 - 0.8	7/145 [5]	12/145 [8]	7/144 [5]
	>0.8 - 3	11/132 [8]	12/132 [9]	10/131 [8]
	>3	8/140 [6]	8/140 [6]	9/140 [6]
	Mancozeb			
	0	86/1,250 [7]	116/1,251 [9]	87/1,248 [7]
	> 0 - 2,869	3/77 [4]	4/77 [5]	5/76 [7]
	>2,869 - 33,135	5/73 [7]	9/73 [12]	4/76 [5]
	>33,135	3/70 [4]	3/70 [4]	4/70 [6]
	Nicosulfuron			
	0	71/1058 [7]	100/1,059 [9]	74/1,057 [7]
	> 0 - 34	7/144 [5]	12/144 [8]	7/143 [5]
	>34 - 111	11/131 [8]	12/131 [9]	10/130 [8]
	>111	8/137 [6]	8/137 [6]	9/137 [7]

Table S3: (continued)

Buffer	Amount of pesticides (g of active ingredient/year)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
500 m	Terbutylazine1			
	0	71/1,058 [8]	100/1,059 [9]	74/1,057 [7]
	> 0 - 485	7/144 [5]	12/144 [8]	7/143 [5]
	>485 - 1,588	11/131 [8]	12/131 [9]	10/130 [8]
	>1,588	8/137 [6]	8/137 [6]	9/137 [7]
1,000 m	Any pesticide			
	0	42/549 [8]	54/550 [10]	37/551 [7]
	>0	55/921 [6]	78/921 [8]	63/916 [7]
	Chlormequat			
	0	83/1,240 [7]	110/1,241 [9]	82/1,239 [7]
	> 0 - 2,806	8/76 [11]	8/76 [11]	8/76 [11]
	>2,806 - 11,611	1/73 [1]	5/73 [9]	4/71 [6]
	>11,611	5/81 [6]	9/81 [11]	6/81 [7]
	Chlorothalonil			
	0	85/1,294 [7]	118/1,295 [9]	88/1,291 [7]
	> 0 - 30	6/62 [10]	6/62 [10]	5/62 [8]
	>30 - 80	4/58 [7]	6/58 [10]	2/58 [3]
	> 80	2/56 [4]	2/56 [4]	5/56 [9]
	Diquatdibromide			
	0	78/1,227 [6]	109/1,228 [9]	80/1,225 [7]
	> 0 - 1,377	8/79 [10]	6/79 [8]	4/79 [5]
	> 1,377 - 5,192	1/81 [1]	3/81 [4]	8/80 [10]
	>5,192	10/83 [12]	14/83 [17]	8/83 [10]

Table S3: (continued)

Buffer	Amount of pesticides (g of active ingredient/year)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N (%)	n/N (%)	n/N (%)
1,000 m	Florasulam			
	0	48/671 [7]	65/672 [10]	46/672 [7]
	>0 - 3	17/267 [6]	29/267 [11]	23/264 [9]
	>3 - 9	15/271 [6]	21/271 [8]	16/270 [6]
	>9	17/261 [7]	17/261 [7]	15/261 [6]
	Iodosulfuron- Methyl- Sodium			
	0	83/1,240 [7]	110/1,241 [9]	82/1,239 [7]
	>0 - 13	8/76 [11]	8/76 [11]	8/76 [11]
	>13 - 53	1/73 [1]	5/73 [7]	4/71 [6]
	>53	5/81 [6]	9/81 [11]	6/81 [7]
	Mancozeb			
	0	73/1,050 [7]	96/1,051 [9]	74/1,049 [7]
	> 0 - 2,917	8/141 [6]	9/141 [6]	7/141 [5]
	>2,917 - 83,323	6/136 [4]	16/136 [12]	8/ 134 [6]
	>83,323	10/143 [7]	11/ 143 [8]	11/143 [8]
	Mecoprop-P			
	0	81/1,260 [6]	113/1,261 [9]	85/1,257 [7]
	>0 - 9	7/80 [6]	9/80 [11]	5/80 [6]
	>9 - 73	4/68 [9]	5/68 [7]	5/68 [7]
	>73	5/62 [8]	5/62 [8]	5/62 [8]

Table S3: (continued)

Buffer	Amount of pesticides (g of active ingredient/year)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
1,000 m	Mesosulfuron-Methyl	83/1,240 [7]	110/1,241 [9]	82/1,239 [7]
	0	8/76 [11]	8/76 [11]	8/76 [10]
	>0 - 32	1/73 [1]	5/73 [7]	4/71 [6]
	>32 - 132	5/81 [6]	9/81 [11]	6/81 [7]
	>132			
	Metsulfuron-Methyl			
	0	80/1,268 [6]	111/1,269 [10]	86/1,266 [7]
	>0 - 9	7/71 [10]	7/71 [10]	8/71 [11]
	>9 - 23	6/64 [9]	8/64 [13]	4/64 [6]
	>23	4/67 [6]	6/67 [8]	2/66 [3]
	Nicosulfuron			
	0	48/680 [7]	66/681 [10]	47/681 [7]
	>0 - 121	18/264 [7]	29/264 [11]	22/261 [8]
	>121 - 371	12/258 [5]	18/258 [7]	14/257 [5]
	>371	19/268 [7]	19/268 [7]	17/268 [6]
	Prosulfocarb			
	0	82/1,286 [6]	113/1,287 [9]	85/1,284 [7]
	> 0 - 5,945	5/58 [9]	4/58 [7]	3/58 [5]
	> 5,945 - 20,630	2/62 [3]	4/62 [6]	6/61 [10]
	>20,630	8/64 [13]	11/64 [17]	6/64 [9]

Table S3: (continued)

Buffer	Amount of pesticides (g of active ingredient/year)	Asthma	Shortness of breath	Dry night cough
		[N = 1,470]	[N = 1,471]	[N = 1,467]
		n/N [%]	n/N [%]	n/N [%]
1,000 m	Terbutylazine			
	0	48/680 [7]	66/681 [10]	47/681 [7]
	> 0 - 1,736	18/264 [7]	29/264 [11]	22/261 [8]
	>1,736 - 5,316	12/258 [5]	18/258 [7]	14/257 [5]
	>5,316	19/268 [7]	19/268 [7]	17/268 [6]
	Triadimenol			
	0	81/1201 [7]	109/1,202 [9]	83/1,199 [7]
	>0 - 14	7/94 [7]	9/94 [10]	5/94 [5]
	>14 - 90	5/90 [6]	8/90 [9]	7/90 [8]
	>90	4/85 [4]	6/85 [7]	5/84 [6]
	Sulphur			
	0	85/1,294 [7]	118/1,295 [9]	88/1291 [7]
	>0 - 777	6/62 [10]	6/62 [10]	5/62 [8]
	> 77 - 1977	4/58 [7]	6/58 [10]	2/58 [3]
	>1,977	2/56 [4]	2/56 [4]	5/56 [9]

Table S4: Crude and adjusted associations between area of crops within 500 m buffer and asthma symptoms at age 14.

	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m²)	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Any crop	0.88	0.88	0.98	1.01	1.03	1.21	1.01	1.01	1.05
>0 vs 0	[0.58, 1.35]	[0.57, 1.35]	[0.60, 1.62]	[0.70, 1.45]	[0.71, 1.48]	[0.79, 1.85]	[0.67, 1.53]	[0.66, 1.53]	[0.65, 1.71]
Cereals	p = 0.675 ^d	p = 0.712 ^d	p = 0.977 ^d	p = 0.606 ^d	p = 0.617 ^d	p = 0.342 ^d	p = 0.808 ^d	p = 0.768 ^d	p = 0.857 ^d
> 0 – 16,372 vs 0	1.40	1.44	1.59	1.03	1.03	1.17	1.20	1.23	1.24
>16,372- 59,862 vs 0	[0.63, 3.15]	[0.64, 3.23]	[0.68, 3.76]	[0.46, 2.29]	[0.46, 2.30]	[0.51, 2.69]	[0.51, 2.85]	[0.52, 2.93]	[0.51, 3.03]
	1.17	1.20	1.31	1.69	1.70	1.87	1.58	1.62	1.60
	[0.49, 2.77]	[0.51, 2.84]	[0.52, 3.27]	[0.87, 3.29]	[0.87, 3.31]	[0.91, 3.82]	[0.74, 3.40]	[0.75, 3.49]	[0.71, 3.58]
	0.56	0.57	0.67	0.86	0.85	1.03	0.75	0.76	0.74
> 59,862 vs 0	[0.17, 1.82]	[0.18, 1.84]	[0.20, 2.27]	[0.37, 2.02]	[0.36, 2.00]	[0.42, 2.52]	[0.27, 2.10]	[0.27, 2.12]	[0.25, 2.14]

Table S4: (continued)

	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m ²)	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Corn	p = 0.924 ^d	p = 0.861 ^d	p = 0.561 ^d	p = 0.223 ^d	p = 0.241 ^d	p = 0.578 ^d	p = 0.877 ^d	p = 0.814 ^d	p = 0.936 ^d
>0 – 15,003 vs 0	0.71 [0.32, 1.58]	0.73 [0.33, 1.62]	0.73 [0.32, 1.69]	0.87 [0.47, 1.63]	0.89 [0.47, 1.66]	0.91 [0.47, 1.76]	0.68 [0.31, 1.52]	0.70 [0.32, 1.55]	0.71 [0.31, 1.61]
>15,003-49,092 vs 0	1.27 [0.66, 2.47]	1.19 [0.60, 2.37]	1.37 [0.65, 2.91]	0.97 [0.52, 1.81]	0.99 [0.53, 1.87]	1.09 [0.56, 2.15]	1.11 [0.56, 2.20]	1.02 [0.50, 2.10]	1.08 [0.51, 2.31]
>49,092 vs 0	0.86 [0.41, 1.83]	0.87 [0.41, 1.85]	1.13 [0.50, 2.54]	0.60 [0.28, 1.25]	0.60 [0.28, 1.25]	0.72 [0.33, 1.58]	0.93 [0.46, 1.91]	0.94 [0.46, 1.93]	0.96 [0.45, 2.06]

Table S4: (continued)

	Asthma			Shortness of breath			Dry night cough		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
Area of crop (m²)	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Potatoes	p = 0.916 ^d	p = 0.948 ^d	p = 0.749 ^d	p = 0.936 ^d	p = 0.922 ^d	p = 0.732 ^d	p = 0.831 ^d	p = 0.799 ^d	p = 0.836 ^d
>0 – 18,536 vs 0	1.47 [0.62, 3.50]	1.48 [0.62, 3.54]	1.49 [0.59, 3.75]	1.66 [0.80, 3.45]	1.65 [0.79, 3.42]	1.72 [0.80, 3.73]	0.91 [0.33, 2.57]	0.92 [0.33, 2.60]	0.88 [0.31, 2.55]
>18,536-69,699 vs 0	1.64 [0.68, 3.92]	1.68 [0.70, 4.04]	2.10 [0.83, 5.32]	1.17 [0.49, 2.79]	1.18 [0.50, 2.81]	1.45 [0.59, 3.58]	1.00 [0.35, 2.82]	1.02 [0.36, 2.90]	0.99 [0.34, 2.88]
>69,699 vs 0	0.47 [0.11, 1.94]	0.47 [0.11, 1.96]	0.55 [0.13, 2.42]	0.69 [0.25, 1.93]	0.68 [0.24, 1.91]	0.80 [0.27, 2.34]	1.16 [0.46, 2.97]	1.17 [0.46, 3.00]	1.18 [0.44, 3.17]

^a Crude estimates for full population including participants with missing confounder data.^b Crude estimates for the population with complete confounder data.^c Adjusted for sex of the child, smoking in the child's home at age 14, SES (parental education i.e. combination of mother or father), pets at home at age 14 year follow up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnicity group of mother and father, and traffic-related air pollution (NO₂) at age 14 year follow up in multiple logistic regression models.^d p-value trend test

* P < 0.05.

Table S5: Crude and associations between estimated amounts of pesticide applied within 500 m of the participants' homes and asthma symptoms at age 14.

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Adjusted			Adjusted			Adjusted		
	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c	Crude OR [95% CI] ^a	Crude OR [95% CI] ^b	Adjusted OR [95% CI] ^c
	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Any pesticide ^b	0.86	0.86	0.95	0.88	0.90	1.02	1.00	0.99	1.04
>0 vs 0	[0.56, 1.33]	[0.55, 1.33]	[0.57, 1.57]	[0.61, 1.28]	[0.62, 1.31]	[0.66, 1.56]	[0.66, 1.51]	[0.65, 1.52]	[0.64, 1.68]
Florasulam	p = 0.858 ^d	p=0.797 ^d	p = 0.751 ^d	p = 0.190 ^d	p=0.206 ^d	p = 0.470 ^d	p = 0.811 ^d	p=0.750 ^d	p = 0.830 ^d
>0 - 0.8 vs 0	0.70	0.72	0.72	0.86	0.87	0.90	0.68	0.69	0.70
>0.8 - 3 vs 0	[0.32, 1.56]	[0.32, 1.60]	[0.31, 1.66]	[0.46, 1.61]	[0.47, 1.64]	[0.47, 1.73]	[0.31, 1.50]	[0.31, 1.53]	[0.31, 1.58]
	1.26	1.17	1.36	0.95	0.98	1.08	1.09	1.01	1.06
>3 vs 0	[0.65, 2.44]	[0.59, 2.34]	[0.64, 2.88]	[0.51, 1.79]	[0.52, 1.84]	[0.55, 2.11]	[0.55, 2.17]	[0.49, 2.07]	[0.50, 2.25]
	0.84	0.85	1.03	0.58	0.58	0.67	0.91	0.92	0.91
Mancozeb	[0.40, 1.78]	[0.40, 1.80]	[0.46, 2.34]	[0.28, 1.22]	[0.28, 1.22]	[0.31, 1.48]	[0.44, 1.86]	[0.45, 1.88]	[0.43, 1.96]
	p = 0.373 ^d	p=0.398 ^d	p = 0.660 ^d	p = 0.354 ^d	p=0.348 ^d	p = 0.629 ^d	p = 0.551 ^d	p=0.582 ^d	p = 0.491 ^d
>0 - 2,869 vs 0	0.55	0.56	0.56	0.54	0.54	0.54	0.94	0.96	0.96
	[0.17, 1.78]	[0.17, 1.82]	[0.17, 1.86]	[0.19, 1.49]	[0.19, 1.50]	[0.19, 1.54]	[0.37, 2.39]	[0.38, 2.45]	[0.37, 2.48]
>2,869 - 33,135 vs 0	1.00	1.02	1.05	1.38	1.38	1.43	0.77	0.79	0.70
	[0.39, 2.53]	[0.40, 2.60]	[0.39, 2.85]	[0.67, 2.84]	[0.67, 2.85]	[0.66, 3.12]	[0.28, 2.17]	[0.28, 2.22]	[0.24, 2.04]
	0.61	0.61	0.79	0.44	0.43	0.55	0.81	0.82	0.77
>33,135 vs 0	[0.19, 1.97]	[0.19, 1.99]	[0.23, 2.78]	[0.14, 1.42]	[0.13, 1.40]	[0.16, 1.88]	[0.29, 2.27]	[0.29, 2.29]	[0.26, 2.32]

Table S5: (continued)

Amount of pesticides (g/year)	Asthma			Shortness of breath			Dry night cough		
	Crude OR	Crude OR	Adjusted OR	Crude OR	Crude OR	Adjusted OR	Crude OR	Crude OR	Adjusted OR
	[95% CI] ^a	[95% CI] ^b	[95% CI] ^c	[95% CI] ^a	[95% CI] ^b	[95% CI] ^c	[95% CI] ^a	[95% CI] ^b	[95% CI] ^c
	N = 1,470	N = 1,434	N = 1,434	N = 1,471	N = 1,435	N = 1,435	N = 1,467	N = 1,431	N = 1,431
Nicosulfuron	p = 0.924 ^d	p = 0.861 ^d	p = 0.618 ^d	p = 0.223 ^d	p = 0.241 ^d	p = 0.578 ^d	p = 0.877 ^d	p = 0.814 ^d	p = 0.936 ^d
>0 - 34 vs 0	0.71 [0.32, 1.58]	0.73 [0.33, 1.62]	0.73 [0.32, 1.69]	0.87 [0.47, 1.63]	0.89 [0.47, 1.66]	0.91 [0.47, 1.76]	0.68 [0.31, 1.52]	0.70 [0.32, 1.55]	0.71 [0.31, 1.61]
>34 - 111 vs 0	1.27 [0.66, 2.47]	1.19 [0.60, 2.37]	1.37 [0.65, 2.91]	0.97 [0.52, 1.81]	0.99 [0.53, 1.87]	1.09 [0.56, 2.15]	1.11 [0.56, 2.20]	1.02 [0.50, 2.10]	1.08 [0.51, 2.31]
>111 vs 0	0.86 [0.41, 1.83]	0.87 [0.41, 1.85]	1.13 [0.50, 2.54]	0.60 [0.28, 1.25]	0.60 [0.28, 1.25]	0.72 [0.33, 1.58]	0.93 [0.46, 1.91]	0.94 [0.46, 1.93]	0.96 [0.45, 2.06]
Terbutylazine	p = 0.924 ^d	p = 0.861 ^d	p = 0.618 ^d	p = 0.223 ^d	p = 0.241 ^d	p = 0.578 ^d	p = 0.877 ^d	p = 0.814 ^d	p = 0.936 ^d
>0 - 485 vs 0	0.71 [0.32, 1.58]	0.73 [0.33, 1.62]	0.73 [0.32, 1.69]	0.87 [0.47, 1.63]	0.89 [0.47, 1.66]	0.91 [0.47, 1.76]	0.68 [0.31, 1.52]	0.70 [0.32, 1.55]	0.71 [0.31, 1.61]
>485 - 1,588 vs 0	1.27 [0.66, 2.47]	1.19 [0.60, 2.37]	1.37 [0.65, 2.91]	0.97 [0.52, 1.81]	0.99 [0.53, 1.87]	1.09 [0.56, 2.15]	1.11 [0.56, 2.20]	1.02 [0.50, 2.10]	1.08 [0.51, 2.31]
>1,588 vs 0	0.86 [0.41, 1.83]	0.87 [0.41, 1.85]	1.13 [0.50, 2.54]	0.60 [0.28, 1.25]	0.60 [0.28, 1.25]	0.72 [0.33, 1.58]	0.93 [0.46, 1.91]	0.94 [0.46, 1.93]	0.96 [0.45, 2.06]

^a Crude estimates for full population.^b Crude estimates for the population with complete confounder data.^c Adjusted for sex of the child, smoking in the child's home at age 14, SES (parental education i.e. combination of mother or father), pets at home at age 14 year follow up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnicity group of mother and father, and traffic-related air pollution (NO₂) at age 14 year follow up in multiple logistic regression models.^d p-value trend test

* P < 0.05.

Table S6: Overview of studies assessing associations of residential pesticide exposure with asthma, wheezing, dry night cough, and shortness of breath in children by the last name of the first author and by year of publication within authors.

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Gascon (2014b)	Prenatal	Spain	Birth cohort	405 participants of a general population birth cohort (12% live in rural areas, 7% live on farms).	Cord blood samples were collected and analyzed for DDE and HCB. Because original distributions were skewed, levels of DDE and HCB were log ₂ -transformed.	Mothers were asked questions regarding the wheezing of children at ages 1, 2, 3, 4, 6.5, 10 and 14. In addition, doctor-diagnosed asthma ever at ages 10 and 14 was analyzed	Prenatal DDE exposure was associated with wheezing at age 4 years [adjusted RR = 1.35, 95% CI (1.07 - 1.71) per doubling of exposure], but not at other ages {RR (95% CI) 1.04 (0.79-1.37) for age 6.5, 1.22 (0.91-1.63) for age 10, 0.92 (0.64-1.31) for age 14}. Also, prenatal DDE exposure was associated with Ever-wheeze before 18 months [adjusted RR doubling of exposure RR (95% CI) 1.16 (1.01–1.32)] for highest vs. lowest tertile.

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							No association was found between DDE and doctor-diagnosed asthma ever at ages 10 and 14 [RR = 1.03, 95%CI (0.71 - 1.50) and 0.89, 95% CI (0.61 - 1.31), respectively] or HCB and doctor-diagnosed asthma ever at ages 10 and 14 [RR = 1.21, 95%CI, (0.67, 2.18) and RR = 1.08, 95%CI, (0.61, 1.90), respectively].

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Gascon (2014a)	Prenatal	Seven European countries (Germany, Belgium, Norway, Slovakia, Greece, Spain and France)	10 Birth cohorts	4608 live newborns	Concentrations of DDE was analyzed in maternal serum/whole blood collected during pregnancy, cord serum/plasma, or breast milk. Concentrations of DDE were analyzed as continuous variables and by tertiles increment	Parental-reported wheeze before the age of 18 months and between 18 and 49 months of age (postal questionnaires: FLEHS I, HUMIS, and PÉLAGIE; telephone interview: RHEA; face-to-face interview otherwise).	No association was found between DDE and ever-wheeze assessed after and before 18 months. [RR = 1.02, 95% CI (0.96–1.07) per doubling of DDE concentration; 1.07, 95% (0.94–1.22) for medium vs low tertile, 1.16, 95% (1.01–1.32) for high vs low tertile] and after 18 months [RR = 1.03, 95%CI (0.98–1.08)]) per doubling of DDE concentration, [RR = 0.93, 95% CI (0.75–1.15)]) per doubling of DDE concentration and [RR = 1.04, 95% CI (0.90–1.20)] per doubling of DDE concentration

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Karmaus (2001)	Postnatal	Germany	Cross-sectional	343 second-grade school children aged 7 – 10 years from 18 townships in 3 areas of southern Hesse (1 industrial, 1 industrial and agricultural, 1 less industrial).	DDE in children's blood (at 7 – 10 years categorized as \geq vs < median concentration.	Parent-reported asthma-like symptoms (wheeze, cough or shortness of breath in the morning/at night, cough after exercise or exposure to cold air or fog, attacks of dyspnea)	Exposure to DDE was associated with asthma-like symptoms [OR= 3.71, 95% CI (1.10 – 12.56)]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Karmaus (2003)	Postnatal	Germany	Cross-sectional	Same as in Karmaus, 2001, but n=338 (non-biological children of mothers were excluded)	Children's blood (at age 7 - 8 years) for DDE. DDE concentrations were categorized using quartiles as cut-offs; all observations below the detection limit of 0.02 µg/L was part of the lowest quartile.	Parental self-reported definite asthma (doctor diagnosed asthma) Self-reported probable asthma (DD asthmoid bronchitis, spastic bronchitis, obstructive bronchitis)	No association between asthma symptoms (definite or probable) and DDE [OR = 1.18, 95% (0.44 - 3.35) for 2 nd vs 1 st quartile, 1.18, 95%CI (0.41, 3.50) for 3 rd vs 1 st quartile, 1.48, 95%CI (0.50 - 4.63) for 4 th vs 1 st quartile]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Liu (2012)	Prenatal	USA	Birth cohort	224 children of African American and Dominican mothers residing in upper Manhattan or the South Bronx, aged: 5-6 years.	Residential air samples in the third trimester of pregnancy: PBO (mean 1.1 ng·m ⁻³); Cis-permethrin (not calculated); Trans-permethrin (mean 0.8 ng·m ⁻³) Residential air samples at 5-6 years: PBO (LODs 0.06 ng·m ⁻³); Cis-permethrin (LOD 0.1 ng·m ⁻³) Trans-permethrin (LOD 0.2 ng·m ⁻³).	Face-to-face questionnaire reports of doctor-diagnosed asthma ever and wheezing during the past 12 months based on the ISAAC questionnaire were administered to the mothers of 5 and 6-year-old children.	No significant association between prenatal exposure to PBO or Permethrin and asthma or wheeze aged 5-6 years children. For PBO exposure at age 5-6 years • Asthma and wheezing at age 5: [OR = 1.00, 95% CI (0.80 - 1.30)] and [OR = 1.10, 95% CI (0.90 - 1.40)] Asthma and wheezing at age 6: [OR = 1.00, 95% CI (0.85 - 1.25)] and [OR = 0.90, 95% CI (0.70 - 1.10)]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							<p>For Permethrin</p> <ul style="list-style-type: none"> • Asthma and wheezing at age 5: [OR = 1.00, 95% CI (0.50 - 2.0)] and [OR = 0.70, 95% CI (0.40 - 1.80)] • Asthma and wheezing at age 6: [OR = 1.40, 95% CI (0.70 - 2.50)] and [OR = 1.50, 95% CI (0.90 - 2.80)]
Mamane (2016)	Postnatal	Niger	Cross-sectional study during the rainy season when pesticides are usually sprayed	229 children mean age 10.2 years \pm 2.4.; 125 children from a pastoral area and 104 children from an agricultural area.	Area (agricultural vs pastoral). In the agricultural area is where agricultural pesticides are applied whereby in a pastoral area no agricultural pesticides are applied.	Parent-reported wheeze ever	No significant association between living in an agricultural area and the risk of wheezing in children [OR = 1.38, 95% CI (0.66 - 2.86)].

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Merchant (2005)	Postnatal	USA	Birth cohort	644 children (224 farms, 155 rural nonfarm and 265 towns) aged 0-17 years Farms primarily produced corn, soybeans and hogs	Self-reported application of pesticides inside and outside the child's home was collected by using environmental questionnaires and a checklist by an industrial hygienist.	Parent-/self-reported doctor-diagnosed asthma, Parent-/self-reported asthma/medication for wheezing, Parent-/self-reported current wheeze obtained from childhood respiratory questionnaire	No association between the prevalence of current wheeze and applied pesticides outside the child's home [OR = 0.69, 95%CI (0.43–1.11)] and [OR = 0.58, 95%CI (0.35–0.96)].

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Perla (2015)	Postnatal	USA	Several cross-sectional surveys (NHANES 1999-2008)	Participants aged 6-15 years (DDE dataset n = 962, OP dataset n = 3,622).	Serum DDE, 6 possible DAP metabolites of organophosphate pesticides (DMP, DMTP, DMDTP, DEP, DETP, DEDTP) in urine Exposure levels were categorized based on the 25th percentile for DAP and the 40th percentile for DDE as the referent categories.	Parent-reported doctor-diagnosed asthma ever, current asthma, and wheeze (past 12 months) were examined by using NHANES medical examination and respiratory health survey questionnaires	No association between dialkyl phosphates (DAP) or p,p'-DDE and asthma outcomes (ever asthma, current asthma and current wheeze). For DAP in 6-11-year-olds <ul style="list-style-type: none"> DD asthma ever: OR = 1.16, 95% CI (0.62-2.17) for < P75 vs> P25 Current asthma: 1.42, 95%CI (0.64-3.16) for < P75 vs>P25 Current wheeze: OR = 1.43, 95%CI (0.83-2.46) for < P75 vs> P25.

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							<p>For DDE in 12-15-year-olds:</p> <ul style="list-style-type: none"> • DD asthma ever: OR = 0.81, 95%CI (0.33-2.00) for < P80 vs> P40 • Current asthma: OR = 0.78, 95%CI (0.24-2.55) for < P80 vs> P40 • Current wheeze: OR = 1.79, 95%CI (0.79-4.09) for < P80 vs> P40.
Raanan (2015)	prenatal, postnatal	USA	Birth cohort	Recruitment through clinics serving families N=364 children living in the Salinas (agricultural) Valley	Six nonspecific DAP metabolites three dimethyl phosphate (DM) and three diethyl phosphate (DE) metabolites in urine from mothers twice during pregnancy	Maternal-reported symptoms at ages 5 and 7 years: during the previous 12 months: a) wheezing or whistling in the chest;	<p>Adj. OR (95% CI) for a 10-fold increase in conc. for any respiratory symptoms observed at age 5 or 7: - 1st half of pregnancy: total DAPs 1.11 (0.72-1.72), DEs 1.03 (0.64-1.65), DMs 1.08 (0.74-1.58)</p>

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
Publication	Exposure timing	Location	Study design	Population characteristics	Exposure assessment	Health outcomes	Findings
				Respiratory symptomatology was assessed for 344 children at age 5, 347 children at age 7, 327 children at both time points and 364 children at least once.	and from children at 0.5, 1, 2, 3.5, and 5 years of age. Total concentrations of DEs, DMs, and total DAPs were log10-transformed.	b) wheezing, whistling, or shortness of breath so severe that the child could not finish saying a sentence; c) trouble going to sleep or being awakened from sleep because of wheezing, whistling, shortness of breath, or coughing that was not associated with a cold; or	- 2 nd half of pregnancy: total DAPs 1.77 (1.06-2.95), DEs 1.61 (1.08-2.39), DMs 1.45 (0.90-2.33) - Age 0.5-5 yrs: total DAPs 2.53 (1.32-4.86), DEs 2.35 (1.27-4.34), DMs 2.17 (1.19-3.98)

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
						d) having to stop running or playing active games because of wheezing, whistling, shortness of breath, or coughing that was not associated with a cold; e) use of asthma controller or rescue medications	

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Reardon (2009)	Prenatal	USA	Birth cohort	72 children of non-smoking African American and Dominican mothers	Organophosphates (chlorpyrifos and diazinon) and pyrethroids (<i>cis</i> -permethrin and <i>trans</i> -permethrin) were measured in personal air samples collected from monitors worn by the mothers for 2 days during the last trimester of pregnancy.	Questionnaires explored wheeze over the previous 12 months at 2, 3, and 5 years.	No association between <i>Cis</i> -Permethrin, Chlorpyrifos, Diazinon or <i>Trans</i> -Permethrin and wheezing at age 5 in children. For Chlorpyrifos <ul style="list-style-type: none"> Wheeze: [OR = 0.91, 95% CI (0.76–1.09)] Diazinon <ul style="list-style-type: none"> Wheeze: [OR = 0.83, 95% CI (0.72–0.95)] <i>Cis</i> -Permethrin <ul style="list-style-type: none"> Wheeze: [OR = 1.10, 95% CI (0.86–1.33)]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							<p>Trans-Permethrin</p> <ul style="list-style-type: none"> • Wheeze: [OR = 1.10, 95% CI (0.88–1.40)] • No association between Chlorpyrifos and cough (without a cold) at age 5 [OR = 0.88, 95% CI (0.72–1.07)]. • No association between Diazinon and cough (without a cold) at age 5 [OR = 0.78, 95% CI (0.67–0.91)]. • A significant association between Cis-Permethrin and cough (without a cold) at age 5 [OR = 1.30, 95% CI (1.03–1.56)].

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Salam (2004)	Postnatal	USA	Nested Case-control study	691 children from public schools, including 279 cases (doctor diagnosed asthma by age 5) and 412 controls	Retrospective Self-reported (structured telephone interview) farm-related exposures to crops, herbicides and pesticides: never, 1 st year and later, not in 1 st year of life.	Parental-reported (telephone questionnaire) doctor-diagnosed asthma before age 5 years Parent-reported early transient wheezing, early persistent asthma, and late-onset asthma.	<ul style="list-style-type: none"> No association between Trans-Permethrin and cough (without a cold) at age 5 [OR = 1.2, 95% CI (0.93–1.43)]. <p>Increased risk of doctor-diagnosed asthma by age 5 years in children exposed to herbicides, [OR = 4.58, 95% CI (1.58 – 5.56) in 1st year or later vs never] and pesticides [OR = 2.39, 95% CI (1.17 – 4.89) in 1st year or later vs never])</p>

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							No association between any asthma by age 5 and exposure to herbicides or any pesticides [OR = 0.58, 95% CI (0.24–1.39)] and [OR = 1.00, 95% CI (0.46–2.19)] not in the first year vs never.
Salameh (2003)	Postnatal	Lebanon	Cross-sectional	3,291 children in public schools, aged 5 – 16 years	Residential, para-occupational and domestic defined by the following questions: 1) Any household-member ever used pesticides at work; 2) Ever used pesticides in the house or garden;	Parental self-report of doctor-diagnosed asthma from questionnaires.	Any exposure (yes vs no) was significantly associated with doctor-diagnosed asthma [OR = 1.71, 95% CI (1.20–2.43)], Para-occupational exposure associated with risk of asthma [OR = 4.61, 95% CI (2.06–10.29)], Residential exposure associated with wheezing [OR = 2.73, 95% CI (1.85–4.05)]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Sunyer (2005)	Prenatal	Spain	Prospective cohort. Same as Gascon et al. 2014a		3) Living in a region heavily treated by pesticides; 4) Living in proximity of fields heavily treated with pesticides		
				405 mother-infant pairs, with complete outcome data at 4 years	Cord serum: DDE (median 1.03 ng/mL); HCB (median 0.68 ng/mL) Exposure was log-transformed and categorized by its quartiles of distribution.	Face-to-face maternal questionnaire: reported wheezing, persistent wheezing, and doctor-diagnosed asthma at age 4 years	Wheezing at 4 years of age increased when DDE concentration >1.90 ng/mL (highest quartile) vs< 0.57 ng/mL [RR 2.63, 95% CI (1.19–4.69)] and persistent wheezing [RR 1.26, 95% CI (1.04–1.54)]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							No association between wheezing at age 4 and exposure to DDE within the 2 nd quartile. 0.57–1.03 vs< 0.57 ng/mL • [RR = 1.32, 95% CI (0.37–4.70)] or the 3d quartile 1.03–1.90 vs< 0.57 ng/mL • [RR = 2.63, 95% CI (0.96–7.20)] > 1.90 vs< 0.57 ng/mL 2.49 (1.00–6.19)

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Sunyer (2006)	Prenatal and postnatal	Spain	Prospective cohort. Same as Gascon et al. 2014a and Sunyer et al. 2005	402 mother-infant pairs, with complete outcome data at 6.5 years	Cord serum: DDE (median 1.03 ng/mL); DDT (median 0.08 ng/mL) Children's blood (at 4 years): DDE (median 0.08 ng/mL); DDT (median 0.05 ng/mL)	Face-to-face maternal questionnaire: report of wheezing at ages 1, 2, 3, 4, and 6.5 years, persistent wheezing, DD asthma at age 6.5 years	A significant association between asthma diagnosis at 6.5 years and DDE exposure at birth [OR = 1.18, 95%CI (1.01–1.39)] for odds ratio per each increase in 1 ng/mL of DDE at birth. No association between persistent wheezing at 6.5 and DDE exposure at birth [OR = 1.13, 95% CI (0.98–1.30)]. No significant association between wheezing at ages 1, 2, 3 and 6.5 and exposure to DDE at birth but a significant association between exposure to DDE at birth and wheezing at age 4.

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
							<ul style="list-style-type: none"> At age 1: [OR = 0.92, 95%CI (0.80–1.07)]. At age 2: [OR = 1.02, 95%CI (0.92–1.13)]. At age 3: [OR = 1.07, 95%CI (0.96–1.19)] At age 4: [OR = 1.14, 95%CI (1.02–1.28)]for odds ratio per each increase in 1 ng/mL of DDE at birth. At age 6.5: [OR = 0.99, 95% CI (0.82–1.19)]

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Tagiyeva (2010)	Postnatal	UK	Prospective cohort	Between 8,131 and 11,398 subjects were included in the analysis per age	Potential antenatal and post-natal exposure of children to parentally transported sources of recognized occupational sensitizers was determined by a parental job-exposure matrix based on exposure intensity i.e. none, low, medium and high.	Parental report of children's wheeze at age 6, 18, 30, 42, 54, 69 and 81 months At 91 months: question on ever doctor-diagnosed asthma in children	No association between Antenatal biocide/fungicide and wheeze at 0–81 months [OR = 1.06, 95%CI (0.93–1.20)] low vs none. A significant association between Medium/high antenatal biocide/fungicide exposure and Wheeze at 0–81 months [OR = 1.23, 95% CI (1.07–1.40)] Medium/high vs Low. No association between wheezing at 0–81 months and low-level post-natal exposure to biocide/fungicide [OR = 1.04, 95% CI (0.87–1.25)] low vs none.

Table S6: (continued)

Publication	Exposure timing	Location	Study design	Summary of method			Findings
				Population characteristics	Exposure assessment	Health outcomes	
Weselak(2007)	Prenatal	Canada	Retrospective cohort	3,405 children aged 0 - ≥12 years living on full-time family-run farms	Questionnaire on current and past pesticide use including agric. chemicals used on the 6 largest crops sown or harvested in 1991 (area sprayed/dusted and quantity used). Pesticide exposure during pregnancy period.	Parental self-report of doctor-diagnosed asthma.	A significant association between wheezing at 0–81 months and medium/high-level exposure to biocide/fungicide [OR = 1.22, 95%CI (1.02–2.05)] medium/high vs Low.
							No significant association between asthma in children and any agricultural chemical used on the farm (Fungicides, Insecticides, Herbicides, Other Pesticides or organo-phosphates) [OR =1.00, 95% CI (0.71 - 1.40)].

*DDE: dichlorodiphenyldichloroethy/lene, HCB: hexachlorobenzene, DDT: Dichlorodiphenyltrichloroethane, PBO: Piperonyl butoxide.

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Chapter 4: Use of cleaning agents at home and respiratory and allergic symptoms in adolescents: the PIAMA birth cohort study

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Abstract

Background: It has been suggested that adults who use cleaning agents in their homes have a higher risk of asthma and allergic symptoms. The associations of asthma and allergic symptoms with household use of cleaning agents in adolescents have not been investigated yet.

Objectives: To examine the associations of household cleaning agents use with the prevalence of asthma, rhinitis and eczema in adolescents.

Methods: In this cross-sectional analysis, we included participants of the PIAMA birth cohort study with data on household use of 10 types of cleaning agents and information on asthma, rhinitis and/or eczema from parent-completed questionnaires at age 14 (N = 2,333). For the cleaning agents, we developed a composite score ranging from 0 (no exposure) to 30 points (household use on 4-7 days per week for all 10 types of cleaning agents). Logistic regression was used to analyse associations between household cleaning agents use (composite score and specific cleaning agents) and outcomes, adjusting for potential confounders.

Results: Seven, 13 and 11% of the participants had asthma, rhinitis and eczema, respectively, at age 14. The composite score for household use of cleaning agents was not associated with asthma, rhinitis and eczema. For instance, adjusted odds ratios (95% confidence interval) for the prevalence of asthma, rhinitis and eczema comparing those with the highest use of cleaning agents (≥ 10 points) to those with never/seldom use (0-4 points) were 0.95 (0.56, 1.63), 1.23 (0.82, 1.82) and 0.95 (0.56, 1.63), respectively. For individual cleaning agents, we only found the use of ammonia to be significantly associated with a lower risk of rhinitis [0.60, (0.44, 0.82)].

Conclusions: There was no indication of an increased prevalence of asthma, rhinitis or eczema among adolescents living in households within the highest category of cleaning agents use.

Keywords: Cleaning agents, Asthma, Rhinitis, Eczema, Birth cohort, Adolescence.

1.0 Introduction

Cleaning agents are used in households to enhance domestic cleanliness and hygiene. Cleaning agents consist of a wide range of active ingredients (Lynch, 2000, Franzblau and Sahakian, 2003, Deschamps et al., 1994a, Gorguner et al., 2004b). Many of these active ingredients are risk factors for skin and lung diseases such as eczema and asthma in children and adults (Weinmann et al., 2017, Zock et al., 2009, Casas et al., 2013a, Krauss-Etschmann et al., 2009). The possible mechanisms underlying the adverse associations of cleaning agents use with asthma, rhinitis and eczema include irritation of mucous membranes and skin, a potential reduction of the epithelial barrier function, and occasionally, a sensitizing potential of the cleaning agents (Quirce and Barranco, 2010).

Most of the published epidemiological studies on the effects of cleaning agents use on asthma (Kogevinas et al., 1999, Medina-Ramon et al., 2003, Medina-Ramon et al., 2005, Zock et al., 2010, Arif et al., 2003) focused on the professional user. These studies found a significantly higher risk of asthma and lower respiratory tract infections in adult professional users of cleaning agents. Moreover, some studies also suggested that non-professional users of cleaning agents may have a higher risk of asthma, wheezing and lower-airway symptoms (Matulonga et al., 2016, Weinmann et al., 2017, Bedard et al., 2014b, Zock et al., 2007). These associations maybe restricted to adults involved in cleaning activities in the home, subjecting themselves to a high level of exposure to cleaning agents. For instance, an epidemiological study found that weekly household use of cleaning sprays was associated with an increased risk of current asthma in elderly women involved in cleaning activities in their homes, but not in elderly women who had their homes cleaned by a household help (Bedard et al., 2014b). Some studies have suggested that household chemical use including cleaning agents during pregnancy increases the risk of early childhood wheezing (Henderson et al., 2008, Sherriff et al., 2005, Casas et al., 2013a, Herr et al., 2012). Moreover, children living in a household with regular

use of cleaning agents have been found to have a higher risk of rhinitis (Liu et al., 2016). The evidence from epidemiological studies regarding the association of cleaning agents use with respiratory and allergic symptoms in children, however, is inconsistent as another study found that children living in a house frequently cleaned with chlorine bleach had a lower risk of developing asthma and eczema (Nickmilder et al., 2007).

Although children do not use cleaning agents themselves, it is of interest to investigate associations in children because they are potentially exposed to cleaning agents used in their homes and they may be more susceptible to the adverse effects than adults as their organs and immune system are still developing.

To our knowledge, no studies so far have investigated the associations of cleaning agents used in a household with respiratory and allergic symptoms in adolescents. We examined the associations of cleaning agents use in households with the prevalence of asthma, rhinitis and eczema symptoms in adolescents participating in the PIAMA birth cohort study at age 14 years.

2.0 Methodology

2.1 Study design and population

The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study is a prospective Dutch birth cohort study. The baseline study population consisted of 3,963 new born from the northern, middle and western parts of The Netherlands, who were born in 1996 and 1997 (Wijga et al., 2014). The PIAMA study has been designed to study the influence of lifestyle and environmental factors on the development of asthma and allergies in children. Questionnaires were administered to the parents during pregnancy, at the child's ages of 3 months and 1 year, and then annually until the age of 8 years. When the children were 11, 14, and 17 years old, both parents and children completed questionnaires. In this study, we performed a cross-sectional analysis using data from the questionnaires completed by the

parents when the children were about 14 years old. The questionnaire administered at that age was the only one in which we included detailed questions on the use of household cleaning agents. The questions on the use of cleaning agents were adapted from the questions used within the European Respiratory Health Survey (ECRHS) (Zock et al., 2009) and also used by other birth cohorts (Casas et al., 2013b).

2.2 Health outcomes

Asthma in the last 12 months was defined based on the presence of at least 2 out of 3 criteria (doctor-diagnosed asthma ever, wheezing during the past 12 months, and prescribed asthma medication during the past 12 months), a definition developed by a panel of experts within the MeDALL consortium (Pinart et al., 2014). Rhinitis in the last 12 months and eczema in last the 12 months were included as additional health outcomes. Rhinitis was defined according to MeDALL as sneezing or a runny/blocked nose without having a cold in the last 12 months that was accompanied by itchy, watering eyes. Atopic eczema was defined as an itchy rash that was coming and going in the last 12 months at one or more of the following locations: in the folds of the elbows, behind the knees, in front of the ankles, around the ears or eyes.

2.3 Use of cleaning agents at home

When the participants were 14 years old, we asked their parents about the use of the following cleaning agents in the home in the past 12 months (“never“, “less than once a week“, “1-3 times per week“ and “4-7 times per week“): bleach/chlorine, ammonia, acids and (liquid) decalcifiers, solvents (including stain removers); furniture sprays, glass cleaning sprays (for windows and mirrors), fat removing sprays (including oven cleaning sprays), floor or furniture polish (no sprays), non-electric air fresheners, and automatic (electric) or plug-in air fresheners.

We used the questionnaire that reported the use of specific agents to define exposure to specific cleaning agents. For most of the individual cleaning agents, we combined some of the answering categories to have sufficient numbers (at least 10% of the subjects) in all exposure categories. For instance, answering categories “1-3 times a week” and “4–7 times a week” were merged for bleach/chlorine, acids and (liquid) decalcifiers, glass cleaning sprays and fat-removing sprays (including oven cleaning sprays). “Less than once a week”, “1-3 times a week” and “4-7 times a week” were combined into one category (“ever”) for ammonia and solvents (including stain removers), furniture sprays, floor or furniture polish (no sprays) and use of automatic (electric) or plug-in air fresheners.

In addition, we developed a composite score based on the use of the ten cleaning agents described above. This approach has been previously used by others (Sherriff et al., 2005, Weinmann et al., 2017, Liu et al., 2016, Mehta et al., 2012, Bedard et al., 2014b). The score was developed to take into account that multiple cleaning agents may be used in the homes of the participants. For calculation of the score, first, points were assigned based on the reported use of cleaning agents as follows: never = 0 points, less than once a week = 1 point, 1-3 times per week = 2 points, 4-7 times per week = 3 points. Then, the points were summed up to produce a composite score which ranged from 0 (no use at all of any agent) to 30 (use on 4-7 days per week of all types of cleaning agents).

2.4 Potential confounding variables

We considered a number of potential confounding variables that we defined based on parental questionnaire reports: sex of the participant (male or female), smoking in the participant’s home (yes or no), furry pets at home (cat, dog and/or rodent; yes or no), parental education (defined as the maximum of the mother’s and the father’s educational level and categorised as low (primary school, lower vocational, or lower secondary education), intermediate

(intermediate vocational education or intermediate/higher secondary education) or high (higher vocational education and university)), damp stains/mould spots in participant's bedroom and/or living room (yes or no), maternal and paternal allergy (yes or no), use of gas for cooking (yes or no), parental country of birth (both parents born in the Netherlands, yes or no), and active smoking of the participant. In addition, we considered estimated levels of traffic-related air pollution (annual average of nitrogen dioxide (NO₂)) at the participant's home address at the time of the outcome assessment (as a continuous variable) as a potential confounder as NO₂ has been found to be associated with asthma in earlier analyses within our cohort (Gehring et al., 2015). NO₂ levels were estimated by a land-use regression model developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Beelen et al., 2013a). These potential confounding variables were selected because they have been identified in previous studies (Weinmann et al., 2017, Herr et al., 2012, Nickmilder et al., 2007, Krauss-Etschmann et al., 2009, Asher et al., 1995) as determinants of the outcomes of interest (asthma, rhinitis and eczema).

2.6 Statistical analysis

For demographic variables, we performed descriptive statistical analyses calculating absolute numbers (n) and percentages (%) for categorical variables and means with standard deviations (SD) for continuous variables.

The composite score was categorised into four categories using quartiles as cut-offs: 'never/seldom' (0-4 points), 'low' (5-7 points), 'medium' (8-9 points) and 'high' (10 or more points).

We assessed associations of the composite score (categorical and continuous) and the use of specific cleaning agents with the prevalence of asthma, rhinitis and eczema by logistic

regression without and with adjustment for potential confounders and calculated odds ratios (ORs) with 95% confidence intervals (CIs).

As a sensitivity analysis, we assessed the associations of the use of cleaning agents with the prevalence of asthma, rhinitis, and eczema in the subset of participants that was reported to be sometimes or mostly present during cleaning activities.

We used Wald tests to determine the statistical significance of the relationships of cleaning agents with the prevalence of asthma, rhinitis, and eczema. Statistical significance was defined as a $p\text{-value} < 0.05$. Statistical analyses were performed using SAS version 9.4.

3.0 Results

Approximately half of the study participants were male and for 92% of the participants both parents were born in the Netherlands (Table 1). The prevalence of asthma, rhinitis and eczema among the study participants were 7%, 13% and 11%, respectively (Table 1). The mean (standard deviation) of the composite score of cleaning agent use was 7.3 (3.3).

Tables 2 and S1 present the frequency distributions of parental-reported use of individual cleaning products after and before combining answering categories, respectively. The cross tables of individual cleaning product use with asthma, rhinitis, and eczema are presented in Table S2.

No statistically significant associations were observed between the composite score (categorical and continuous) and the prevalence of asthma, rhinitis and eczema (Table 3). For instance, the adjusted odds ratio (95% confidence interval) for the high vs. the never/low exposure category was 0.95 (0.56, 1.63) for asthma, 1.23 (0.83, 1.82) for rhinitis and 0.95 (0.56, 1.63) for eczema, respectively (Table 3). When we investigated the associations of the use of individual cleaning products in the participants' homes with the prevalence of asthma, rhinitis and eczema in the adolescents, we did not find a higher prevalence among those living in homes

where the cleaning products were used; on the contrary, the prevalence of rhinitis was found to be lower among study participants living in homes where ammonia was used as a cleaning product [adj. OR (95% CI) ever vs never 0.60 (0.44,0.82), Figure 1 and Table S3].

The results of the sensitivity analysis among the subset of 988 study participants, who were sometimes or mostly present indoors when the cleaning activities were conducted provided no evidence for an association of the composite score (continuous and categorical) with the prevalence of asthma, rhinitis and eczema (Table 4).

Table 1: Distribution of covariates, health outcomes and composite exposure score in the study population at age 14 years [N=2,333].

Covariates		
Male sex, n/N [%]	1,182/2,333	[51]
Smoking in the child's home, n/N [%]	256/2,333	[11]
Pets at home (cat, dog and/or rodent), n/N [%]	1,389/2,330	[60]
Damp stains/mould spots in child's bedroom and/or living room, n/N [%]	188/2,329	[8]
Gas cooking, n/N [%]	1,790/2,331	[77]
Parental education, n/N [%]		
Low	231/2,328	[10]
Intermediate	802/2,328	[34]
High	1,295/2,328	[56]
Maternal and paternal allergy, n/N [%]		
Allergic father	730/2,332	[31]
Allergic mother	681/2,333	[29]
Both parents born in the Netherlands, n/N [%]	2,093/2,286	[92]
Active smoker , n/N [%]	102/ 2,333	[4]
Traffic-related air pollution (NO ₂) at the home address, mean (SD) [n]	22.6 (6.5)	[2,320]
Health outcomes		
Asthma, n/N [%]	161/2,329	[7]
Rhinitis, n/N [%]	301/2,330	[13]
Eczema, n/N [%]	251/2,329	[11]
Exposure to cleaning agents		
Composite score (categorical) , n/N [%]		
Never/seldom (score 0 – 4 points)	469/2,323	[20]
Low (score 5 – 7 points)	816/2,323	[35]
Medium (score 8 – 9 points)	482/2,323	[212]
High (score 10 or more points)	556/2,323	[24]
Composite score as a continuous variable, mean (SD) [n]	7.3 (3.3)	[2,323]
Participants were present during cleaning activities, n/N [%]		
Nearly never/Mostly not	344/2,332	[58]
Sometimes/Mostly yes	988/2,332	[42]

Table 2: Frequency distribution of use of cleaning agents in the household in the past 12 months in the study population at age 14 years (after combining of some of the answering categories, N=2,333).

Agent used	n/N	%
Bleach/chlorine		
Never	367/2,333	[16]
Less than once a week	936/2,333	[40]
1-7 times a week	1,030/2,333	[44]
Ammonia		
Never	1,649/2,328	[71]
Ever	679/2,328	[29]
Acids and (liquid) decalcifiers		
Never	460/2,333	[20]
Less than once a week	1,290/2,333	[55]
1-7 times a week	583/2,333	[25]
Solvents (including stain removers)		
Never	1,078/2,332	[46]
Ever	1,254/2,332	[54]
Furniture spray		
Never	2,018/2,333	[87]
Ever	315/2,333	[13]
Glass cleaning spray		
Never	752/2,331	[32]
Less than once a week	990/2,331	[42]
1-7 times a week	589/2,331	[25]
Fat removing spray (also oven cleaning spray)		
Never	859/2,332	[37]
Less than once a week	1,037/2,332	[44]
1-7 times a week	436/2,332	[19]
Floor/furniture polisher (no spray)		
Never	1,470/2,331	[63]
Ever	861/2,331	[37]
Air freshener (non-electric)		
Never	909/2,331	[39]
Less than once a week	379/2,331	[16]
1-3 times a week	380/2,331	[16]
4-7 times a week	663/2,331	[28]
Automatic (electric) or plug-in air freshener		
Never	2,049/2,332	[88]
Ever	283/2,332	[12]

Table 3: Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for associations of exposure to cleaning agents as a composite score (as a categorical and continuous variable) with asthma, rhinitis and eczema at age 14 years.

Composite score	Asthma			Rhinitis		Eczema	
	N = 2,319	N = 2,249		N = 2,321	N = 2,250	N = 2,319	N = 2,249
	Crude OR [95% CI]	Adjusted OR [95% CI] ^a		Crude OR [95% CI]	Adjusted OR [95% CI] ^a	Crude OR [95% CI]	Adjusted OR [95% CI] ^a
Categorical							
Never/seldom (0 – 4 points)	Ref	Ref		Ref	Ref	Ref	Ref
Low (5 – 7 points)	1.10 [0.70, 1.74]	0.99 [0.61, 1.60]		1.16 [0.82, 1.64]	1.16 [0.81, 1.66]	1.24 [0.87, 1.78]	0.99 [0.61, 1.60]
Medium (8 – 9 points)	1.32	1.27		0.97	0.97	1.06	1.27
High (10 or more points)	0.96 [0.81, 2.17]	0.95 [0.76, 2.12]		1.17 [0.66, 1.44]	1.23 [0.64, 1.46]	0.78 [0.70, 1.60]	0.95 [0.76, 2.12]
Continuous (per 1 point increase)	1.00 [0.58, 1.59]	1.01 [0.56, 1.63]		1.00 [0.81, 1.69]	1.00 [0.83, 1.82]	0.97 [0.51, 1.19]	1.01 [0.56, 1.63]
	0.95, 1.05]	[0.95, 1.06]		[0.96, 1.04]	[0.96, 1.04]	[0.93, 1.01]	[0.95, 1.06]

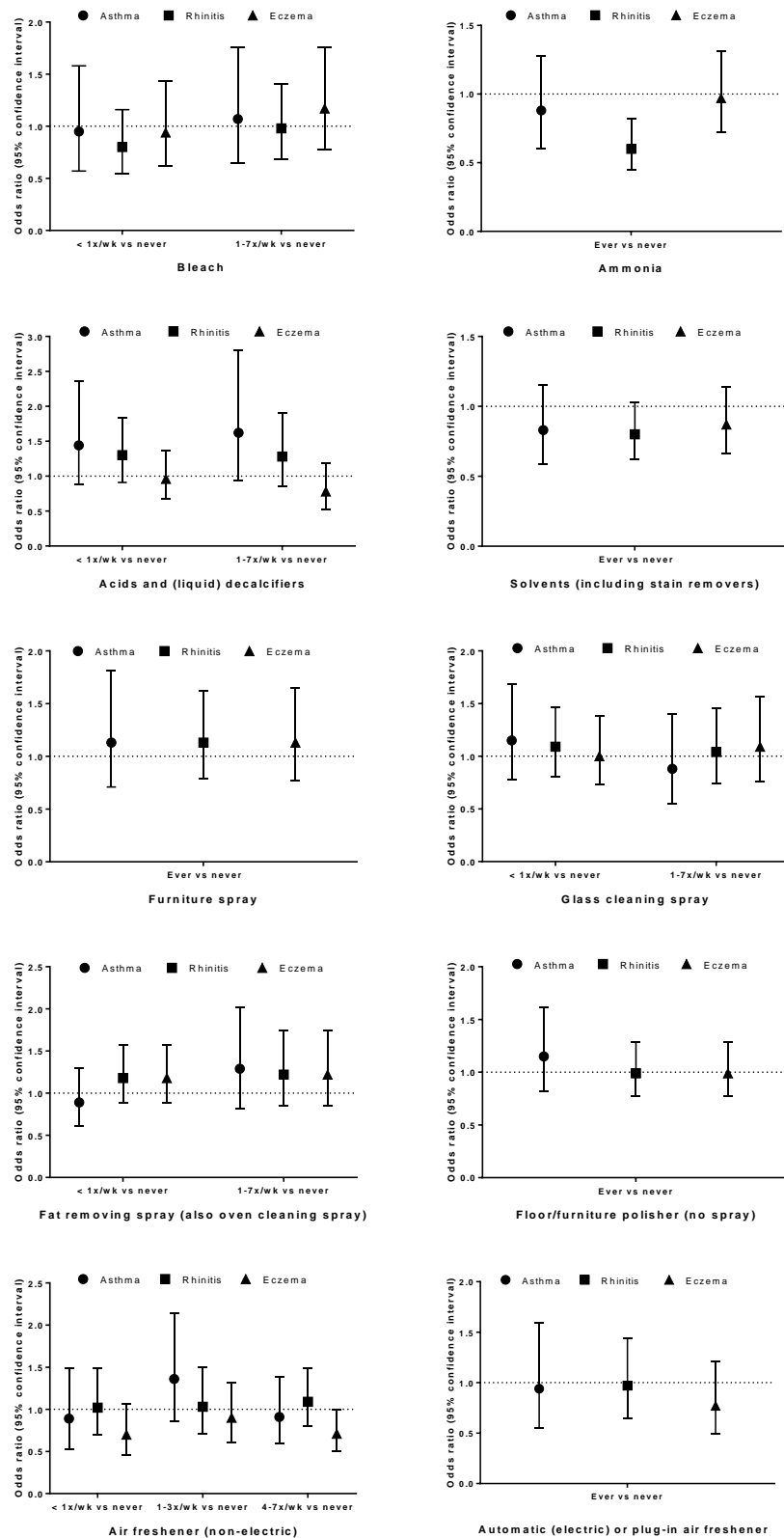
^aAdjusted sex of the child, smoking in the child's home at age 14, active smoking of the participant, parental education, pets at home at age 14, maternal and paternal allergy, both parents Dutch nationality, gas cooking, damp/mould spots in the child's bedroom and/or living room, and traffic-related air pollution (NO₂) at age 14.

Table 4: Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for associations of exposure to cleaning agents as a composite score (categorical and continuous variable) with asthma, rhinitis and eczema at age 14 years for the subset of participants who were mostly and sometimes present in the home when cleaning activities were conducted.

Composite score	Asthma			Rhinitis			Eczema		
	N = 982	N = 957		N = 985	N = 959		N = 984	N = 957	
	Crude OR [95% CI]	Adjusted OR [95% CI] ^a		Crude OR [95% CI]	Adjusted OR [95% CI] ^a		Crude OR [95% CI]	Adjusted OR [95% CI] ^a	
Categorical									
Never/seldom (0 – 4 points)	ref	ref		ref	ref		ref	ref	
Low (5 – 7 points)	0.94 [0.43, 2.08]	0.91 [0.39, 2.14]		1.70 [0.86, 3.35]	2.14 [1.04, 4.41]		1.56 [0.81, 3.03]	0.91 [0.39, 2.14]	
Medium (8 – 9 points)	1.08 [0.47, 2.48]	0.99 [0.41, 2.40]		1.43 [0.69, 2.97]	1.43 [0.65, 3.10]		1.30 [0.64, 2.66]	0.99 [0.41, 2.40]	
High (10 or more points)	0.83 [0.37, 1.84]	0.91 [0.38, 2.17]		1.67 [0.85, 3.27]	1.95 [0.94, 4.01]		0.96 [0.48, 1.92]	0.91 [0.38, 2.17]	
Continuous (per 1 point increase)	0.99 [0.92, 1.07]	1.01 [0.93, 1.10]		1.03 [0.97, 1.09]	1.03 [0.97, 1.09]		1.00 [0.94, 1.06]	1.01 [0.93, 1.10]	

^aAdjusted for sex of the child, smoking in the child's home at age 14, active smoking, parental education, pets at home at age 14, maternal and paternal atopy, both parents Dutch nationality, gas cooking, damp/mould spots in the child's bedroom and/or living room, and traffic-related air pollution (NO₂) at age 14.

Figure 1: Adjusted^a odds ratios with 95% confidence intervals for the associations of exposure to cleaning agents with asthma, rhinitis and eczema at age 14 years.



^aAdjusted for sex of the child, smoking in the child's home at age 14, active smoking of the participant, parental education, pets at home at age 14, maternal and paternal allergy, both parents Dutch nationality, gas cooking, damp/mould spots in the child's bedroom and/or living room, and traffic-related air pollution (NO₂) at age 14.

4.0 Discussion

This paper describes the associations of household use of cleaning agents with the prevalence of asthma, rhinitis and eczema at age 14 in participants of a Dutch prospective birth cohort study. The findings of this study suggest that the use of cleaning agents in the household, including cleaning products in spray form that may stay longer in the air and therefore pose a specific risk for asthma and allergic symptoms, is not associated with higher risks of asthma, rhinitis and eczema in this population.

In reviewing the relevant literature (a summary of that literature is provided in Table S4), we found that the reported associations between cleaning agent use in the household and asthma, rhinitis and eczema in children are inconsistent.

Herr et al. found no indication of a higher risk of mild or severe wheeze in children with an average age of 19 months when their parents used cleaning sprays (Herr et al., 2012). Another study reported no association between the use of cleaning agents during and after pregnancy and the risk of wheezing in children during the first year of life (Casas et al., 2013a).

To the best of our knowledge, there is only one study, which involved participants of similar age (although somewhat older, aged 19-24 years) as the current study participants. That study found that cleaning disinfectant use was associated with a higher risk of incident asthma in young adults (Weinmann et al., 2017). The fact that this study has found an association while no associations were found in other studies including ours might be at least partially explained by a higher active involvement in household cleaning in early adulthood than in childhood and adolescence. Also, Weinmann et al. included both, occupational and residential exposures to disinfectants and they were not able to disentangle the effects of occupational exposure from the effects of residential exposure. Therefore, the study by Weinmann et al. is not directly comparable with our study as a) occupational exposure has not been included in our study and in addition, occupational exposure is unlikely in our study among 14-year-olds living in the

Netherlands, and b) occupational exposures are likely higher than residential exposures. In addition, the same study found no association between the use of cleaning sprays and the risk of asthma and wheezing in young adults (Weinmann et al., 2017).

Also, one study found that children of women with a higher household chemical exposure (composite score, including cleaning agents and insecticides) during pregnancy had a higher risk of persistent wheeze during the first 42 months of life (Sherriff et al., 2005), and early-onset persistent wheeze and intermediate-onset transient wheeze at age 7 years (Henderson et al., 2008). As we did not collect data on the use of cleaning agents during pregnancy, we cannot directly compare those findings with ours.

A study in elderly women with an average age of 68 years found a significant association between weekly use of at least one cleaning spray and current asthma in women without household help, but not in women with a household help (Bedard et al., 2014b). This suggests that active involvement in cleaning activities might be necessary to increase the risk of asthma. We do not have data on active involvement in cleaning activities in the PIAMA study, but active involvement in cleaning activities is likely not very common at the age studied, which may explain the lack of association in the present study. However, the lack of association in the current study could be due to a true non-effect of cleaning agents use in relation with asthma, rhinitis and eczema among adolescents.

The current study found that the use of ammonia was associated with a lower risk of rhinitis in our study participants. Currently, evidence on the association of cleaning agents use with the risk of rhinitis in children is limited (a summary of that literature is provided in Table S4). One study reported that cleaning agents use in the household was associated with a higher risk of rhinitis in children aged 10 years (Liu et al., 2016). Exposure in that study was defined as the total chemical burden (TCB) to 14 different types of chemicals including cleaning agents and insecticides and the fact that the association estimates were significant for the 3rdtertile, but not

the 2ndtertile versus the 1sttertile suggests that the increase in risk is limited to the group with the highest exposure. That study did not only involve study participants somewhat younger than the participants of our study but also cleaning agents use might be different from the present study. Also, the use of insecticides was included in the TCB score in addition to cleaning agents in that study, but not in ours. This may explain the discrepancy between the findings of that study and our study. Moreover, we cannot rule out that the association between ammonia use and rhinitis in our study is a chance finding as many associations were tested. Unfortunately, we lack more detailed data and power on the use of ammonia cleaning products to explore this in more detail. Therefore, it should be interpreted with caution.

Our findings for eczema are consistent with the findings of another study which also found no indication of an increase in the risk of allergic dermatitis in relation to the household use of cleaning agents in children with an average age of 10 years (Liu et al., 2018). In another study, however, children who lived in a household where disinfectants were used had a higher risk of atopic eczema and rash ever at age 4 years (Krauss-Etschmann et al., 2009). We did not investigate specifically the association between allergic dermatitis or atopic eczema and cleaning agents use, but most eczema in children is allergic (Krauss-Etschmann et al., 2009). The study by Krauss-Etschmann et al., however, is not directly comparable with our study because of the differences in the timing of the exposure (prenatal versus postnatal) as well as the age of the study participants. Also, younger children may be more likely to be exposed to the cleaning agents used as they spend more time at home compared to adolescents.

The lack of association with cleaning agents use in the household might be explained by the fact that most of the adolescents at age 14 in the Netherlands are not directly involved in cleaning activities and that they, therefore, are likely exposed to low levels of cleaning agents. Moreover, many of our study participants were not present during the cleaning activities. However, a sensitivity analysis in the subsample of our study population that was sometimes

or mostly present during cleaning activities confirmed the lack of association that was observed in the main analysis.

Previous studies and our study have only focused on the self-reported cleaning agents use and failed to address associations of individual chemical constituents present in cleaning agents with the risk of respiratory and allergic symptoms. We would suggest research that would look at the associations of the chemical constituents present in cleaning agents with a higher risk of respiratory and allergic symptoms in adolescents as this will provide an understanding of the associations of each chemical constituents present in cleaning agents used with the risk of asthma and allergic diseases.

This work was conducted in the Netherlands within the Dutch PIAMA birth cohort study. The participants were recruited from the general population as described previously (Wijga et al., 2014), to represent the general Dutch population of all children living in the Netherlands. However, children of highly educated parents were over-represented and children of parents from non-western countries were underrepresented. There is currently no evidence for an increased or decreased susceptibility to the effects of cleaning agents in children of highly educated parents or children of parents from non-western countries. Therefore, we think that the over-representation of children of highly educated and Dutch parents likely does not affect the generalisability of our study findings to the general population of all adolescents living in the Netherlands.

5.0 Conclusion

There was no indication of an increase in the prevalence of asthma, rhinitis or eczema among adolescents living in households within the highest category of cleaning agents use.

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Conflict of interest statement

None of the authors declares an actual or potential conflict of interest.

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SUPPLEMENTARY TABLES

Table S1: Frequency distribution of use of cleaning agents in the household in the past 12 months in the study population at age 14 years (original answering categories, N=2,333).

Agent used	n/N	%
Bleach/chlorine		
Never	367/2,333	[16]
Less than once a week	936/2,333	[40]
1-3 times a week	889/2,333	[38]
4-7 times a week	141/2,333	[6]
Ammonia		
Never	1649/2,328	[71]
Less than once a week	648/2,328	[28]
1-3 times a week	29/2,328	[1]
4-7 times a week	2/2,328	[0]
Acids and (liquid) decalcifiers		
Never	460/2,333	[20]
Less than once a week	1290/2,333	[55]
1-3 times a week or	560/2,333	[24]
4-7 times a week	23/2,333	[1]
Solvents (including stain removers)		
Never	1078/2,332	[46]
Less than once a week	1192/2,332	[51]
1-3 times a week	52/2,332	[2]
4-7 times a week	10/2,332	[0]
Furniture spray		
Never	2018/2,333	[87]
Less than once a week	266/2,333	[11]
1-3 times a week	46/2,333	[2]
4-7 times a week	3/2,333	[0]
Glass cleaning spray		
Never	752/2,331	[32]
Less than once a week	990/2,331	[42]
1-3 times a week	521/2,331	[22]
4-7 times a week	68/2,331	[3]
Fat removing spray (also oven cleaning spray)		
Never	859/2,332	[37]
Less than once a week	1037/2,332	[44]
1-3 times a week	312/2,332	[13]
4-7 times a week	124/2,332	[5]
Floor/furniture polisher (no spray)		
Never	1470/2,331	[63]
Less than once a week	795/2,331	[34]
1-3 times a week	59/2,331	[3]
4-7 times a week	7/2,331	[0]
Air freshener (non-electric)		
Never	909/2,331	[39]
Less than once a week	379/2,331	[16]
1-3 times a week	380/2,331	[16]
4-7 times a week	663/2,331	[28]
Automatic (electric) or plug-in air freshener		
Never	2049/2,332	[88]
Less than once a week	91/2,332	[4]
1-3 times a week	56/2,332	[2]
4-7 times a week	136/2,332	[6]

Table S2: Cross tabulation of use of cleaning products with asthma, rhinitis and eczema at age 14.

Agent used	Asthma	Rhinitis	Eczema
	n/N [%]	n/N [%]	n/N [%]
Bleach/chlorine			
Never	24/367 [7]	50/367 [14]	38/367 [10]
Less than once a week	62/935 [7]	110/934 [12]	91/935 [10]
1-3 times a week/ 4-7 times a week	75/1,027 [7]	141/1,029 [14]	122/1,027 [12]
Ammonia			
Never	118/1,646 [7]	237/1,647 [14]	182/1,647 [11]
Ever	43/678 [6]	63/678 [9]	69/677 [10]
Acids and (liquid) decalcifiers			
Never	23/460 [5]	50/460 [11]	53/459 [12]
Less than once a week	94/1,287 [7]	174/1,287 [13]	145/1288 [11]
1-3 times a week/ 4-7 times a week	44/582 [8]	77/583 [13]	53/582 [9]
Solvents, stain removers			
Never	83/1,077 [8]	150/1,077 [14]	123/1,077 [11]
Ever	78/1,251 [6]	151/1,253 [12]	128/1,251 [10]
Furniture spray			
Never	137/2,014 [7]	258/2,015 [13]	214/ 2015 [11]
Ever	24/315 [8]	43/315 [14]	37/314 [12]
Glass spray			
Never	53/751 [7]	93/752 [12]	82/750 [11]
Less than once a week	75/987 [8]	132/987 [13]	105/988 [11]
1-3 times a week/ 4-7 times a week	33/589 [6]	76/589 [13]	64/589 [11]
Fat removing spray (also oven cleaning spray)			
Never	59/858 [7]	102/857 [12]	97/858 [11]
Less than once a week	65/1036 [6]	137/1,036 [13]	107/1035 [10]
1-3 times a week/4-7 times a week	37/434 [9]	62/436 [14]	47/435 [11]
Floor/furniture polisher (no spray)			
Never	96/1,468 [7]	191/1,469 [13]	156/1,467 [11]
Ever	65/859 [8]	110/859 [13]	95/860 [11]
Air fresher (non-electric)			
Never	62/908 [7]	117/908 [13]	114/907 [13]
Less than once a week	24/378 [6]	45/379 [12]	33/378 [9]
1-3 times a week	34/380 [9]	50/379 [13]	43/380 [11]
4-7 times a week	41/661 [6]	88/662 [13]	61/662 [9]
Automatic or plug-in air fresher			
Never	143/2,046 [7]	266/2,047 [13]	227/2,046 [11]
Ever	18/282 [6]	34/282 [12]	24/282 [9]

Table S3: Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) for associations of exposure to individual cleaning agents with asthma, rhinitis and eczema at age 14 years.

	Asthma N = 2,325	Rhinitis N = 2,330	Eczema N = 2,329
Agent used	Crude OR [95% CI]	Crude OR [95% CI]	Crude OR [95% CI]
Bleach/chlorine			
Never	ref	ref	ref
Less than once a week	1.02 [0.62, 1.65]	0.85 [0.59, 1.21]	0.84 [0.59, 1.21]
1-7 times a week	1.13 [0.70, 1.81]	1.01 [0.71, 1.43]	1.01 [0.71, 1.42]
Ammonia			
Never	ref	ref	ref
Ever	0.88 [0.61, 1.26]	0.61 [0.45, 0.82]*	0.91 [0.68, 1.22]
Acids and (liquid) decalcifiers			
Never	ref	ref	ref
Less than once a week	1.50 [0.94, 2.39]	1.28 [0.92, 1.79]	1.28 [0.92, 1.79]
1-7 times a week	1.55 [0.92, 2.61]	1.25 [0.85, 1.82]	1.25 [0.85, 1.82]
Solvents (including stain removers)			
Never	ref	ref	ref
Ever	0.80 [0.58, 1.10]	0.85 [0.67, 1.08]	0.88 [0.68, 1.15]
Furniture spray			
Never	ref	ref	ref
Ever	1.13 [0.72, 1.77]	1.08 [0.76, 1.52]	1.08 [0.76, 1.53]
Glass cleaning spray			
Never	ref	ref	ref
Less than once a week	1.08 [0.75, 1.56]	1.09 [0.82, 1.45]	1.09 [0.82, 1.45]
1-7 times a week	0.78 [0.50, 1.22]	1.05 [0.76, 1.45]	1.05 [0.76, 1.45]
Fat removing spray			
Never	ref	ref	ref
Less than once a week	0.91 [0.63, 1.31]	1.13 [0.86, 1.48]	0.91 [0.68, 1.21]
1-7 times a week	1.26 [0.82, 1.94]	1.23 [0.87, 1.72]	0.95 [0.66, 1.38]
Floor/furniture and polisher (no spray)			
Never	ref	ref	ref
Ever	1.17 [0.84, 1.62]	0.98 [0.76, 1.26]	1.04 [0.80, 1.37]
Air freshener (non-electric)			
Never	ref	ref	ref
Less than once a week	0.93 [0.57, 1.51]	0.91 [0.63, 1.32]	0.67 [0.44, 1.00]
1-3 times a week	1.34 [0.87, 2.08]	1.03 [0.72, 1.47]	0.89 [0.61, 1.29]
4-7 times a week	0.90 [0.60, 1.36]	1.04 [0.77, 1.40]	0.71 [0.51, 0.98]*

Table S3: (continued)

	Asthma N= 2,325	Rhinitis N = 2,330	Eczema N = 2,329
Agent used	Crude OR [95% CI]	Crude OR [95% CI]	Crude OR [95% CI]
Automatic (electric) or plug-in air freshener	ref	ref	ref
Never	0.91	0.92	0.75
Ever	[0.55, 1.51]	[0.63, 1.34]	[0.48, 1.16]

*P < 0.05.

Table S4: Overview of studies assessing associations of household chemical use (cleaning agents only or and household chemical use including cleaning agents) and asthma, rhinitis, eczema and related symptoms in children by the last name of the first author and by year of publication within authors.

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Sherriff [2005], United Kingdom, prospective cohort. 8,134 children whose parents completed both exposure and health outcomes questionnaires were enrolled in this study.	Prenatal. Self-reported use of indoor chemicals during pregnancy as categorical and continuous variables. These chemicals include disinfectants, bleach, carpet cleaner, window cleaner, dry cleaning fluid, aerosols, turpentine/white spirit, air fresheners (spray, stick or aerosol, paint stripper, paint or varnish and pesticides/insect killers.	The questionnaire on wheezing of the study children was completed by parents or primary care (usually the mothers) at 0 - 6, 6 - 18, 18 - 30 and 30 - 42 months after the child was born. This information was used to produce four mutually exclusive pattern of wheezing between birth and 3.5 years. These include never, transient early, persistent and late onset of wheeze.	Total chemical burden (TCB) score (continuous): <ul style="list-style-type: none"> • Transient early wheeze: OR = 1.01, 95%CI (0.99, 1.02). • Persistent wheeze OR: = 1.06, 95%CI (1.03, 1.09). • Late onset wheeze: OR = 1.02, 95%CI (0.98, 1.06). Total chemical burden (TCB) score (bottom decile versus top decile). <ul style="list-style-type: none"> • Transient early wheeze: OR = 0.94, 95%CI (0.60, 1.40). • Persistent wheeze: OR = 2.30, 95%CI (1.20, 4.39). • Late onset wheeze: OR = 2.02, 95% CI (0.80, 5.15).
Nickmilder [2007], Belgium and Cross-sectional. 341 schoolchildren were selected, and 107 children were excluded because of having a backyard swimming pool, having swum when they were babies or being members of a swimming club. Finally, 234 were included in this study from a population of schoolchildren of an average age of approximately 11 years.	Postnatal. Self-reported use of home cleaning with chlorine bleach at least once per week during early life and infancy period.	The parent completed a questionnaire on sets of respiratory symptoms and allergic diseases such as asthma and allergic sensitization IgE.	Chlorine bleaching <ul style="list-style-type: none"> • asthma diagnosed by doctor: OR = 0.10, 95%CI (0.03, 0.80). • indoor allergens IgE: OR = 0.70, 95%CI (0.11, 1.00). • house dust mite IgE: OR = 0.80, 95%CI (0.11, 1.00). • dog/catIgE: OR = 0.60, 95%CI (0.10, 1.10). • pollenIgE: OR = 1.10, 95%CI (0.70, 1.70).

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Henderson [2008], United Kingdom, prospective cohort. The study population involved 13,988 infants who survived to 1 year of age.	Pregnant women were asked to complete questionnaires during pregnancy on how often they have used the following (a list of 15 chemical-based products in-house). These chemicals include disinfectants, bleach, carpet cleaner, window cleaner, dry cleaning fluid, aerosols, turpentine/white spirit, air fresheners (spray, stick or aerosol, paint strippers, paint or varnish and pesticides/insect killers.	Parental (usually the mother) completed questionnaires on wheezing patterns of the study child at 0–6 months, 6–18 months, 18–30 months, 30–42 months and 69–81 months after birth. These were categorized as Never wheezed, i.e. any wheezing at any of the five time-points. Early-onset transient wheeze i.e. wheezed at 0–18 months but not at 69–81 months. Intermediate-onset transient wheeze, i.e. no wheeze at 0–18 months and wheeze at 18–42 months and no wheeze at 69–81 months. Early-onset persistent wheeze, i.e. wheeze at 0–18 and 69–81 months; Intermediate onset persistent wheeze, i.e. no wheeze at 0–18 months and wheeze at 18–42 and 69–81 months. Late-onset wheeze, i.e. onset of wheeze after 42 months and before 81 months between birth and 7 years.	<p>Composite Household Chemical Exposure z-score as a continuous variable (per unit increase in z-score) and</p> <ul style="list-style-type: none"> • Early-onset transient wheeze: OR = 1.07, 95%CI (0.99, 1.14). • Early-onset persistent wheeze: OR = 1.21, 95%CI (1.10, 1.35). • Intermediate-onset transient wheeze: OR = 1.13, 95%CI (1.01, 1.28). • Intermediate-onset persistent wheeze: OR = 1.11, 95%CI (0.91, 1.40). • Late-onset wheeze: OR = 1.02, 95%CI (0.88, 1.30).

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Herr [2012], France, population-based cohort study. A total of 2012 infants participated in the health examination with an average age of 19 months.	Prenatal. Parentals completed a questionnaire regarding the use of cleaning sprays in homes when the child was 1 month old.	Parents completed questionnaires regarding wheezing during the first 18 months of life. i.e. mild wheeze or severe wheeze.	Daily use of cleaning sprays <ul style="list-style-type: none"> Mild wheeze [OR = 1.58, 95%CI (0.96, 2.61)]. Severe wheeze [OR = 1.40, 95%CI (0.78, 2.49)].
Weinmann [2017], Germany, population-based cohort study. 1695 young adults aged 19-24 years.	Postnatal. Participants were asked to fill out a questionnaire on one or more of the following sprays/disinfectants on 0, <1, 1-3 or 4-7 days per week: For sprays and disinfectants, a composite score was developed. These scores range from 0 - 27 for sprays and 0 - 18 for disinfectants. Again, the score was categorized to form no use (score = 0), low use (score between 1 and the medium), medium use (score between the medium and the 90 th percentile) and high use (score above the 90 th percentile).	Participants were asked to fill out the questionnaire regarding current asthma and current wheezing within the last 12 months prior to the survey. The outcomes were categorized as incident asthma, persistent asthma, and remittent asthma for current asthma. While current wheezing were categorized as incident wheezing, persistent wheezing and remittent wheezing.	Incident asthma and spray use (never = reference): <ul style="list-style-type: none"> Low: OR = 0.70, 95% CI (0.23, 2.06), Medium: OR = 0.78, 95%CI (0.26, 2.36), High: OR = 2.79, 95%CI (0.84, 9.20). Persistent asthma and spray use (never = reference): <ul style="list-style-type: none"> Low: [OR = 0.66, 95%CI (0.34, 1.28)]. Medium: [OR = 0.65, 95%CI (0.32, 1.29)]. High: [OR = 0.55, 95%CI (0.18, 1.63)]. Remittent asthma and spray use (never = reference): <ul style="list-style-type: none"> Low: [OR = 0.91, 95%CI (0.46, 1.80)]. High: [OR = 1.52, 95%CI (0.65, 3.55)]. Incident asthma and disinfectant use (never = reference): <ul style="list-style-type: none"> High: OR = 2.79, 95%CI (1.14, 6.83). Persistent asthma and disinfectant use (never = reference): <ul style="list-style-type: none"> Low/ medium: OR = 1.79, 95%CI (0.82, 3.91).

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
			<p>Persistent wheezing and spray use (never = reference):</p> <ul style="list-style-type: none"> • Low: OR = 1.02, 95%CI (0.65, 1.61). • Medium: OR = 0.97, 95%CI (0.60, 1.57). • High: OR = 1.24, 95%CI (0.65, 2.39). <p>Remittent wheezing and spray use (never = reference):</p> <ul style="list-style-type: none"> • Low: 0.97, 95%CI (0.64, 1.46). • Medium: OR = 1.03 (0.67, 1.58). <p>High: OR = 1.30, 95%CI (0.73, 2.30).</p> <p>Incident wheezing and disinfectant use (never = reference):</p> <ul style="list-style-type: none"> • High: OR = 0.79, 95% CI (0.40, 1.56). <p>Persistent wheezing and disinfectant use (never = reference):</p> <ul style="list-style-type: none"> • Low/medium: OR =1.22, 95%CI (0.74, 2.01). • High: OR = 0.98, 95%CI (0.56, 1.70). <p>Remittent wheezing and disinfectant use (never = reference):</p> <ul style="list-style-type: none"> • Low/medium: OR = 0.79, 95%CI (0.47,1.30). • High: OR = 0.94, 95% CI (0.58, 1.52). <p>Incident wheezing and disinfectant use</p> <ul style="list-style-type: none"> • Low/ medium: OR = 1.08, 95% CI (0.60, 1.98).

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Casas [2013], Spain, population-based birth cohort study. A total of 2,292 children were followed until 12 – 18 months of age. While available information for wheezing was 2,147 children.	<p>Prenatal. A questionnaire on the use of cleaning products was administered to parents during the third trimester of pregnancy. Questions about common domestic cleaning products in Spain such as bleach, ammonia, solvent, furniture polishes, glass cleaners, air fresheners, multiuse cleaners, ironing sprays, floor cleaning sprays, oven sprays, and carpet sprays were asked.</p>	<p>The information regarding the wheeze status in the first year of life was reported by the mother at the age of 12 – 18 months through interviewer-led questionnaires.</p>	<p>Wheezing</p> <ul style="list-style-type: none"> • Use of bleach (yes vs no?): OR = 0.91, 95% CI (0.72, 1.17). • Use of ammonia (yes vs no?): OR = 1.00, 95% CI (0.80, 1.26). • Use of solvent (yes vs no?): [OR = 1.30, 95% CI (1.03, 1.62)]. • Use of furniture polishes (yes vs no?): OR = 1.01, 95% CI (0.82, 1.24). • Use of glass cleaners (yes vs no?): OR = 0.94, 95% CI (0.74, 1.20). • Use of air fresheners (yes vs no?): OR = 1.09, 95% CI (0.87, 1.37). • Use of multiuse cleaners (yes vs no?): OR = 0.91, 95% CI (0.73, 1.13). • Use of degreasing products (yes vs no?): [OR = 1.32, 95% CI (0.97, 1.79)]. • Use of spray (yes vs no?): [OR = 1.37, 95% CI (1.10, 1.69)]. • Pattern use (furniture polishes, glass cleaners and air fresheners)(yes vs no?): [OR = 0.93, 95% CI (0.73, 1.92)]. •

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
			<p>Wheezing</p> <ul style="list-style-type: none"> • Pattern use (spray and solvent)(yes vs no?): [OR = 1.68, 95% CI (1.21, 2.35)]. • Pattern use (bleach and ammonia)(yes vs no?): [OR = 1.01, 95% CI (0.78, 1.30)]. • Spray use only during pregnancy (yes vs no?): [OR = 1.62, 95% CI (1.11, 2.36)]. • Spray use only after pregnancy (yes vs no?): [OR = 1.34, 95% CI (0.80, 2.24)]. • Spray use during pregnancy and after pregnancy (yes vs no?): [OR = 1.61, 95% CI (1.08, 2.41)]. • Solvent use only during pregnancy (yes vs no?): [OR = 1.04, 95% CI (0.71, 1.51)]. • Solvent use only after pregnancy (yes vs no?): [OR = 0.87, 95% CI (0.55, 1.37)]. • Solvent use during pregnancy and after pregnancy (yes vs no?): [OR = 1.81, 95% CI (0.98, 3.37)]. <p>Air fresheners use only during pregnancy (yes vs no?): [OR = 1.39, 95% CI (0.85, 2.29)].</p> <ul style="list-style-type: none"> • Air fresheners use only after pregnancy (yes vs no?): [OR = 1.75, 95% CI (1.01, 3.04)]. <p>Fresheners use during pregnancy and after pregnancy (yes vs no?): [OR = 1.23, 95% CI (0.79, 1.93)].</p>

TableS4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Liu [2016], China, longitudinal prospective cohort study. A total of 2,299 children from 20 primary schools studied grades 2 to 4 with an average age of 10 years.	Postnatal. Parentals completed a questionnaire regarding household cleaning products at home in the last 12 months. 14 common types of chemical cleaning products such as cleaning the bathroom, floor, glass, kitchen, tiles, and leather; multipurpose cleaners; nonchlorinated bleach; chlorinated bleach; sanitisers; scented air fresheners; nonscented air fresheners; insecticides; and others.	Parental completed questionnaire on non-infectious rhinitis in children. Rhinitis was categorized into one of the 4 mutually exclusive rhinitis patterns, namely never (no rhinitis in any season), occasional (had rhinitis in _3 seasons but did not have rhinitis in >_4 consecutive seasons), and persistent (had rhinitis in >_4 consecutive seasons).	<p>TCB score (continues, ORs expressed for a 10-unit increase):</p> <ul style="list-style-type: none"> Occasional rhinitis pattern: OR = 1.21, 95%CI (1.05,1.41). Frequent rhinitis pattern: OR = 1.36, 95%CI (1.13,1.60). Persistent rhinitis pattern [OR = 1.12, 95%CI (1.01,1.56)]. <p>TCB score (tertile category T2 vs T1)</p> <ul style="list-style-type: none"> Occasional rhinitis pattern [OR = 1.03, 95%CI (0.81,1.31)]. Occasional rhinitis pattern [OR = 1.29, 95%CI (1.01,1.65)]. Frequent rhinitis pattern [OR = 1.35, 95%CI (0.96,1.91)]. Frequent rhinitis pattern [OR = 1.97, 95%CI (1.40, 2.76)]. Persistent rhinitis pattern [OR = 1.08, 95%CI (0.70, 1.67)]. Persistent rhinitis pattern [OR = 1.67, 95%CI (1.10, 2.54)].

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Casas [2015], Spain, Netherlands & Finland, cross-sectional study. Pupils aged 6–12 years from 18 schools in Barcelona province (Spain) N = 2,690, 19 schools in Utrecht province (the Netherlands) N = 2,490 and 17 schools in Eastern and Central Finland (N = 3,922).	Postnatal. Bleach use was defined by a positive answer to the following question “Do you or anybody else use bleach to clean the child’s home at least once a week?”. In addition, information on the weekly use of bleach for school cleaning was asked in a subset of the schools.	Self-administered questionnaires on respiratory health were administered by parents. Frequency (never, once, twice and ≥3 times) of infections (influenza, tonsillitis, sinusitis, otitis, bronchitis and pneumonia) in the past 12 months were reported.	<p>Weekly use of bleach (yes vs no?):</p> <p>Spain</p> <ul style="list-style-type: none"> Once bronchitis [OR = 1.12, 95%CI (0.75,1.64)]. Recurrent bronchitis [OR = 1.22, 95%CI (0.80, 1.85)]. Any infection [OR = 1.21, 95%CI (0.97, 1.51)]. Recurrent any infection [OR = 1.28, 95%CI (1.28, 95% CI (1.00, 1.63)]. <p>Netherlands</p> <ul style="list-style-type: none"> Once bronchitis [1.28, 95%CI (0.78, 2.09)]. Recurrent bronchitis [OR = 0.93, 95%CI (0.56, 1.55)]. Once any infection [1.09, 95% (0.90, 1.33)]. Recurrent any infection [1.02, 95% CI (0.81, 1.29)]. <p>Finland</p> <ul style="list-style-type: none"> Once bronchitis [1.03, 95% (0.60, 1.75)]. Recurrent bronchitis [OR = 1.76, 95% CI (0.68, 4.53) Once any infection [OR = 0.93, 95%CI (0.68, 1.27)]. Recurrent any infection [OR = 1.39, 95% CI (0.97, 2.00)].

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Krauss-Etschmann [2009], Spain, German and Hungary, cross-sectional study, study population consisting of 106 Spanish, 45 German and 25 Hungarian infants.	Prenatal. Parents completed questionnaires on the use of room disinfectant or spray (daily, at least once per week, occasionally, never).	Parents completed questionnaires on respiratory, cutaneous, and allergic symptoms as well as physician-diagnosed allergic disease in children at age 4 years. These include asthma, wheezing, atopic eczema and rash.	<p>Current use of room disinfectants (yes vs no?):</p> <ul style="list-style-type: none"> • Asthma ever: OR = 1.1, 95%CI (0.4-2.8) • Asthma (past 12 months diagnosed): OR = 4.3, 95%CI (0.5-40.3) • Wheezing ever: OR = 0.9, 95% CI (0.5-2.1) • Atopic eczema ever: OR = 2.6, 95%CI (1.2-5.6) • Atopic eczema (past 12 months diagnosed): OR = 7.0, 95%CI (1.8-27.1) • Rash ever: OR = 2.5, 95%CI (1.1-6.0) • Rash (past year for 6 months): OR = 1.8, 95%CI (0.7-4.7)

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
Liu [2018], Hong Kong, Longitudinal prospective cohort study, primary-school children form 20 primary schools (N = 1812) with an average age of 10 years.	Postnatal, parental or guardians completed questionnaires on the use of 14 common types of chemical cleaning products such as bathroom cleaner, floor cleaner, glass cleaner, kitchen cleaner, tile cleaner, leather cleaner, multipurpose cleaner, non-chlorinated bleach, chlorinated bleach, sanitiser, scented air freshener, unscented air freshener, insecticide and other chemical products in the last 12 months.	Parental and guardian completed questionnaires on allergic dermatitis which was defined as skin inflammation with clinical symptoms including a red rash, bumps, a burn-like rash on the skin, itchy, painful or burning skin, blisters and leaking fluid.	allergic dermatitis and cumulative chemical burden score: <ul style="list-style-type: none"> • Tertile 2 vsTertile 1: OR = 1.16, 95% CI (0.67, 2.00). • Tertile 3 vsTertile 1: OR = 1.24, 95% (0.73, 2.14). Cumulative chemical burden score (Every 5-unit increment) <ul style="list-style-type: none"> • Allergic dermatitis: OR = 1.01, 95%CI (0.98, 1.03) Cleaning-product usage and risk of allergic dermatitis: Pattern I <ul style="list-style-type: none"> • Tertile 2 vsTertile 1: OR = 0.80, 95% CI (0.46, 1.38) • Tertile 3 vsTertile 1: OR = 1.08, 95% CI (0.65,1.81) Every 5-unit increment <ul style="list-style-type: none"> • Allergic dermatitis: OR = 1.60, 95% CI (0.64, 3.2) Pattern II <ul style="list-style-type: none"> • Tertile 2 vsTertile: OR = 1.52, 95% CI (0.90, 2.61) • Tertile 3 vsTertile 1: OR = 1.16, 95% CI (0.66, 2.03)

Table S4: (continued)

First Author [year], location, study design & population characteristics	Summary of method		Main findings
	Exposure timing & exposure assessment	Health outcomes	
			<p>Every 5-unit increment</p> <ul style="list-style-type: none"> • Allergic dermatitis: OR = 0.90, 95% CI (0.23, 2.3) <p>Pattern III</p> <ul style="list-style-type: none"> • Tertile 2 vs Tertile1: OR = 1.18, 95%CI (0.69, 2.01) • Tertile 3 vsTertile 1: OR = 1.05, 95% CI (0.61, 1.82) <p>Every 5-unit increment</p> <ul style="list-style-type: none"> • Allergic dermatitis: OR = 1.41, 95% CI (0.48, 2.76) <p>Pattern IV</p> <ul style="list-style-type: none"> • Tertile 2 vs Tertile1: 0.99, 95% CI (0.58, 1.69) • Tertile 3 vsTertile 1: OR = 0.93, 95%CI (0.54, 1.59) • Allergic dermatitis: OR = 0.78, 95%CI (0.26, 2.23)

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Chapter 5: Environmental and Occupational Exposure to Pesticides and Human Health Effects in Tanzania: Current Understanding and Future Opportunities

Joseph S. Bukalasa

INTRODUCTION

Pesticides are substances or mixtures of products intended for preventing, destroying, repelling or mitigating pests. These include herbicides, fungicides, insecticides, nematicides and acaricides that control pests such as weeds, fungi, insects, nematodes and mites. Pesticides are toxic by definition and cannot differentiate target from non-target species of plants and animals, and hence should essentially be subject to safe use by humans.

The non-compliant and indiscriminate use of pesticides can play an important role in accidents that have occurred in different parts of the world including developing countries. Since pests like human beings are eukaryotes in nature, some of the targets of harmful effects of pesticides can occur in the human body too. When a human being is exposed to pesticides, the pesticide interacts with enzymes, receptors, proteins, or membranes, among other human body components.

In most cases, humans come into contact with pesticides in the field during pesticide application on crops for controlling pest and plant diseases, during weeding, pruning or harvesting and re-entry of treated fields during the collection of firewood or vegetables (Kapeleka et al., 2019, Mwabulambo et al., 2018, Manyilizu et al., 2017, Manyilizu et al., 2016, Mrema et al., 2017, Da Silva et al., 2016, Ngowi et al., 2007, Okonya et al., 2019, Soko, 2018). Pesticide exposure can also occur in homes when insecticides are applied for domestic use to kill mosquitoes, cockroaches, fleas and flies (Salameh et al., 2003) or when people are living close to the treated agricultural fields (Bukalasa et al., 2017) or by unsafe storage of pesticides (Debela et al., 2019).

The presence of pesticides in foods such as fish, fruits, maize, vegetables and even in mother's milk is of great concern in African countries as these may be associated with adverse health effects (Muller et al., 2019, Muller et al., 2017, Adeyeye et al., 2019, Forkuoh et al., 2018, Mahugija et al., 2017, Farahy et al., 2021, Galani et al., 2020).

Agricultural Health Surveys have indicated that pesticide exposure might be associated with central nervous system (CNS) inflammation, dermatitis (skin irritation, psoriasis), vision issues (burning, tingling), muscle cramps, respiratory issues (cough), gut disturbances (nausea, vomiting), and reproductive issues (infertility) (Toe et al., 2013, Mathew et al., 2015).

This chapter provides an overview of legislation, the current situation and the way forward in the implementation of research on environmental and occupational exposure to pesticides in relation to human health effects in Tanzania.

AGRICULTURE IN TANZANIA

As the pillar of both the domestic and the export economy, the agricultural sector in Tanzania engaged 80 percent of the labour force, which equaled 13.495 million in 1999 while providing 49 percent of the country's GDP. Agricultural products include coffee, sisal, tea, cotton, pyrethrum, cashew nuts, tobacco, cloves, corn, wheat, cassava, bananas, and vegetables. Agricultural output remains predominately based on smallholder production, as opposed to large farms, though the latter does account for some sisal, tea, coffee, tobacco, rice, wheat, and wattle production. Cash crops, such as coffee, tea, cotton, cashew nuts, sisal, cloves, and pyrethrum account for the vast majority of export earnings. Maize, paddy, wheat, and cassava are produced for both commercial and domestic consumption. In Zanzibar, the major cash crop is cloves, 90 percent of which are produced on the island of Pemba.

PESTICIDES REGISTRATION IN TANZANIA

Pesticides registration in Tanzania is governed by the plant protection Act (PPA) No. 13 of 1997 (PPA) (The United Republic of Tanzania Ministry of Agriculture, 2019a) and the Plant Protection Regulations of 1999 made under Section 42 (1) of the PPA (The United Republic of Tanzania Ministry of Agriculture, 2019b). Section 17 of the PPA sets out procedures for the application for the registration of pesticides, and Section 18 requires registration and publication in the Government Gazette of a list of registered pesticides used in Tanzania. Things to note, all pesticides imported into Tanzania must be registered. However, some of the pesticides are imported illegally into the country from other countries bordering Tanzania.

Furthermore, the registration procedures are conducted by assessing the technical dossiers to evaluate the impacts on human health, ecosystems and the environment. When the pesticides under registration do not pose risks to human health, ecosystems and the environment then permission is granted to carry out bio-efficacy (a measure of the biological efficacy of active ingredients of agrochemicals such as insecticides, fungicides, herbicides, etc.) testing for effectiveness and assessments for the intended uses of the pesticides. The technical dossiers and the bioefficacy reports of the pesticides are subsequently submitted for approval to the Pesticides Approval and Registration Technical Subcommittee (PARTS) and endorsed by the National Plant Protection Advisory Committee (NPPAC).

UNREGISTERED PESTICIDES IN TANZANIA

In Tanzania, like in many other African countries, there is the widespread use of unregistered pesticides in agriculture such as pesticides with the trade name ‘voltrad’ which has not been registered in Tanzania but is registered in Mozambique even though the pesticide active ingredient is not known. This type of pesticide is used by the farmer to control insect pests

in cashnut plantations in the southern part of Tanzania. Other unregistered pesticides that are imported illegally and used for agricultural pests in some parts of the country are abamite (abamectin), doom (dichlorvos 76% EC), boss (permethrin), lava (dichlorvos 1000g/L), lethal (paraquat dichloride) and romectin (abamectin 18g/L). The active substances in most of the unregistered pesticide products are not well known to farmers or regulatory authorities. Therefore, the health risks associated with such unregistered pesticide products are not known by the farmers. These types of pesticides possibly generate human health effects among farming communities, however, no studies have been done on those effects.

There is the smuggling of unregistered pesticides from neighbouring countries (Mozambique, Uganda, Kenya and Burundi) through unofficial points of entry and in the Democratic Republic of Congo through smuggling across Lake Tanganyika. This happens because some of these countries have weak pesticide laws, regulations and control mechanisms. However, some efforts have been made to ensure farmers and other end-users have access to safe and quality pesticide products. These efforts include testing for quality verification of all consignments arriving from the official border, registering all pesticides imported into Tanzania and conducting pesticide control mechanisms such as regular inspections and training in the proper handling of pesticides. It is hoped that regular inspection and training on the identification of unregistered pesticides may reduce the illegal importation of unregistered pesticides. This may increase awareness among the farmers and other end-users on the risks of using unregistered pesticide products on their crops and personal health.

OVERVIEW OF PESTICIDE USE IN TANZANIA

There is a growing use of pesticides in agriculture in Sub Sahara Africa due to an increase in population and demand for food production for consumption and business (Isgren and Andersson, 2021, Soko, 2018). But also, the emerging of new pests and associated plant diseases such as fall armyworm (*Spodoptera frugiperda*) which originated from Latin America contribute to the increase in the importation of pesticides for controlling those pests and diseases on crops. In Uganda, the most widely used active ingredients are glyphosate (79%), cypermethrin (60%), mancozeb (55%) and pyrethroids (49%) (Fuhrmann et al., 2021a, Fuhrmann et al., 2022). This indicates that most of the pesticides used in Uganda are herbicides, insecticides and fungicides. While in Malawi, farmers mostly use insecticides, fungicides, herbicides, fumigants, nematicides, acaricides and rodenticides. These pesticides are mainly used for tobacco, tea, sugarcane, coffee, cotton, and maize crops (Soko, 2018). Moreover, in Tanzania, the most used pesticide group in the Southern Agricultural Growth Corridor of Tanzania (SAGCOT) zone was pyrethroids (31%) followed by carbamates (25%) and organophosphates (21%) (Chilipweli et al., 2021). In addition, most pesticides used in Tanzania are insecticides, herbicides and fungicides (Data from Registrar of Pesticides Tanzania). Most of the pesticides used in Tanzania are imported from China, India, the United States of America and European Countries as formulations of pesticide products. In recent years, pesticide importation has increased due to the liberalisation of agrochemicals trade in the country. For instance, the number of pesticide import permits issued to agro-dealers has increased from 320 to 388 during the financial years 2014/15 and 2015/16, respectively (Data from Registrar of Pesticides Tanzania). Similarly, for the year 2017, the number of pesticides imported was 4,039,243 litres and 4,514,345 kg (Data from Registrar of Pesticides Tanzania). One of the greatest challenges is that the total volume of pesticides used by farmers per year is not well documented because of fragmented data

systems. The country has established a Pesticides Stock Management System (PSMS), therefore, the problem of fragmented data will hopefully be solved soon.

Figure 1: Map of the United Republic of Tanzania

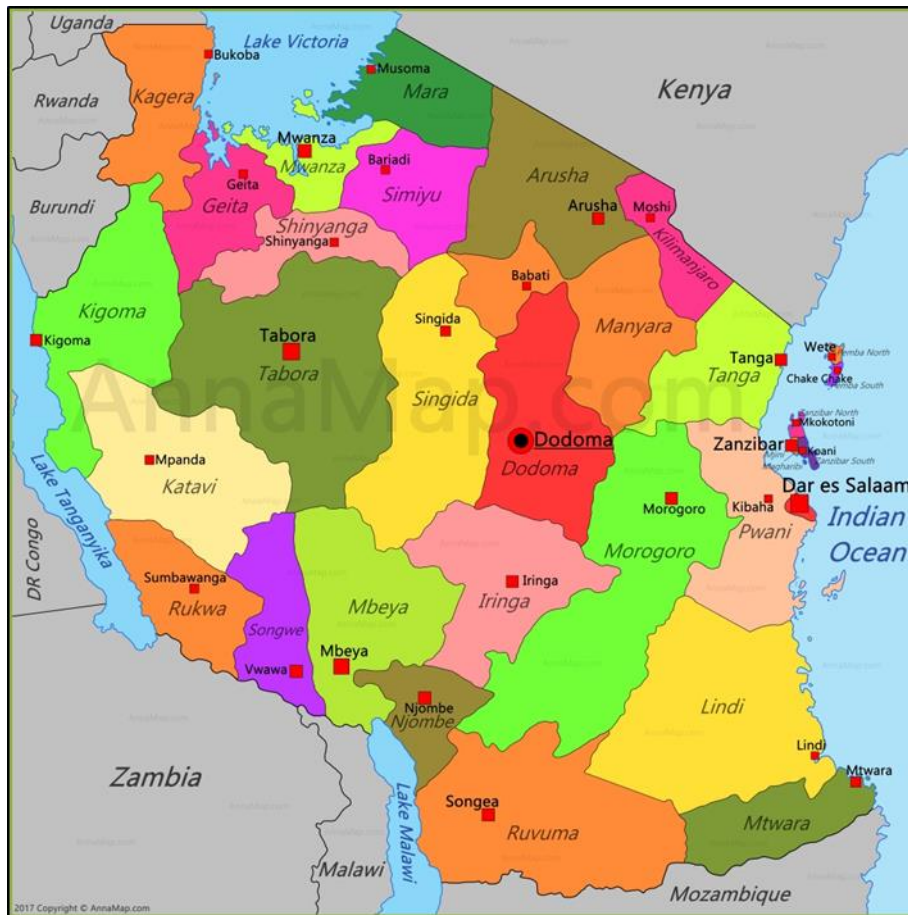


Figure 1 is the map of the United Republic of Tanzania indicating thirty-one regions. Each region is subdivided into districts and the districts are sub-divided into divisions and further into local wards. Moreover, wards are further subdivided for management purposes for urban wards into streets and rural wards into villages and the villages may be further subdivided into hamlets.

There are different crops grown in the thirty-one regions of the United Republic of Tanzania. For instance, cotton is grown in the regions around Lake Victoria while coffee is grown in

the region around Mount Kilimanjaro, Lake Victoria and the southern plains regions. The regions in the southern part of Tanzania are known for cashnut farming, which means different types of pesticides are applied in these thirty-one regions.

LIST OF REGISTERED PESTICIDES IN TANZANIA

There are several pesticides used in Tanzania to control different types of pests and diseases as indicated in Table S1 – 2. Some of the pesticide-active ingredients have been registered in Tanzania and European countries while others have been only registered in Tanzania by local and international registrants from European and Asia countries. However, some of the pesticides active ingredients registered in Tanzania have been banned in the EU for one or the other reason (Table S1 – 2). Pesticides can be registered for use in Tanzania but banned in European countries because alternative pesticides' active ingredients to replace Highly Hazardous Pesticides (HHPs) registered in Tanzania are expensive. Moreover, in the financial year 2020/2021, twenty-one (21) Highly Hazardous Pesticides (HHPs) active ingredients were deregistered from the list of registered pesticides in Tanzania for causing high levels of acute or chronic hazards to health or the environment according to internationally accepted classification systems such as those used by WHO or Global Harmonized System (GHS) (Data from Registrar of Pesticides of Tanzania).

GROUPS OF PESTICIDES

These include the pyrethroids, rotenoids, nicotinoids and a fourth group that includes strychnine and scilliroside. Many pesticides can be grouped into chemical families. Prominent insecticide families include organochlorine, organophosphates and carbamates.

Organophosphorus (OP) Insecticides

Organophosphorus (OP) insecticides are phosphoric acid esters or thiophosphoric acid esters and are commonly applied by farmers around the world to protect crops (John and Shaik, 2015, Grube et al., 2011). They include ethyl parathion, chlorpyrifos, malathion and others. There are health risks of exposure to OP and these have been indicated in Table S1 -2. It is well established that OP can inhibit acetylcholinesterase enzyme by the accumulation of acetylcholine in the nervous tissue and effector organs, with the principal site of action being the peripheral nervous system (Patel and Sangeeta, 2019).

Carbamate Insecticides

A carbamate is an organic compound derived from carbamic acid. A carbamate group, carbamate ester, and carbamic acids are functional groups that are interrelated structurally and are often interconverted chemically. The human toxicity of carbamate insecticides varies according to the phenol or alcohol group. One of the most widely used carbamate insecticides in Tanzania is carbaryl and carbosulfan. They are not persistent in the environment because they are readily hydrolysed. Carbamate insecticides are like organophosphate insecticides, the mode of action of the carbamate insecticides is acetylcholinesterase inhibition with the important difference that the inhibition is more rapidly reversed than with organophosphate insecticides (Patel and Sangeeta, 2019).

Pyrethroid Insecticides

Pyrethroids are a class of synthetic insecticides based on pyrethrins isolated from the *Chrysanthemum* genus of plants (Rauch et al., 2018). They were developed in the 1970s, after two other major classes of insecticides, organophosphates and carbamates were developed (Costa, 2015). Pyrethroids are a special chemical class of active ingredients found

in many modern insecticides. The name pyrethroid means “pyrethrum-like” and refers to the origin of this class of pesticides. Pyrethroids include cypermethrin, deltamethrin, permethrin and lambda-cyhalothrin. They are known to affect nerve membranes by modifying the sodium and potassium channels, resulting in the depolarization of the membranes (Chrustek et al., 2018).

Pyrethroid insecticides contain synergist piperonyl butoxide which acts to increase the efficacy of the insecticide by inhibiting the cytochrome P240 enzyme responsible for the breakdown of the insecticides. They are among the most commonly used insecticides in agriculture; they are also widely used indoors in pet shampoo, lice treatment, and insect repellents. Pyrethroids have a half-life of fewer than 24 hours and they are therefore rapidly metabolized once absorbed into polar metabolites, easily eliminated primarily in the urine (Glorennec et al., 2017).

Herbicides

Herbicides are commonly known as weedkillers and are used to control unwanted plants. They control specific weed species while leaving the desired crop relatively unharmed. They include bentazone, glyphosate, s-metolachlor, 2, 4-D amine salt, iodosulfuron-methyl-sodium and atrazine (Table S1 -2). The mode of action depends upon the specific herbicides at work, it may involve a plant enzyme or a biological system that the herbicides may interrupt, thus injuring or disrupting the regular plant growth and development and causing eventual plant death.

Atrazine may cause endocrine disruptions respiratory tract, skin and eye irritations. Therefore, further studies are needed to address the health effects caused by environmental and occupational exposure to atrazine in children and adults in Tanzania. These pesticides are still registered to be used in Tanzania for agricultural purposes.

There is also great concern about the use of glyphosate in Tanzania and some other African countries due to environmental and human health effects. However, there are no published studies that indicate environmental and human health effects either caused by the use of atrazine or glyphosate in Tanzania. We found that there are other studies on the human effects of exposure to glyphosate in high-income countries (Portier et al., 2016, Andreotti et al., 2018, Agostini et al., 2020). Moreover, there is a study that indicates the groundwater atrazine concentrations are greater than the European maximum permissible level for drinking water in South Africa (Rimayi et al., 2018). This indicates that there is a significant risk of the consumption of contaminated groundwater in South Africa.

Fumigants

Fumigants are gaseous pesticides that control pests in agricultural fields, in structures such as buildings and apartments, storage houses and various other sites. They are generally biocides chemicals that can kill or injure living organisms with which they come in contact. Fumigants include aluminium phosphide, dichlorvos, permethrin plus pirimiphos-methyl, spinosad, pirimiphos-methyl and methyl bromide (Table S1 - 2). However, methyl bromide has been banned from use elsewhere because it may cause serious eye irritation, skin irritation, respiratory irritation, genetic defects and damage to organs such as the central nervous system or kidneys through prolonged or repeated exposure. It may also cause ozone depletion in the stratosphere. In Tanzania, fumigants have been categorised into restricted registration categories for the fumigation of consignments (agricultural produces) going to India only. The use of fumigants is associated with an increased risk of respiratory distress, cardiac arrest and central nerve effects (Table S1 -2).

Organochlorine (OCPs) Insecticides

The period between 1935 and 1950 was characterized by the development of DDT and other chlorinated hydrocarbon insecticides (Costa, 2015). The first patent was obtained in 1940, and from the beginning of 1942, the preparation appeared on the market under the names Gesarol and Neocid, among others (Holmstedt and Liljestrand, 1963). Organochlorine pesticides include DDT, methoxychlor, dieldrin, chlordane, toxaphene, mirex, kepone, lindane, and benzene hexachloride.

Except for DDT and lindane, which still have limited uses, all organochlorine insecticides have been banned in most countries in the past 40 years, primarily because of ecologic considerations (Costa, 2015). In Tanzania, OCPs have been banned for any purpose since the 1990s. However, there is a relatively small body of literature that is concerned with the detection of OCPs in the environment, poultry farms and human biological samples in Tanzania (Muller et al., 2019, Muller et al., 2017, Elibariki and Maguta, 2017, Kishimba et al., 2004, Mwevura et al., 2002, Mahugija et al., 2017). This signifies the existence of illegal uses of these banned pesticides which can be attributed to the lack of rigorous legislation and regulations to control pesticides, lack of training programs for personnel to inspect and monitor the pesticides used as well as lack of training programs for pesticide consumers. Also, the stability of OCPs pesticides in the environment has contributed to their presence in the environment. However, there is no evidence of continued illegal use of OCPs in Tanzania but there is evidence that current OCPs pollution in Kenya originated from recent usage of DDT pesticides to control insect-borne diseases in agriculture (Mungai and Wang, 2019). We suggest further investigation to see whether this is common in Tanzania, especially in areas on the border with Kenya.

BIOLOGICAL MECHANISMS

Pesticides induce disorders in humans through several mechanisms of action such as inflammation, oxidative stress, mitochondrial dysfunction and cell death (Franco et al., 2009). They enter the human body through inhalation, ingestion or dermal exposure (Toe et al., 2013, Atabila et al., 2018). Moreover, the fate of the pesticides in the human body depends on the path of entry such as oral, ocular, dermal, and respiratory tract. Some of the pesticides may enter the blood, interstitial fluid, and lymph fluid, and be transported to different organs. The lipophilic pesticides gravitate towards the human adipose tissues. The sentinel myeloid cells find these exogenous substances alien and offensive (Hovey and Aimo, 2010, Hefetz-Sela and Scherer, 2013, Williams et al., 2016). Consequently, the immune system is activated, to vanquish the invaders, and a series of inflammatory cytokines are released, leading to tissue damage (Trivanovic et al., 2016).

Many pesticides are inflammatory and genotoxic. For instance, organophosphorus pesticides have been proven to induce DNA damage and increase the serum levels of inflammatory markers (IL10, CRP (C-reactive protein)) (Taghavian et al., 2016). These cytokines increase extracellular acidity, which in turn activates the acid-sensing ion channels, leading to pain and anxiety (Wemmie et al., 2013, Li and Xu, 2015, Li et al., 2016). Neurotoxicant pesticides may induce Parkinson's disease, where the progressive degeneration of dopaminergic neurons in the midbrain substantia nigra leads to the impairment of motor skills (Costa et al., 2008, Reeve et al., 2014, Pathak-Gandhi and Vaidya, 2017).

Acetylcholinesterase is an esterase class enzyme and it is expressed in the synapses and on red blood cell membranes, playing a key role in neural functioning through cholinergic pathways (Silman and Sussman, 2008). It hydrolyzes the neurotransmitter acetylcholine, thus terminating nerve impulses (Colovic et al., 2013). Organophosphate and carbamate groups of pesticides target acetylcholinesterase and inhibit their activity, which results in the

accumulation of acetylcholine (Lionetto et al., 2013). The overstimulation of the acetylcholine receptors in synapses leads to diverse neural pathologies (Eddleston et al., 2008, Colovic et al., 2013). Depression is one of the common outcomes of this over-activity of acetylcholine (Strelitz et al., 2014). Others include dizziness, headache, nausea, difficulty in breathing, and, in extreme cases, sudden death.

EPIDEMIOLOGICAL STUDIES

Environmental Exposure to Pesticides and its associated human health risk

There is a relatively small body of literature related to the association between environmental exposure to pesticides and increased risk of asthma and related respiratory symptoms and other health problems in children and adults in African countries (Table S2). The findings from these studies are inconsistent. For instance, lines of evidence suggest that children living in agricultural areas in Niger have an increased risk of wheezing (Mamane et al., 2016), a trend attributed to living in agricultural areas, increasing the likelihood of exposure to pesticides through inhalation or direct contact with pesticides after pesticide applications resulting in an increase in the metabolites of pesticides in human fluids (Rauch et al., 2018, Ikenaka et al., 2019).

It is possible, therefore, that the amounts of serum DDT and DDE and urinary pyrethroid metabolite in humans depend on the level of DDT and pyrethroid exposure, therefore, the association with adverse health effects should be more common in the participants with a high level of exposure. This was proven by a study conducted in South Africa which indicated that concentrations of DDT, DDE, particularly *p,p'*-DDE, were associated with higher rates of persistent fevers for a 10-fold increase in *p,p'*-DDE (Huang et al., 2018). A study by Huang et al., (2018), revealed that exposure to low levels of *p,p'*-DDT, *p,p'*-DDT,

cis-DBCA, cis-DCCA, trans-DCCA, 3-PBA was not associated with persistent fevers (lasting ≥ 4 days), ear infections and severe sore throat (Huang et al., 2018).

There is some evidence suggesting that DDT or malathion use is not associated with an increased risk of wheezing in a study population at the ages of 0 to more than 70 years in Ethiopia (Yemaneberhan et al., 1997). The finding on the association between DDT or malathion and increased risk of wheezing reported by Yemaneberhan et al. (1997) included both children and adults. Therefore, we cannot rely on these findings because they involved participants from different age groups reported in the same study. Hence, it could conceivably be hypothesized that further studies are needed to confirm whether exposure to DDT or malathion at an established level is associated with an increased risk of wheezing in children and adults.

DDT has been still used in some countries in Africa for malaria vector control. Moreover, exposure to DDT among household members can be reduced through educating the community on safe use as established by national and international guidelines (Eskenazi et al., 2019). However, findings regarding health effects associated with the use of DDT for malaria control can be extrapolated to the areas where DDT is used for malaria control but not to areas such as Tanzania or other African countries whereby malaria is controlled by other synthetic pesticides such as pyrethroid insecticides (Rauch et al., 2018) and biological control agents such as *Bacillus thuringiensis* (Mazigo et al., 2019).

We recognize, however, that take-home pesticide exposure by farmers and proximity to treated fields are a source of pesticide exposure (Lopez-Galvez et al., 2019). A study has reported that pesticide drift into the home or living or working or both living and working on farms was associated with asthma symptoms among South African women (Ndlovu et al., 2014). However, Ndlovu et al. (2014) found no association between pesticide use at

home or pesticide drift into the home and ocular-nasal symptoms, doctor-diagnosed asthma, adult-onset asthma and current asthma in South African women.

On the issue of dietary exposure and risk assessment of pesticide residues in African countries, several questions demand answers. For instance, the association between dietary exposure to pesticides and increased risk of asthma and related respiratory symptoms in children and adults in Sub Sahara Africa is unclear. We found only one published study on pesticide dietary exposure and risk assessment (Buah-Kwofie et al., 2019). This study indicated that dietary exposure to organochlorine pesticide residues in rural communities living within iSimangaliso World Heritage Site in South Africa had higher levels of organochlorine than international standards. Although dietary exposure to OCP leads to more gastrointestinal or systemic effects, therefore, studies such as these should be linked to specific health risks posed by OCP-contaminated food.

A literature review in Table S2 revealed that epidemiological findings on environmental exposure to pesticides and increased risk of asthma and allergic symptoms are inconsistent. A possible explanation for this might be the differences in study designs, population characteristics, the timing of the exposure, exposure assessment and definition of the exposure and endpoints in African studies.

Occupational Exposure to pesticides and their associated human health risk

Very little was found in the literature on the question of self-reported symptoms and occupational exposure to pesticides among small-scale farmers in Tanzania (Wumbei et al., 2019, Illyassou et al., 2019, Lekei et al., 2014b). These studies suggest that self-reported disease symptoms, such as dizziness, chest pain, memory loss, vomiting, diarrhoea, and fever were associated with poor use of protective equipment and unsafe practices of pesticides in adult small-scale farmers in Tanzania (Manyilizu et al., 2017, Da Silva et al.,

2016). However, reported disease symptoms are also related to other diseases such as malaria and others and this makes it difficult for health care providers to link self-reported disease symptoms with pesticide poisoning in agricultural communities in Tanzania (Ngowi et al., 2001a, Lekei et al., 2017). Therefore, findings such as these should be interpreted with caution and further studies are needed to confirm the association between pesticide exposure and self-reported symptoms.

There is a suggestion that long-term pesticide exposure may affect the hemato-biochemical and esterase responses in female farmworkers (Manyilizu et al., 2016). However, further studies need to confirm the extent of pesticide exposure and its association with the effect of hemato-biochemical and esterase responses.

Studies have investigated the association between occupational exposure to pesticides and asthma and other respiratory and allergic symptoms, but findings are inconsistent (Table S3). However, evidence suggests that occupational exposure to pesticides is an important factor for human health effects due to poor practice as most of the farmers do not wear any personal protective equipment (PPE) during mixing/loading or application of pesticides and lack of knowledge on health effects associated with pesticides use (Wumbei et al., 2019, Illyassou et al., 2019, Lekei et al., 2014b).

There is a suggestion that occupational exposure to organophosphate metabolites and some pyrethroid pesticides may be associated with asthma-related cytokines and with non-Th2 cytokines demonstrating consistent relationships in South African farmworkers (Mwanga et al., 2016). However, Mwanga et al.(2016) indicated that occupational exposure to organophosphate pesticides including dialkyl phosphates (DAP, DMP, DMTP, DMDTP, DEP, DETP, DEDTP) and 3,5,6-trichloropyridinol (TCPY) and pyrethroid metabolites (cis-DCCA, trans-DCCA, DBCA, 4F3PBA and 3PBA) was not associated with doctor-diagnosed asthma, adult-onset asthma and current asthma in South African farm workers

(Mwanga et al., 2016). This inconsistency may be due to different levels of pesticide exposure among farm workers. Other studies suggest that occupational exposure to pesticides is associated with chronic cough and shortness of breath among farmworkers in Ethiopia (Negatu et al., 2017). However, Negatu et al. (2017) indicate no association was observed between occupational exposure to pesticides and increased risk of chronic phlegm and wheezing but also no association was found with the decline in lung functions among farm workers.

There were eight (8) studies on occupational exposure to pesticides and human health effects in Tanzania (Kapeleka et al., 2019, Mwabulambo et al., 2018, Lekei et al., 2014b, Lekei et al., 2014a, Da Silva et al., 2016, Manyilizu et al., 2017, Manyilizu et al., 2016, Ngowi et al., 2001b). Those studies investigated how pesticide applicators, small-scale farmers and their families are affected by the use of pesticides by measuring the level of acetylcholinesterase (AChE) activity in the red blood cell and self-reported symptoms. In most cases, small-scale farmers, Agricultural Officers and pesticide applicators were considered ignorant about occupational exposure to pesticides, resulting in a significant number of injuries and death in the community (Lekei et al., 2014b, Ngowi et al., 2007, Ngowi et al., 2002, Ngowi et al., 2001b).

In most cases, occupational exposure to organophosphate and carbamate was reported to be associated with a decrease in acetylcholinesterase (AChE) activity among small-scale farmers in Tanzania (Kapeleka et al., 2019, Mwabulambo et al., 2018). Acetylcholinesterase (AChE) activity is used as an indicator of pesticide exposure in occupational settings and can be linked to asthma and related respiratory symptoms in investigating the magnitude of exposure to organophosphate and carbamate pesticides.

The findings in other African countries cannot be unequivocally extrapolated to Tanzania due to differences in pesticide application techniques, level of education of the farmers and

types of pesticides used in other African countries that are different from what is used in Tanzania. For instance, DDT is still used in South Africa for malaria control but it has been banned in Tanzania for all purposes.

RESEARCH GAPS AND FUTURE DIRECTIONS

In reviewing the literature (Tables S2 &3), we identify that there were no published epidemiological findings on the association between environmental exposure to pesticides and increased risk of asthma or other respiratory symptoms, allergic symptoms, or other diseases in children or adults in Tanzania. This creates an opportunity of investigating the association between environmental exposure to pesticides and respiratory diseases and other related endpoints in both children and adult workers occupationally exposed to pesticides.

Pesticide drift is the airborne movement of pesticides from an area of application to any unintended site. A drift may occur during pesticide application when droplets or dust travel away from the target site. It might also occur after the application when some chemicals become vapours that can move off-site. Pesticide drift can cause accidental exposure of people, animals, plants and property to pesticides. Therefore, there is a need to establish an environmental exposure assessment to identify the extent of pesticide exposure in the study population in low-income countries as previously described (Friedman et al., 2020, Molomo et al., 2021). These assessments may be linked with the endpoints to find out whether there is a link. For instance, evidence suggests a possible link between some pesticide measurements and respiratory and allergic symptoms such as rhinitis and wheezing in children (Raheison et al., 2019, Malaeb et al., 2020, Kudagammana and Mohotti, 2018). Children are more vulnerable to pesticide exposure because they might be exposed to different factors such as environmental and take-home exposure to pesticides, ingestion through environmental exposure to pesticides or breastfeeding through an exposed mother.

There are no studies that established the effects associated with pesticide exposure in children in Tanzania. However, there are few published studies on the identification of factors that contribute to the increased health effects among female horticulture workers in Tanzania and how these effects are associated with exposure to pesticides (Mrema et al., 2017). These factors include inadequate knowledge of the hazardous nature of pesticides, poor hygiene practices, lack of availability of washing facilities, and insufficient adherence to precautionary instructions on pesticide labels. There is a need to establish exposure assessments in children and women to establish evidence-based studies in Tanzania.

There is abundant room for further progress in determining the association between occupational exposure to pesticides and adverse human health effects among small-scale farmers in Tanzania. This is because most of the studies conducted on occupational exposure to pesticides and human health effects in Tanzania were based on a cross-sectional study design. This type of study design does not provide a clear indication of the magnitude of the problem compared to longitudinal studies such as cohort studies. Therefore, we suggest longitudinal studies on the association between occupational exposure to pesticides and human health effects, specifically on small-scale farmers.

Most of the pesticides used in Tanzania are organophosphates and carbamates groups. These types of pesticides have been identified as an inhibitor of acetylcholinesterase enzymes. This would be a fruitful area for further work in Tanzania whereby most of the pesticides used are organophosphate and carbamates groups.

Children of farm workers may be exposed to pesticides through the take-home exposure pathway (Lopez-Galvez et al., 2019). However, no study has been established in Tanzania to assess the take-home pesticide exposure pathway, therefore, this would be a fruitful area for further work.

Few studies investigated the presence and concentrations of several organochlorine pesticides and current-use pesticides in the air using spatial and seasonal variations and the occurrence of pesticide mixtures in Africa (Veludo et al., 2021). But also, using silicone wristbands, 16 out of 21 targeted pesticides were detected in children and their guardians (ten current-use pesticides in agriculture or at the household level and six legacies OCPs) in South Africa (Fuhrimann et al., 2021b). There is, therefore, a definite need for similar studies to be conducted in Tanzania as the findings of that study would have several important implications for environmental exposure to pesticides that might be linked with health effects in future studies and policy change.

CONCLUSION

This chapter provides an overview of legislation, the current situation and the way forward in the implementation of research on environmental and occupational exposure to pesticides and human health effects in Tanzania. It is, therefore, described as an opportunity for the development of studies to investigate the effects of environmental exposure to pesticides on the development of asthma and related respiratory symptoms in children. However, this chapter cannot provide a comprehensive review of the effects of pesticide exposure on human health in Tanzania due to limited data and literature on the subject.

Tables

Table S1: Pesticides registered in Tanzania and associated potential human health effects

ACTIVE SUBSTANCES ^a	USAGE IN TANZANIA	POTENTIAL HEALTH ISSUES
Acephate ^a	Control of Aphids and Lepidoptera larvae on Tobacco, cotton and vegetables.	Carcinogen, Endocrine disrupter, Cholinesterase inhibitor, Neurotoxicant or Skin irritant.
Acetochlor	Control of Preemergence and annual grasses and certain broadleaf weeds on Horticultural Crops on maize.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Respiratory tract irritant, Skin irritant or Skin sensitizer.
Alachlor	Control of Preemergence and annual Grasses and certain broadleaf weeds on Maize, Beans and Vegetables.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Skin irritant or Eye irritant.
Aluminum phosphide	Control of larger grain borer (<i>Prostephanutracatus</i>) and weevils (<i>Sitophilus zeamais</i>) on maize storage.	Reproduction/development effects, Respiratory tract irritant or Eye irritant.
Amitraz ^a	Control of Mange, mites, ticks and lice on cattle	Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant or Skin sensitizer.
Azocyclotin	Control of spider mites on roses in Greenhouse and insect pests on roses.	Reproduction/development effects, Respiratory tract irritant, Skin irritant or Eye irritant.
Bentazone	Control of Broad-leaved weeds and sedges on Rice, maize and beans.	Skin sensitizer or Eye irritant.
Beta-Cyfluthrin	Control of <i>Helicoverpa amigera</i> , <i>Aphis gossypi</i> and insect pests on cotton and horticultural crops.	Endocrine disrupter, Reproduction/development effects or Neurotoxicant.
Buprofezin	Control of Various Insect pests on Horticultural Crops	Carcinogen or Reproduction/development effects.
Carbaryl	Control of household pests (bedbugs, cockroaches, etc).	Carcinogen, Endocrine disrupter, reproduction/development effects, Cholinesterase inhibitor or Neurotoxicant.
Carbofuran	Control of Nematodes on Horticultural Crops	Endocrine disrupter, Reproduction/development effects, Cholinesterase inhibitor, Neurotoxicant, Chromosome aberration or Genome mutation.
Chlorpyrifos	Chewing and Sucking insect, Mosquito and Subterranean termites control.	Endocrine disrupter, Reproduction/development effects, Cholinesterase inhibitor, Neurotoxicant or Skin sensitizer.
Copper Hydroxide	Control of Coffee Berry Diseases and various fungal diseases on Coffee, Tomatoes, Beans and peanuts.	Reproduction/development effects, Respiratory tract irritant, Skin irritant, or Eye irritant.

Table S1: Cont.

ACTIVE SUBSTANCES ^a	USAGE IN TANZANIA	POTENTIAL HEALTH ISSUES
Cypermethrin	Control of Aphids on cabbage.	Carcinogen, Chromosome aberration, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Respiratory tract irritant or Eye irritant.
Cyproconazole	Control of Coffee leaf rust on coffee.	Carcinogen, Endocrine disrupter, Reproduction/development effects or Respiratory tract irritant.
Cyproconazole	Control of Coffee leaf rust on coffee.	Carcinogen, Endocrine disrupter, Reproduction/development effects or Respiratory tract irritant.
Cyromazine	Control of various Insect pests on horticultural crops	Reproduction/development effects, Respiratory tract irritant or Skin irritant.
Fenitrothion	Chewing and sucking pests.	Endocrine disrupter, Reproduction/development effects, Cholinesterase inhibitor, Skin irritant or Skin sensitizer.
Fenvalerate	Control of Cotton against chewing & sucking insect pests on cotton.	Endocrine disrupter, Neurotoxicant, Respiratory tract irritant, Skin irritant, Skin sensitizer or Eye irritant.
Fipronil	Control of Various Insect pests on Horticultural Crops.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant or Eye irritant.
Fipronil	Control of Various Insect pests on Horticultural Crops.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant or Eye irritant.
Flufenacet	Control of Pre emergence weeds on Wheat and Barley.	Reproduction/development effects, Respiratory tract irritant, Skin sensitizer or Eye irritant.
Fluometuron	Control of Broad-leaved weeds on cotton.	Carcinogen, Reproduction/development effects, Cholinesterase inhibitor or Respiratory tract irritant.
Glyphosate	Control of Annual and perennial grasses and broad-leaved weeds on wheat.	Carcinogen, DNA damage/repair Endocrine disrupter, Skin irritant or Eye irritant.
Hexaconazole ^a	Control of Leaf Rust on coffee; Powdery Mildew on cashew and Various fungal diseases on horticultural crops.	Carcinogen, Endocrine disrupter, Skin irritant, Skin sensitizer or Eye irritant.
Imidacloprid	Control of Aphids and Various insects pests on Horticultural and roses	Reproduction/development effects, Neurotoxicant, Skin irritant or Eye irritant.
Malathion	Control of Aphids on cabbages	Carcinogen, Endocrine disrupter, Reproduction/development effects, Cholinesterase inhibitor, Neurotoxicant, Respiratory tract irritant or Skin sensitiser.

Table S1: Cont.

ACTIVE SUBSTANCES^a	USAGE IN TANZANIA	POTENTIAL HEALTH ISSUES
Mancozeb	Control of Anthracnose scab, late blight, rust and Mildews on Vegetables, beans and fruits.	Carcinogen, Unspecified genotoxicity type, Endocrine disrupter, Reproduction/development effects, Respiratory tract irritant or Eye irritant.
Metolachlor ^a	Control of Weed on beans.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Skin irritant, Skin sensitizer or Eye irritant.
Metribuzin	Control of Pre-emergence weed on sugarcane.	Endocrine disrupter or Reproduction/development effects.
MSMA (methyl arsonic acid)	Control of Weed on sugarcane.	Carcinogen, Respiratory tract irritant, Skin irritant or Eye irritant.
Nicosulfuron	Control of Weeds on horticultural Crops.	Respiratory tract irritant, Skin irritant, Skin sensitizer or Eye irritant.
Novaluron	Control of Diamondback moth and various insect pests on Cabbage and horticultural crops.	Respiratory tract irritant or Skin irritant.
Oxadiazon	Control of Various Weeds on Lowland Rice	Carcinogen, Reproduction/development effects or Respiratory tract irritant.
Permethrin	Control of Mosquitoes by treated net	Carcinogen, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant or Eye irritant.
Pirimiphos-methyl	Control of larger grain borer(<i>Prostephanus truncatus</i>) and weevils (<i>Sitophilus zeamais</i>) on maize.	Eye irritant
Profenofos ^a	Chewing and Sucking insects pests, mealy bugs.	A cholinesterase inhibitor, Neurotoxicant, Skin irritant or Eye irritant.
Propiconazole ^a	Control of Rust on Wheat, barley, sugarcane, coffee and grapevine.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Respiratory tract irritant or Skin sensitizer.
Propineb ^a	Control of Various Fungal diseases on Avocado, Onions, pineapple and horticultural crops.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Respiratory tract irritant or Skin irritant.
Prosulfocarb	Control of Grass weeds on Wheat and barley.	Respiratory tract irritant, Skin irritant, Skin sensitizer or Eye irritant.
Pyridaben	Control of Various Insect pests on Horticultural Crops	Reproduction/development effects, Neurotoxicant or Respiratory tract irritant.

Table S1: Cont.

ACTIVE SUBSTANCES ^a	USAGE IN TANZANIA	POTENTIAL HEALTH ISSUES
Sulphur	Control of Brown rot, scab, mildew, mites and scales on Grapes, vegetables, cashew nuts and ornamentals.	Respiratory tract irritant, Skin irritant or Eye irritant.
Thiamethoxam ^a	Control of Seedling pests on Maize, wheat, barley and cotton.	Skin irritant
Triadimefon	Control of Powderly mildew on roses.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant, Skin sensitizer or Eye irritant.
Triadimefon ^a	Control of Coffee Leaf rust, and powdery mildew on Coffee, wheat, cashew and horticultural crops	Carcinogen, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant, Skin sensitizer or Eye irritant.
Triadimenol	Control of leaf rust on coffee and powdery mildew, fungal diseases on cashew.	Carcinogen, Endocrine disrupter, Reproduction/development effects, Neurotoxicant, Skin irritant, Skin sensitizer or Eye irritant.

^aNot registered(banned or not approved)in the EU for any purpose but registered in Tanzania by local and international registrants based in EU and Asian countries.

Table S2: Overview of studies assessing associations of environmental exposure to pesticides and human health effects in Africa by the last name of the first author and by year of publication.

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN & POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
Mamane [2016], Niger, Cross-sectional study during the rainy season when pesticides are usually sprayed, 229 children mean age 10.2 years \pm 2.4.;125 children from a pastoral area and 104 children from an agricultural area.	Postnatal, Area (agricultural vs pastoral). The agricultural area is where agricultural pesticides are applied whereby in pastoral areas no agricultural pesticides are applied.	Parent-reported wheeze ever	<ul style="list-style-type: none"> No significant association between living in an agricultural area and the risk of wheezing in children [OR = 1.38, 95% CI (0.66, 2.86)].
Ndlovu [2014], South Africa, A cross-sectional study. A total of 211 women i.e. 121 farm workers and residents and 90 women who neither lived nor worked on a farm	Postnatal. Questionnaires on self-reported domestic, occupational, and environmental exposure to pesticides.	Questionnaires on self-reported nasal allergies including hay fever or itchy and watery eyes/nose in the last 12 months, asthma in the last 12 months, adult-onset of asthma as the presence of doctor-diagnosed asthma and having had the first asthma attack at the age of 16 years or later. Asthma symptom score as a continuous outcome from the sum of positive responses to four questions related to asthma-related symptoms in the last 12 months.	<p>PESTICIDES EXPOSURE AND ASTHMA SYMPTOM SCORE</p> <ul style="list-style-type: none"> No association between the use of pesticides at home and asthma symptom scores [1.17 (0.82, 1.69)]. Association between the history of living or working on farms and asthma symptom score [2.22 (1.30, 3.80)]. Association between currently living and working on farms and asthma symptom score [2.25 (1.45, 3.48)]. Association between pesticide drifts into the home and asthma symptom score [2.03 (1.38, 2.98)]. PESTICIDE EXPOSURE, UPPER AIRWAY AND ASTHMA SYMPTOMS. No association between the use of pesticides at home and ocular-nasal symptoms [1.40 (0.70, 2.90)]. No association between a history of living or working on farms and ocular-nasal symptoms [1.65 (0.57, 4.76)]. No association between currently living and working on farms and ocular-nasal symptoms [0.87 (0.40, 2.10)].

Table S2:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN & POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<p>PESTICIDE EXPOSURE, UPPER AIRWAY AND ASTHMA SYMPTOMS.</p> <ul style="list-style-type: none"> • No association between pesticide drift into the home and ocular-nasal symptoms [1.30 (0.60, 2.80)]. • No association between the use of pesticides at home and doctor-diagnosed asthma [0.97 (0.40, 2.50)]. • No association between a history of living or working on farms and doctor-diagnosed asthma [0.68 (0.20, 2.25)]. • No association between currently living and working on farms and doctor-diagnosed asthma [0.80 (0.30, 2.30)]. • No association between pesticide drift into the home and doctor-diagnosed asthma [0.90 (0.30, 2.70)]. • No association between the use of pesticides at home and adult-onset asthma [1.30 (0.50, 3.50)]. • No association between a history of living or working on farms and adult-onset asthma [0.53 (0.14, 2.02)]. • No association between currently living and working on farms and adult-onset asthma [0.76 (0.25, 2.30)]. • No association between pesticide drift into the home and adult-onset asthma [0.90 (0.30, 2.80)]. • No association between the use of pesticides at home and current asthma [0.40 (0.10, 1.70)].

Table S2:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN & POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<ul style="list-style-type: none"> No association between a history of living or working on farms and current asthma [0.69 (0.15, 3.16)]. No association between currently Living and working on farms and current asthma [0.70 (0.20, 3.00)].
Huang [2018], South Africa, a prospective birth cohort study, the final sample size for this study was 674.	<p>Prenatal.Serum DDT/E, o,p'-DDT, p,p'-DDE and p,p'-DDT.</p> <p>Urinary pyrethroid metabolites, cis-DBCA, cis-DCCA, trans-DCCA and 3-PBA</p>	At the 2-year follow-up, mothers were administered questionnaires on the number of persistent fevers lasting ≥ 4 days, the number of ear infections and a number of severe sore throats the child had since the child's last visit(i.e., at 1yof age).	<p>PERSISTENT FEVERS AND PESTICIDES</p> <ul style="list-style-type: none"> No association between o,p'-DDT and persistent fevers(lasting ≥ 4 days) [1.10 (0.94, 1.30)] per 10-fold higher pesticide concentration. Association between p,p'-DDE and persistent fevers(lasting ≥ 4 days)[1.21(1.01,1.46)]per 10-fold higher pesticide concentration. No association betweenp,p'-DDT and persistent fevers(lasting ≥ 4 days)[1.14(0.99,1.32)]per 10-fold higher pesticide concentration. No association between cis-DBCA and persistent fevers(lasting ≥ 4 days)[1.07(0.82,1.39)] per 10-fold higher pesticide concentration. No association between cis-DCCA and persistent fevers(lasting ≥ 4 days) [1.09(0.82,1.45)] per 10-fold higher pesticide concentration. No association between trans-DCCA and persistent fevers(lasting ≥ 4 days)[1.11(0.87,1.42)] per 10-fold higher pesticide concentration.

Table S2:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN & POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<ul style="list-style-type: none"> • No association between 3-PBA and persistent fevers (lasting ≥ 4 days) [1.06 (0.80, 1.40)] per 10-fold higher pesticide concentration. <p>EAR INFECTIONS AND PESTICIDES</p> <ul style="list-style-type: none"> • No association between o,p'-DDT and ear infections [0.83 (0.60, 1.15)] per 10-fold higher pesticide concentration. • No association between p,p'-DDE and Ear infections [1.03 (0.75, 1.41)] per 10-fold higher pesticide concentration. • No association between p,p'-DDT and Ear infections [1.06 (0.80, 1.40)] per 10-fold higher pesticide concentration. • No association between cis-DBCA and Ear infections [0.70 (0.45, 1.08)] per 10-fold higher pesticide concentration. • No association between cis-DCCA and Ear infections [0.84 (0.50, 1.41)] per 10-fold higher pesticide concentration. • No association between trans-DCCA and Ear infections [0.84 (0.57, 1.25)] per 10-fold higher pesticide concentration. • No association between 3-PBA and Ear infections [0.71 (0.42, 1.20)] per 10-fold higher pesticide concentration.

Table S2:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN & POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			SEVERE SORE THROAT AND PESTICIDES <ul style="list-style-type: none"> • No association between o,p'-DDT and severe sore throat [1.53 (0.77, 3.03)]per 10-fold higher pesticide concentration. • No association between DDE and severe sore throat[1.78 (0.82, 3.84)]per 10-fold higher pesticide concentration. • No association between DDT and severe sore throat [1.58 (0.80, 3.14)]per 10-fold higher pesticide concentration. • No association between cis-DBCA and severe sore throat [0.63 (0.21, 1.87)]per 10-fold higher pesticide concentration. • No association between cis-DCCA and severe sore throat[0.80 (0.14, 4.50)]per 10-fold higher pesticide concentration. • No association between trans-DCCA and severe sore throat[0.86 (0.29, 2.52)]per 10-fold higher pesticide concentration. • No association between 3-PBA and severe sore throat [0.68 (0.19, 2.42)]per 10-fold higher pesticide concentration.

Table S2:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN & POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
Yemaneberhan [1997], Ethiopia, Cross-sectional study, A total of 12,876 participants of which 9844 were from urban and 3032 were from rural.	Prenatal. Any Insecticide use in the home, DDT or malathion was assessed via questionnaire.	Wheeze was obtained via questionnaires.	Insecticide use in the home and wheeze <ul style="list-style-type: none"> • No association between any insecticide use in the home and wheezing [1·16 (0·93–1·43)]. • No association between DDT and wheezing [1·04 (0·81–1·34)]. • No association between malathion and wheezing [1·17 (0·92–1·50)].

Table S3: Overview of studies assessing associations of occupational exposure to pesticides in relation to human health effects in Africa by the last name of the first author and by year of publication.

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
Mwanga [2016], South Africa, A cross-sectional study. A total of 211 farm workers and residents were selected from the 5 to 10 most accessible and representative farms in each area, and town women from the most accessible and representative houses in each area.	Postnatal. The exposure variables of interest comprised individual levels of OP metabolites in urine, including (DMP, DEP, DMTP, DMDTP, DETP and DEDTP), TCPY, and PYR metabolites (3PBA, 4F3PBA, DBCA, and cis- and trans-DCCA). Two additional variables were created and these include the sum of all six DAP metabolites and the sum of all five pyrethroid metabolites.	Administered questionnaire on doctor-diagnosed asthma, adult-onset of asthma and current asthma. Also, any Th2 cytokine detected and any non-Th2 cytokine detected in the blood sample.	<ul style="list-style-type: none"> • No association between doctor-diagnosed asthma and ΣDAP, DMP, DMTP, DMDTP, DEP, DETP, DEDTP, TCPY, Pyrethroids, cis-DCCA, trans-DCCA, DBCA, 4F3PBA and 3PBA, respectively. [0.68 (0.23, 2.05), 0.16 (0.02, 1.29), 0.12 (0.02, 0.94), 1.52 (0.53, 4.33), 0.78 (0.23, 2.62), 1.45 (0.46, 4.60), 1.19 (0.38, 3.78), 1.35 (0.47, 3.92), 0.62 (0.19, 2.02), 0.11 (0.01, 0.93), 0.14 (0.02, 1.19), 0.17 (0.02, 1.30), 1.01 (0.30, 3.40) and 1.06 (0.35, 3.19), respectively]. • No association between adult-onset asthma and ΣDAP, DMP, DMTP, DMDTP, DEP, DETP, DEDTP, TCPY, Pyrethroids, cis-DCCA, DBCA, 4F3PBA and 3PBA, respectively. [0.66 (0.20, 2.20), 0.22 (0.03, 1.72), 0.16 (0.02, 1.29), 1.91 (0.62, 5.82), 1.08 (0.31, 3.71), 2.03 (0.61, 6.73), 1.67 (0.51, 5.45), 1.41 (0.45, 4.44), 0.84 (0.26, 2.77), 0.16 (0.02, 1.29), 0.22 (0.03, 1.74), 1.40 (0.40, 4.90) and 1.15 (0.35, 3.76)]. • No association between Current Asthma and ΣDAP, DMP, DMDTP, DEP, DETP, DEDTP, TCPY, Pyrethroids, cis-DCCA, trans-DCCA, 4F3PBA and 3PBA, respectively. [1.38 (0.33, 5.76), 0.54 (0.06, 4.83), 2.47 (0.60, 10.13), 0.74 (0.13, 4.31), 1.53 (0.26, 8.97), 0.77 (0.13, 4.51), 1.26 (0.27, 5.76), 2.04 (0.48, 8.59), 0.23 (0.02, 2.62), 0.28 (0.02, 3.47), 1.74 (0.29, 10.56) and 2.64 (0.61, 11.47)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<ul style="list-style-type: none"> No association between any Th2 cytokine detected and ΣDAP, DMP, DMTP, DMDTP, DEP, DETP, DEDTP, TCPY, Pyrethroids, cis-DCCA, trans-DCCA, DBCA, 4F3PBA and 3PBA, respectively. [1.77 (0.90, 3.46), 1.69 (0.83, 3.46), 0.85 (0.42, 1.72), 0.79 (0.39, 1.62), 1.99 (0.95, 4.19), 2.75 (1.27, 5.92), 7.70 (3.00, 19.74), 1.56 (0.57, 2.34), 1.32 (0.69, 2.55), 1.47 (0.73, 2.93), 1.04 (0.52, 2.10), 1.33 (0.66, 2.67), 2.51 (1.20, 5.22) and 1.30 (0.64, 2.64)]. No association between any non-Th2 cytokine detected and ΣDAP, DMP, DMTP, DMDTP, DEP, DETP, DEDTP, TCPY, Pyrethroids, cis-DCCA, trans-DCCA, DBCA, 4F3PBA and 3PBA, respectively. [1.77 (0.81, 3.87), 4.23 (1.54, 11.65), 1.34 (0.60, 3.00), 0.46 (0.22, 0.98), 2.71 (1.05, 7.00), 23.25 (3.08, 175.49), 23.84 (3.15, 180.74), 1.93 (0.83, 4.45), 2.18 (0.98, 4.88), 2.10 (0.92, 4.80), 1.21 (0.56, 2.63), 1.74 (0.78, 3.88), 4.32 (1.58, 11.82) and 1.63 (0.72, 3.69)]

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
Negatu [2019]. Ethiopia, cross-sectional, the First survey comprised of a total 1104 study subjects and the Second survey comprised a total of 387 study subjects.	Postnatal. A structured questionnaire was used to obtain data on pesticide exposure.	Respiratory symptoms were assessed using a standardised questionnaire. A lung function test was performed using the Easy One model 2001 spirometer.	FIRST SURVEY (RESPIRATORY SYMPTOMS) <ul style="list-style-type: none"> • Association between pesticide exposure and chronic cough among farm workers [3.15 (1.56, 6.36)]. • Association between chronic cough and median and high exposure category to pesticides among male applicators [6.16 (1.24, 32.89) and 8.14 (1.59, 41.42)]. • No association between chronic cough and median exposure category to pesticides among female re-entry workers [1.54 (0.46, 5.18)]. • FIRST SURVEY (RESPIRATORY SYMPTOMS) • Association between chronic cough and high pesticide exposure category among male re-entry workers [10.16 (1.20, 85.89) and 21.24 (3.78, 119.16)]. • No association between pesticide exposure and chronic Phlegm among farm workers [2.02 (0.58, 7.01)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<p>FIRST SURVEY (RESPIRATORY SYMPTOMS)</p> <ul style="list-style-type: none"> • No association between chronic Phlegmand median and high pesticide exposure category among female re-entry workers [1.42 (0.22, 9.25) and 0.57 (0.06, 6.00)]. • No association between pesticide exposure and wheezing among farm workers [3.16 (0.96, 10.47)]. • Association between shortness of breath and high pesticide exposure category among female re-entry workers [7.86 (2.10, 29.45)]. <p>SECOND SURVEY (RESPIRATORY SYMPTOMS)</p> <ul style="list-style-type: none"> • Association between pesticide exposure and chronic cough among farmworkers [5.76(1.90, 17.42)]. • Association between chronic cough and median and high pesticides exposure category among male applicators [6.69 (1.03, 43.48) and 13.15 (2.90, 59.53)]. • No association between chronic cough and median and high pesticide exposure category among female re-entry workers [6.90 (0.70, 67.70) and 3.00 (0.31, 29.00)]. • No association between pesticide exposure and chronic Phlegm among farmworkers [2.98 (0.76, 11.58)]. •

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<ul style="list-style-type: none"> • No association between chronic cough and median and high pesticide exposure category among male applicators [4.80 (0.61, 38.13) and 4.67 (0.88, 24.73)]. • No association between pesticide exposure and wheezing among farmworkers [1.75 (0.81, 3.78)]. • No association between wheeze and median pesticide exposure category among male applicators [1.97 (0.48, 8.01)]. • Association between occupational pesticide exposure and decline in FEV1 among farm workers [-0.14 (-0.25, -0.03)]. • No association between a decline in FEV1 and Median and high pesticide exposure among male applicators [-0.19 (-0.39, 0.02) and -0.15 (-0.33, 0.03)]. • No association between a decline in FEV1 and Median and high pesticide exposure among female re-entry workers [-0.08 (-0.29, 0.13) and -0.15 (-0.35, 0.06)]. • Association between wheeze and high pesticides exposure category among male applicators [4.65 (1.55, 13.91)]. • No association between wheeze and median and high pesticide exposure category among female re-entry workers [1.05 (0.19, 5.72) and 0.68 (0.11, 4.22)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<ul style="list-style-type: none"> • Association between pesticide exposure and shortness of breath among farmworkers [4.09 (2.12, 7.90)]. • No association between shortness of breath and median pesticide exposure category among male applicators [2.61 (0.88, 7.69)]. • SECOND SURVEY (RESPIRATORY SYMPTOMS) • Association between shortness of breath and high pesticide exposure category among male applicators [6.62 (2.09, 16.94)]. • Association between shortness of breath and median and high pesticides exposure category among male applicators [6.23 (1.50, 25.73) and 6.51(1.70, 24.82)]. • CUMULATIVE EXPOSURE AND LUNG FUNCTION • No association between occupational pesticides exposure and a decline in FVC among farm workers [−0.05 (−0.18, 0.07)], • No association between a decline in FVC and Median and high pesticide exposure among male applicators [−0.04 (−0.28, 0.20) and −0.06 (−0.26, 0.15)]. • No association between a decline in FVC and Median and high pesticide exposure among female re-entry workers[−0.01 (−0.24, 0.23) and −0.12 (−0.36, 0.11)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING EXPOSURE ASSESSMENT	HEALTH & OUTCOMES	
			DAILY EXPOSURE AND LUNG FUNCTION <ul style="list-style-type: none"> • No association between a decline in FVC and Median and high pesticide exposure among male applicators [0.01 (−0.21, 0.22) and −0.10 (−0.32, 0.10)]. • No association between a decline in FVC and Median and high pesticide exposure among female re-entry workers [−0.02 (−0.21, 0.22) and −0.10 (−0.32, 0.11)]. • No association between decline in FV1 and male applicators [−0.11 (−0.30, 0.07)] • Association between FV1 and male applicators [−0.21 (−0.39, −0.03)]. • No association between the decline of FV1 and female re-entry workers [−0.07 (−0.27, 0.13) and −0.16 (−0.37, 0.05)].
Ndlovu [2014], South Africa, A cross-sectional study, A total of 211 women i.e. 121 farm workers and residents and 90 women who neither lived nor worked on a farm.	Postnatal. Questionnaires self-reported exposure to domestic, occupational, and environmental exposure to pesticides. measurements as an objective marker for exposure to cholinesterase-inhibiting CAs and OPs.	Questionnaires on self-reported nasal allergies including hayfever or itchy and watery eyes/nose in the last 12 months, asthma in the last 12 months, adult-onset of asthma as the presence of doctor-diagnosed asthma and having had the first asthma attack at the age of 16 years or later.	PESTICIDES EXPOSURE AND ASTHMA SYMPTOM SCORE <ul style="list-style-type: none"> • Association between the history of living or working on farms and asthma symptom score [2.22 (1.30, 3.80)]. • Association between currently living and working on farms and asthma symptom score [2.25 (1.45, 3.48)]. • No association between permanent versus seasonal farm workers and asthma symptom scores [1.06 (0.70, 1.70)]. • No association between immediate versus delayed re-entry and asthma symptom scores [1.21 (0.75, 1.90)]. • No association between the number of years in a current farm job and asthma symptom score [1.02 (1.00, 1.04)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	MAIN FINDINGS
		Asthma symptom score as a continuous outcome from the sum of positive responses to four questions related to asthma-related symptoms in the last 12 months.	<ul style="list-style-type: none"> • Association between the number of days of pesticide spraying/year in the current farm and asthma symptom score [1.01 (1.00, 1.01)]. • Association between low cholinesterase levels and asthma symptom score [1.93 (1.09, 3.44)]. <p>PESTICIDE EXPOSURE, UPPER AIRWAY AND ASTHMA SYMPTOMS.</p> <ul style="list-style-type: none"> • No association between a history of living or working on farms and ocular-nasal symptoms [1.65 (0.57, 4.76)]. • No association between currently living and working on farms and ocular-nasal symptoms [0.87 (0.40, 2.10)]. • No association between permanent vs seasonal farmworkers and ocular-nasal symptoms [2.24 (0.80, 6.30)]. • Association between immediate vs delayed re-entry and ocular-nasal symptoms [2.97 (0.93, 9.50)]. • No association between the number of years in a current farm job and ocular-nasal symptoms [1.00 (0.97, 1.06)]. • No association between the Number of days of pesticide spraying/year on the current farm and ocular-nasal symptoms [1.00 (0.99, 1.01)]. • No association between low cholinesterase levels and ocular-nasal symptoms [1.10 (0.30, 3.80)]. • No association between a history of living or working on farms and doctor-diagnosed asthma [0.68 (0.20, 2.25)]. • No association between currently living and working on farms and doctor-diagnosed asthma [0.80 (0.30, 2.30)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			<p>PESTICIDE EXPOSURE, UPPER AIRWAY AND ASTHMA SYMPTOMS.</p> <ul style="list-style-type: none"> • No association between permanent vs seasonal farmworkers and doctor-diagnosed asthma [0.19 (0.04, 1.05)]. • No association between immediate vs delayed re-entry and doctor-diagnosed asthma _ [4.81 (0.55, 42.20)]. • No association between the number of years in a current farm job and doctor-diagnosed asthma [1.01 (0.95, 1.10)]. • No association between the number of days of pesticide spraying/year on the current farm and doctor-diagnosed asthma [1.00 (0.99, 1.00)]. • No association between a history of living or working on farms and adult-onset asthma [0.53 (0.14, 2.02)]. • No association between currently living and working on farms and adult-onset asthma [0.76 (0.25, 2.30)]. • No association between permanent vs seasonal farm worker and adult-onset asthma [0.23 (0.04, 1.30)]. • No association between immediate vs delayed re-entry and adult-onset asthma [3.49 (0.40, 31.00)]. • No association between the number of years in a current farm job and adult-onset asthma [1.01 (0.96, 1.08)]. • No association between the number of days of pesticide spraying/year in the current farm [1.00 (0.99, 1.01)]. • No association between a history of living or working on farms and current asthma [0.69 (0.15, 3.16)].

Table S3:(Cont.)

FIRST AUTHOR [YEAR], LOCATION, STUDY DESIGN& POPULATION CHARACTERISTICS	SUMMARY OF METHOD		MAIN FINDINGS
	EXPOSURE TIMING & EXPOSURE ASSESSMENT	HEALTH OUTCOMES	
			PESTICIDE EXPOSURE, UPPER AIRWAY AND ASTHMA SYMPTOMS. <ul style="list-style-type: none"> • No association between currently living and working on farms and current asthma [0.70 (0.20, 3.00)]. • No association between permanent vs seasonal farm worker and current asthma [0.30 (0.02, 4.30)]. • No association between the number of years in current farm jobs and current asthma [1.00 (0.90, 1.10)]. • No association between the number of days of pesticide spraying/year on the current farm and current asthma [1.00 (0.99, 1.01)]

*Dialkyl phosphate (DAP), metabolites(dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), diethyl thiophosphate (DETP), diethyl dithiophosphate (DEDTP) and 3,5,6-trichloropyridinol (TCPY), carbamates (CAs), organophosphates (OPs), cholinesterase enzyme (ChE), and cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DCCA), cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DBCA), 4-fluorophenoxybenzoic acid (4F3PBA) and 3-phenoxybenzoic acid (3PBA).

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Chapter 6: General Discussion

This thesis aimed to examine the associations of residential exposure to pesticides and household cleaning products with the prevalence of asthma, related respiratory symptoms, rhinitis, and eczema in adolescents. The study also sought to compare the knowledge gained from the work described in this thesis and the situation in Tanzania in providing a framework for recommendations for future research.

Environmental exposure to pesticides was evaluated by assessing the residential proximity of the homes of the PIAMA birth cohort study participants at the time of their 14 years of follow-up to crop fields which had been treated with pesticides and the estimated amount of pesticides known to have respiratory effects applied on these fields. The thesis is based on the hypothesis that children exposed to pesticides through multiple pathways may experience respiratory health problems. We also intended to examine whether cleaning agents used in homes were associated with the prevalence of asthma, related respiratory symptoms, rhinitis, and eczema in adolescents at 14 years of age. The potential effects of cleaning agents on asthma, related respiratory symptoms, rhinitis, and eczema in children are a continuing public health concern, as cleaning agents in either liquid or solid form are suspected to cause respiratory irritation (Abrams, 2020).

This chapter describes the main findings and discusses the validity of the study findings, methodological considerations and implications for future research.

MAIN FINDINGS

In **Chapter 2**, we assessed the proximity to fields treated with pesticides (as a proxy for environmental exposure to agricultural pesticides) for the home addresses of the participants of the Dutch PIAMA birth cohort study at the age of 14 years. This investigation intended to quantify the number and percentage of households located close to agricultural fields

cultivated with crops treated with pesticides. A second aim was to estimate the average annual pesticide use on crops grown on these fields based on farmer-reported pesticide use.

The results show that a small proportion (7%) of the study participants lived near (i.e. within 100 m of) agricultural fields with selected crops relevant for pesticide use. Furthermore, the results described in **Chapter 2** indicate that large proportions of the study participants (40 and 64%, respectively) lived within 500 m or 1,000 m of agricultural fields. These study participants who lived within 500 or 1,000 m of agricultural fields are likely to have low exposure to pesticides compared with the 7% of the study participants who lived within 100 m of agricultural fields.

In **Chapter 3**, we evaluated the association between residential exposure to pesticides and the prevalence of asthma and related respiratory symptoms. Our analysis indicated that there was no association between proximity to agricultural fields on which pesticides were applied and asthma and related respiratory symptoms. Our findings are not in line with the findings of other studies which suggest that there is an association between exposure to pesticides and an increased risk of asthma and related respiratory symptoms in adults (Fareed et al., 2013, Chakraborty et al., 2009, Baldi et al., 2014, Kim et al., 2017). However, there is still little evidence on the effects of environmental exposure to pesticides on the development of asthma in children and adolescents worldwide.

In **Chapter 4**, the association of exposure to household cleaning agents with asthma and allergic symptoms in adolescents was investigated. This association was investigated because inhalation of irritants from cleaning agents may cause injury of the airway epithelium, oxidative stress and neutrophilic airway inflammation (Dumas et al., 2015), which are relevant to asthma. Also, evidence suggests that adults who are occupationally exposed to cleaning agents have an increased risk of asthma (Zock et al., 2001, Medina-Ramon et al., 2005). A recent literature review indicated growing epidemiological evidence for an adverse effect of

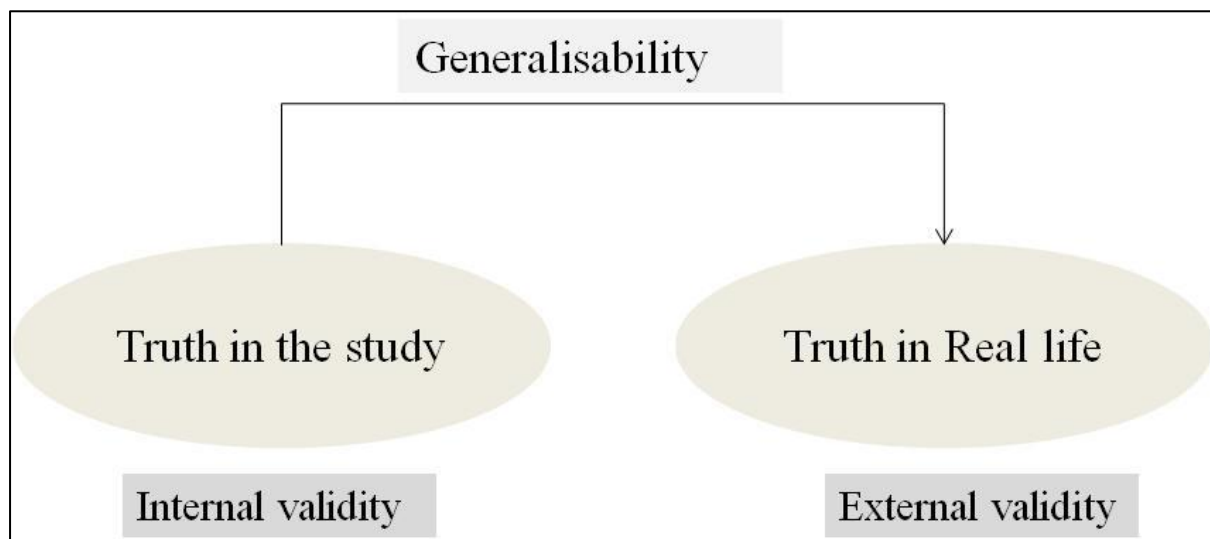
exposure to cleaning products and disinfectants on respiratory health, not only in adults with a high level of exposure at work but also in children during early life (Dumas and Le Moual, 2020). This has been further illustrated by a recent Canadian cohort study which suggested that a higher frequency of the use of cleaning products in the home during infancy is associated with an increased risk of recurrent wheeze, recurrent wheeze with atopy and asthma diagnosis in children at the age of 3 years (Parks et al., 2020). However, the findings in **Chapter 4** suggest no association of cleaning agents use with the prevalence of asthma and allergic symptoms among our study participants.

Chapter 5 was developed to provide an overview of the legislation, current situation and ways forward in the implementation of research on the impact of environmental and occupational exposure to pesticides on human health in Tanzania. As mentioned in **Chapter 5**, no epidemiological studies have been conducted in Africa to date to examine the respiratory effects among children exposed to pesticides, despite the intensive use of pesticides in Africa (Buralli et al., 2020). Therefore, **Chapter 5** also describes opportunities for the development of studies to investigate the effects of environmental exposure to pesticides on the development of asthma and related respiratory symptoms in children in Tanzania.

VALIDITY OF STUDY FINDINGS

The validity of a research study refers to how well the results among the study participants represent the ‘truth’ for the study population itself (internal validity) and for similar individuals outside the study population (external validity, see Figure 1). Our work was based on data from the PIAMA study which is a large ongoing population-based birth cohort study with prenatal inclusion and follow-up until to date.

FIGURE 1: Internal and External validity (Source:(Patino and Ferreira, 2018))



In this thesis, exposure to pesticides was estimated based on crops grown within several circular buffers around the participants' homes. Crops were identified through the basic registration (Ministry of Agriculture Nature and Food Quality, 2021) whereby 69 different types of crops were identified from maps with annually updated crop information at an underlying scale of 1:10,000. We used a maximum buffer radius of 1,000 m to investigate environmental exposure to pesticides as described in **Chapter 2**. The use of distances from fields to homes as a proxy for exposure has been described in other studies (Brody et al., 2002, Brouwer et al., 2018). Also, other study observed an increase in the detection of tetramethrin in homes of children living in proximity (< 500 m) to grain crops and protein peas (Glorennec et al., 2017).

In **Chapter 2**, it has been described that the 14-year questionnaires were completed by the participant's parents between October 2011 and August 2013. At that time, almost all participants were living with their parents.

In this thesis, the described environmental exposures can not easily be generalised to other settings such as the United States of America or low and middle-income countries where both aerial and ground pesticide application (Pearce et al., 2002, Weppner et al., 2006,

Manikowski, 1988, Moshi et al., 2015) is still permitted while in the Netherlands ground application only is permitted. Also, for example in Tanzania, it is assumed that a large fraction of the farming community in rural areas lives within a short distance (10 to 100 m) from agricultural fields. Therefore, it is suspected to have a higher pesticide exposure in the homes of the farming community living in the rural areas of Tanzania.

As mentioned in the literature, significantly higher levels of pesticide exposure have been shown in the spraying vs non-spraying season (Dereumeaux et al., 2020). This also was supported by a study from Washington which assessed the differences in children's urinary pesticide metabolite levels between spraying and non-spraying seasons and found that the urinary metabolites of study participants were higher during spraying seasons (Thompson et al., 2014). However, in this thesis, we did not have information on the exact timing and location of ground pesticide application as we only had information about the location of crops and the annual amount of pesticides used on specific crops. Therefore, the pesticide exposure assessment explained in **Chapter 2** does not reflect temporal variations related to the seasonal application.

In **Chapter 3**, we observed that environmental exposure to pesticides was not associated with asthma and related respiratory symptoms among our study participants living within 500 and 1,000 m of agricultural fields treated with pesticides. However, in **Chapter 3** we lacked statistical power to assess whether living at a distance less than 100 m from agricultural fields likely treated with pesticides is associated with the prevalence of asthma due to the small number ($n = 90$, 7 %) of the population living within 100m of fields. The findings presented in **Chapter 3** cannot be compared to the situation in the United States of America and Canada where pesticides are still being sprayed from the air and exposure was associated with an increased risk of asthma symptoms in children within 100m buffers. The findings presented

in **Chapter 3**, also may be limited by exposure misclassification due to a lack of data on crop rotation and actual pesticide use on specific fields.

In **Chapter 4**, we observed that there was no clear evidence for an association between the use of cleaning agents at home and respiratory and allergic symptoms in adolescents aged 14 years. We noted that a large proportion of our study participants were not present during cleaning activities in their homes, which reduced the power to detect any health effects of exposure to cleaning agents. We observed that most of the published studies assessing the health effects of cleaning activities in homes or other buildings such as hospitals, schools and other private and public buildings were conducted among professional or non-professional (adult) cleaners. Exposure to cleaning agents may have been very low in the participants in our study compared to the exposure of professional and non-professional cleaners.

In reviewing the literature, we found one single study suggesting that frequent use of household cleaning products increases the risk of rhinitis in children at an average age of 11 years (Lao et al., 2019, Abrams, 2020). Another study suggested that frequent use of household cleaning products in the home in early life was associated with an increased risk for wheezing and asthma in children at the age of 3 years (Parks et al., 2020). The differences in the association with the use of cleaning products between those studies indicated an increased risk of wheezing and asthma in children and our study, where no association was found, might be due to differences in the level of exposure, the timing of exposure, chemical constituents and the study design. This is why some of the studies on the effects of the use of cleaning agents with increased risk of asthma, and related respiratory and allergic symptoms cannot easily be generalised to other study settings due to reasons that have been explained previously.

The findings in **Chapter 4** can likely be extrapolated to other adolescents living in the Netherlands at the age of 14 years. However, they cannot be generalised to low and middle-income countries due to socio-economical differences in chemical constituents of cleaning

agents and cleaning behaviours such as the use of cleaning agents while children are at home or the involvement of children in the cleaning of their homes. However, other than the two studies mentioned above, no studies have been published on the association between the use of cleaning agents and increased risk of asthma and related respiratory symptoms and allergic symptoms in children.

METHODOLOGICAL CONSIDERATIONS

It is important to discuss methodological considerations to understand the validity and reliability of the study findings. This section discusses the strengths and limitations of the study design and population, selection of participants, information bias, confounding, methods of the determination of outcomes, exposure assessment and data quality concerning the published chapters of this thesis.

Study design and population

The strength of the studies presented in this thesis is that they use data from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study which is a prospective Dutch birth cohort study. One of the major advantages of a prospective birth cohort study over a cross-sectional or case-control study is that allows the collection of accurate information about exposures, outcomes and several covariates as well as biological material. A prospective birth cohort study can provide an observational study with the highest level of evidence regarding the relationship between exposure and outcome. In this type of study, the sample is selected based on the exposure of interest and then moving forward temporally to evaluate the development of pre-specified outcomes. In the prospective birth cohort study, because the exposure assessment starts at the recruitment before or around birth, and the outcome occurs at a later date, the temporality of the exposure-outcome relation can be established (cause

precedes effect). In this thesis, the pesticide analyses were performed as a cross-sectional study within a cohort. An advantage over a cross-sectional study (not performed within a cohort setting) is that information on residential histories is available and that it is known how long participants had lived at a specific address and whether current exposure also reflects at least to some extent historical exposure preceding the outcomes.

A possible limitation of the (prospective birth) cohort study is the loss of follow-up when study participants are being followed over a long period. In the PIAMA study, the response rates were still good, however, there was a loss of follow-up. For instance, in **Chapter 2**, we included 2291 adolescents who had participated in the 14-year follow-up and geocoded residential addresses. This is 57 % of the baseline study population of the PIAMA birth cohort study. Also, in **Chapter 3**, we included 1473 adolescents who had participated in the 14-year follow-up. This is also 37% of the baseline study population of the PIAMA birth cohort study. Moreover, in **Chapter 4**, fifty-eight percent of the study population from the baseline had complete information on exposure (to cleaning agents) and health outcomes (asthma, related respiratory and allergic symptoms) at age 14.

Selection of participants

PIAMA participants were recruited from the general population (Wijga et al., 2014) to represent all children living in the Netherlands. Pregnant women were recruited from fifty-two antenatal clinics in three regions of the Netherlands, from which approximately 12,000 children were delivered annually (Brunekreef et al., 2002). However, in the PIAMA birth cohort study, selection bias might be a potential concern as highly educated parents were over-represented (Wijga et al., 2014). For instance, in the PIAMA baseline population, 35%, 42% and 24% of the mothers of the study participants had high, intermediate and low maternal education. While 40%, 34% and 26% of the fathers of the study participants had high,

intermediate and low paternal education. This is reflecting the common phenomenon that in research involving lengthy questionnaires, highly educated parents are more likely to participate than parents with a lower level of education.

Missing data are unavoidable in epidemiological studies but their potential to undermine the validity of research results has often been overlooked in the medical literature (Wood et al., 2004). Missing information on exposure (pesticides exposure and cleaning agents), endpoints (asthma, shortness of breath, dry night cough, rhinitis and eczema) and potential confounders at the age of 14 years was not a problem. Since study participants with missing exposure and endpoints were about 821 (approximately 36 %) but more than half of the participants have both exposure and endpoint. For instance, the number of study participants with pesticides exposure, asthma, shortness of breath and dry night cough were as follows; 2291, 1470, 1471 and 1467, respectively. Also, the differences in the number of participants between crude ($n = 1470$) and adjusted ($n = 1434$) analyses were 36 (approximately 2%) this was not a major problem. Therefore, we did not consider multiple imputations to handle missing information on potential confounders in **Chapter 3** due to the small percentages of missing values. Also in **Chapter 4**, a small number of study participants ($n = 70$, approximately 3%) had missing information coming on potential confounders.

Information bias

Information bias has been discussed in detail in subsections on methods for the determination of health outcomes or endpoints, exposure assessment, and confounders. Moreover, they can occur during data collection and the most important type of information bias is misclassification bias. Misclassification bias can be the result of misclassification of the exposure status and/or the disease status and/or confounders, that is, from the fact that exposed

individuals are classified as a non-exposure group and individuals with the disease are classified as a non-diseases group.

Bias is an unavoidable problem in epidemiological studies. However, the correct selection of the study design, a careful choice of procedures for data collection and handling and the correct definition of exposure and disease represent important strategies for minimising systematic errors in epidemiological studies (Tripepi et al., 2010).

Methods for the determination of health outcomes or endpoints

In this thesis, asthma and allergic symptoms were considered because of the pre-existing known biological mechanisms which provided plausibility to a potential relationship (as discussed in **Chapters 3 and 4**).

In this thesis, we used data from parentally completed questionnaires on asthma and related respiratory symptoms, rhinitis and eczema of their children. We did not find much difference between the child and parental completed questionnaires with regard to the presence/absence of asthma, wheezing, shortness of breath, cough, rhinitis and eczema. Therefore, the parentally completed questionnaire was considered. The agreement between information provided by parents and children in completed questionnaires increases confidence in the validity of the data. The PIAMA questionnaires were also based on the validated ISAAC questionnaires (Caudri et al., 2007). The parent-completed questionnaire was also chosen because it had more detailed information compared to the child-completed questionnaire.

In **Chapter 3**, statistical analyses were restricted to participants with health information collected in the year 2012 and left out participants who had missing information either in exposure or endpoints, or both. In the PIAMA birth cohort study, we had no data on the misclassification of asthma and related symptoms at the time of the 14-year follow-up. We do note that this study used validated questionnaires to obtain endpoints (Valle et al., 2012).

Exposure assessment

In **Chapter 2**, environmental exposure to pesticides was estimated based on land-use data from one cropping season (i.e. 2012) and the information was collected from the farmers by Statistics Netherlands (Statistics Netherlands (CBS), 2012). The information on the participants' residential home addresses was combined with the information on the location of crops that demand pesticides and used for the calculation of distances from agricultural fields to the home address of the study participants. Therefore, we have no direct information on the validity of exposure estimates in **Chapter 2**. Although the previously mentioned study from The Netherlands suggested reasonable agreement with measured concentrations of selected pesticides in air and in rainfall (Brouwer et al., 2018). However, since we rely on objective data and not on self-reports of exposure by our study participants, exposure misclassification is likely to be non-differential (i.e. not related to the health status).

In **Chapter 2**, the exposure estimates were based entirely on recent exposures and did not take into account any information on prenatal or early-life exposures. However, other studies included information on prenatal or early life exposures (Smit et al., 2015, Sunyer et al., 2005, Abellan et al., 2019, Park et al., 2020, Mora et al., 2020). This is because information on crop locations and pesticide use is not available for the period when the PIAMA study started (i.e. the late 1990s). It is currently unclear whether there is a window of increased vulnerability, but if pregnancy or early life would be such a windows, we may have missed this as only information on recent exposure was available. Also, the relevance of lifetime over current exposure is currently not clear. By being limited to current exposures, the effects of past exposures could not be assessed.

Chapter 4 was based on the reported exposure to cleaning agents at the time of the 14-year follow-up. We did not collect information on prenatal exposure to cleaning agents so we

cannot address the question raised by the Canadian Birth Cohort study, which suggested that prenatal exposure to cleaning agents increased the risk of recurrent wheeze with atopy and asthma diagnosis in children at the age of 3 years (Parks et al., 2020).

In **Chapter 4**, we knew whether participants were at home when the cleaning activities took place, but we missed information on whether the participants sometimes participated in cleaning activities, e.g. in their bedrooms. Therefore, we may have overestimated the exposure of those who did not participate in cleaning activities. It is unclear whether this exposure misclassification is non-differential or differential and how this may have affected the results of our study.

In **Chapter 4**, exposure estimates were based on the parental-reported use of cleaning agents. Measurements of individual chemical constituents in the indoor air were not considered during the PIAMA study design. However, a similar study to ours (Farrow et al., 2003), which likewise did not use objective measurements of indoor air exposure performed a validation study in a subset of the population ($n = 170$) and found a positive association between the total level of volatile chemical constituents (TVOC) and self-reported use of air fresheners and aerosol. The study also indicated that when air fresheners are frequently used, other aerosols and carpet cleaners in the bedroom during pregnancy, the homes were 2-3 times more likely to be in the upper quartile of TVOC concentrations compared to homes with infrequent use. However, we do acknowledge that cleaning agents and usage may differ between countries (i.e. the Farrow study is from the UK) and that such validations are available for a limited set of cleaning agents only.

Confounding

Confounding bias is the systematic distortions in the measure of association that may occur when the primary exposure of interest is mixed up with some other factors that are associated

with the outcomes of interest. In **Chapters 3 and 4**, we adjusted potential confounding variables such as sex of the child, smoking in the child's home at age 14, active smoking of the participant, parental education, furry pets at home at age 14 years, maternal and paternal allergy (which includes asthma, hay fever and allergy), maternal and paternal country of birth, gas cooking, damp/mould spots in the child's bedroom and/or living room and traffic-related air pollution (NO₂) at age 14 years. Very few (n=72, 5%) of children in the PIAMA birth cohort study at the time of 14-year follow-up were reported to be active smokers. We excluded active smokers as part of a sensitivity analysis in **Chapter 3** and found the association estimated to remain unchanged. In **Chapter 4** we adjusted for active smoking.

In the analysis in **Chapter 3**, dietary pesticide intake and domestic pesticides use against household insect pests were not considered as they were not considered during the PIAMA study design. It remains therefore unclear whether dietary pesticide intake and domestic pesticides use against household insect pests are potential confounders of the associations of residential pesticide exposure with asthma and related respiratory symptoms.

In general, measurement errors in confounders compromise the ability to control for effect measure, leaving residual confounding (Armstrong, 1998). Therefore, the effect measure adjusted with the approximate confounder will on average lie between the crude, unadjusted effect measure and the effect measure adjusted with the true confounder.

INTERNATIONAL DEVELOPMENT AND ASTHMA IN AFRICAN COUNTRIES

As was discussed in **Chapters 3 and 4**, pesticides and cleaning agents exposure may be determinants of asthma and allergic diseases in children in high-income countries. However, there is limited evidence on the causes of asthma in African countries despite the increase in the number of cases. For instance, a systematic analysis showed that the number of asthma cases in Africa rose from 74 million in 1990 to 120 million in 2010 (Skevaki et al., 2021).

Moreover, over 30 million people in Africa have allergic rhinitis, while a large proportion suffers from asthma as well (Bousquet et al., 2008). Data suggest that more than 80 percent of asthma deaths occur in low-income countries (LICs) (Lozano et al., 2012).

The effects of pesticide and cleaning agent exposure extend beyond respiratory health effects (asthma and allergic diseases) and have profound impacts on social and economic development within communities. In the following paragraphs, we discuss Sustainable Development Goals (SDGs) in relation to the Tanzanian situation and Africa as a whole where we could learn more about the lack of evidence as a call to action. SDGs were adopted by the United Nations in 2015 as a universal call to action to end poverty, protect the planet, and ensure that by 2030 all people enjoy peace and prosperity (United National Development Programme (UNDP), 2021). The 17 SDGs are integrated and recognise that action in one area will affect outcomes in others, and that development must balance social, economic and environmental sustainability. In this thesis, five (5) SDGs are being discussed because they are directly or indirectly related to environmental exposure to pesticides and so to an increased risk of asthma and allergic symptoms in children. These goals are purposefully broad and impact many aspects of the daily life of human beings. The social ramification of the effects of pesticides and cleaning agents exposure on the development of asthma and allergic symptoms may have direct and indirect impacts on the achievement of SDGs. Using Sustainable Development Goals as a framework, we briefly discuss how the effects of pesticides and cleaning agents exposure on the development of asthma and allergic symptoms in children may have an impact on the achievement of these goals in African countries.

Goal 1. End poverty in all its forms everywhere

There is a direct link between poverty and environmental exposure to pesticides. This happened more in the rural parts of African countries whereby there are poor households. Also, most

people living in the rural parts of African countries live close to agricultural fields treated with highly hazardous pesticides (HHPs). Moreover, there are no studies on the effects of cleaning agents in LMIC settings. However, it seemed that some women in Tanzania have been engaged in making liquid soap and other cleaning agents to sustain their families. These activities increased the level of exposure to cleaning agents among household members, especially children. However, we have no data on how often women either in Africa as a whole or Tanzania have been involved in making liquid soap as well as other cleaning agents. This would be a fruitful area for further work.

In this goal, we did not only realise the direct link between poverty and asthma but also the environmental exposure to hazardous chemicals such as pesticides and poverty. For instance, there is the suggestion that living in poor neighbourhoods is associated with an increased risk of asthma in children (Aligne et al., 2000). This happens probably due to an increase in environmental contaminants, therefore, further studies are needed to confirm this.

Goal 2. End hunger, achieve food security and improve nutrition and promote sustainable agriculture

The goal does directly relate to environmental exposure to pesticides and increased risk of asthma and other respiratory-related diseases in children in low-income countries. For instance, this goal requires the doubling of the agricultural productivity and incomes of small-scale food producers by 2030, in particular women, indigenous peoples, family farmers, pastoralists and fishers through secure and equal access to land, other productive resources and inputs, knowledge and opportunities for value addition and non-farm employment. These requirements need to be monitored by promoting sustainable agriculture with the use of low-risk pesticides which protect crops from pests and diseases but also minimised pesticide

exposure and the risk of developing asthma and related respiratory diseases in low-income countries including Tanzania.

Goal 3. Ensure healthy lives and promote well-being for all at all ages

There is an increase in the prevalence of asthma, rhinitis and eczema from 18 to 20% for children between the age of 13 to 14 in Africa (Ait-Khaled et al., 2007). Moreover, a study has indicated an asthma prevalence of 11 percent among individuals older than 12 years in Uganda (Kirenga et al., 2019). Furthermore, the Uganda Registry for Asthma and COPD (URAC) reported that 60% of Ugandan asthmatics experienced more than three attacks per year in a cohort of 449 asthmatics (Kirenga et al., 2019). However, environmental exposure to pesticides and cleaning agents may have implications for the development of respiratory and allergic diseases including asthma, rhinitis, and eczema in children. If the use of pesticides and cleaning agents will not be controlled, this goal is not going to be realised in African countries. As we hardly know anything about the use of cleaning agents by children in Africa, therefore, further studies are needed to understand the effects associated with exposure to cleaning agents in African countries.

Goal 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all

This goal is not directly related to environmental exposure to pesticides and cleaning agents with increased risk of asthma and allergic symptoms in adolescents. However, studies have revealed that maternal education may influence child health outcomes (Frost et al., 2005, Victoria et al., 1992, Laksono et al., 2022).

It is believed that the level of pesticide and cleaning agent exposure may be reduced by increased community awareness of the effects associated with pesticides and cleaning agents.

For instance, high educational attainment improves health directly and indirectly through work and economic conditions, social-psychological resources and a healthy lifestyle (Ross and Wu, 1995, Cutler and Lleras-Muney, 2012). Training and education are important as intervention programs in any community. They may help in reducing the prevalence of asthma and allergic symptoms in children in African countries.

Goal 5. Achieve gender equality and empower all women and girls

This goal is not directly related to environmental exposure to pesticides and cleaning agents. It is about promoting women's sense of self-worth, their ability to determine their own choices, and their right to influence social change for themselves and others. As it was discussed in goal number 1, it is possible that many women residing in urban areas are engaged in making liquid soaps and detergents and that may increase the likelihood of exposing themselves and their children. We can say that goal number 5 is indirectly related as most of the women in low-middle-income countries spend with their children and thus increased dependability and being subjected to environmental exposure to pesticides or cleaning detergents. Therefore, women need to be empowered by government-supported programs by enabling them to access funds and education on entrepreneurship that may enable them to make liquid soaps and detergents with safer active substances for the environment and human health.

IMPLICATIONS FOR FUTURE RESEARCH

In **Chapter 2**, exposure assessment was based on proximity to crops and the estimated amounts of pesticides used around the home of participants. However, some of the crops might be grown using organic farming techniques that exclude the use of synthetic pesticides. Therefore, future work should focus on the improvement of exposure assessment by considering better control or reference groups such as data on organic farming.

Very little was found in the literature regarding environmental exposure to pesticides in low-income countries such as African countries. In the literature review, it was reported that there are only four published studies from Africa, and these studies were conducted in South Africa only (Dereumeaux et al., 2020). This means, there is hardly any knowledge related to the assessment of environmental exposure to pesticides in African countries. Therefore, more studies are needed to fill the knowledge gap on the assessment of environmental exposure to pesticides in African countries as most of the crops grown in Africa use pesticides to increase productivity.

Given the published data of the current study, the take-home pesticide exposure pathway was not considered. This is because there was no information regarding take-home pesticide exposure among PIAMA study participants. Take-home pesticide exposure means pesticides used in agriculture which can be taken into workers' homes and pose a potential health risk for children and other family members. If the data about take-home pesticide exposure would be available in the PIAMA birth cohort study, they would be combined with the data on the residential pesticide exposure to provide an overall residential exposure to pesticides at the time of 14 years of follow-up. Therefore, further research should be undertaken to investigate the influence of the take-home pesticide exposure pathway on the increased risk of asthma and related respiratory diseases in children.

Also, the literature review suggests that the take-home exposure pathway is one of the contributors to disproportionate pesticide exposures among children of farmworkers living in agricultural communities (Hyland and Laribi, 2017). Furthermore, other studies suggest that children living in agricultural communities may be disproportionately exposed to pesticides through take-home exposure pathways compared to children in the general population (Butler-Dawson et al., 2016, Fenske et al., 2002). Future studies should therefore include a greater emphasis on comparison between non-farm workers as a control group and farmworkers as

an exposed group to investigate the effects of take-home pesticide exposure to children residing in the same settings in order to come up with true control and exposed groups through take-home exposure pathways. This has not been covered in this thesis due to limited information on the occupational status of the parents of the study participants regarding their participation in agricultural activities.

In **Chapter 2**, we considered specific crops and the amount of pesticides used in the agricultural fields as a surrogate of pesticide exposure among the study participants. Future research should include repeated measurements of combined biological and environmental samples as these may improve the assessment of environmental exposure to pesticides of participants living in proximity to the agricultural field but also for the group of participants living further away from the agricultural field. This has been demonstrated by a previous study that used repeated measurements for urine specimens for the determination of metabolites of organophosphate pesticides in children concerning asthma morbidity (Benka-Coker et al., 2020). A study by Becka-Coker et al. (2020) revealed that increased exposure to OP pesticides was associated with a higher risk of asthma exacerbation through inflammation in children with asthma in an agricultural community in the United States. However, the exposure assessment in the study by Benka-Coker et al. (2020) was not similar to the exposure assessment used in **Chapter 2**.

In **Chapter 3**, only agricultural pesticides were investigated concerning the prevalence of asthma and did not consider domestic pesticide use as one of the confounding factors or contributing risk factors. Therefore, domestic pesticide use should be included in future studies as one of the potential contributing factors to the increased risk of asthma and related respiratory symptoms in children. As this has been indicated in previous studies which found that pesticide use in the home was associated with respiratory symptoms among children (Beranger et al., 2019). However, we did not find in the literature any evidence for the

relationship between agricultural use and domestic use. Also, further study is needed to establish evidence for the relationship between agricultural use and domestic use.

In **Chapter 4**, the exposure estimate for cleaning agents was obtained from the self-reported use of cleaning agents in adolescents' homes. Cleaning agents should be characterised in both self-reported and by using the measuring device for detecting personal exposure to cleaning agent constituents in future studies.

The effects of using a cleaning agent on the development of asthma and allergic diseases in children have never been addressed in any of the African Countries. In this thesis, we found that few studies in low-income countries and others presumably non in low-middle-income countries on the effects of cleaning agents on the prevalence of asthma and allergic symptoms (**Chapter 4**). Therefore, there is room for further progress in determining the effects of cleaning agents on the development of asthma and related symptoms as well as allergic symptoms in children and women in developing countries.

CONCLUSION

In **Chapter 2**, we concluded that there is a definite need for future work that uses data on crops based on pesticide use and individual amount of pesticides to investigate the association with respiratory symptoms.

In **Chapter 3**, we conclude that there is a needed to determine quantitative exposure assessment methods using measurements of pesticides in environmental and/or biological samples, and on methods to develop exposure models usable in large-scale epidemiological studies.

Since there are no studies in Africa on the effects of cleaning agents on the risk of respiratory and allergic symptoms in children similar to the study presented in **Chapter 4**, this is an important area for future studies.

Chapter 5, we conclude that since there are no studies in Tanzania regarding the association between environmental exposure to pesticides and increased risk of asthma and related respiratory and allergic symptoms in children, this is an important area for future studies.

Moreover, the work presented was on adolescents aged 14 years. To get a better understanding of associations across the life course, future studies should investigate the association between environmental exposure to pesticides and cleaning agents and the development of asthma as well as allergic symptoms from childhood to adolescent stages.

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Appendices

English Summary

Evidence suggests that the prevalence of asthma and allergic symptoms have risen rapidly over the past decades. It has been suggested that occupational exposure to pesticides is associated with an increased risk of asthma and related respiratory symptoms in adults. There is also the suggestion that adults who use cleaning agents professionally or in the home have an increased risk of asthma and related respiratory symptoms. In addition, there is increasing concern that some cleaning agents being used in households might be associated with an increased risk of asthma and allergic symptoms in children. Moreover, there is a growing body of literature that recognises the importance of investigating the association between environmental exposures to pesticides and cleaning products with the prevalence of asthma and related symptoms in children. However, the current evidence on the effect of exposure to pesticides and cleaning products among children and adolescents is limited.

Chapter 2 evaluates the proximity to agricultural fields which had likely been treated with pesticides as a proxy for environmental exposure to agricultural pesticides at the home addresses of the PIAMA participants at the time of the 14-year follow-up. It was found that a small proportion of the study participants lived near (i.e. within 50 or 100 m) agricultural fields with the selected crops relevant for pesticide use (approximately 7% of the population residing within the 100 m). The results indicated further that 40 and 64 percent of the PIAMA participants lived within 500 and 1,000m buffers, respectively. It was hypothesised that participants who lived within 500 and 1,000m buffers tend to have minimal pesticide exposure compared to participants who lived within 50 and 100 m.

Chapter 3 intended to determine the association between residential exposure to agricultural pesticides and the prevalence of asthma among adolescents. It examined whether living close to crops that are likely treated with pesticides is associated with asthma and related respiratory symptoms among PIAMA participants at the time of 14 years of follow-up. However, we

found no evidence that living close to agricultural fields assumed to have been treated with pesticides is associated with an increased risk of asthma and related respiratory symptoms.

Chapter 4 examined the associations between the use of cleaning agents in households and the prevalence of asthma, rhinitis and eczema symptoms in adolescents. In this chapter, it was found that the use of cleaning agents in the household was not associated with increased risks of asthma, rhinitis, and eczema in adolescents who participated in the PIAMA study at the time of 14 years of follow-up.

Chapter 5 aimed to provide an overview of the legislation, the current situation, and a way forward in the implementation of research on the impact of environmental and occupational exposure to pesticides on human health in Tanzania. Most of the published studies in Tanzania focused on the health effects associated with occupational exposure to pesticides among farm workers. There are limited epidemiological studies on the relationship between environmental exposure to pesticides and respiratory effects on children in Tanzania, despite the intensive use of pesticides. Therefore, **Chapter 5** presents the opportunity for the development of studies investigating the effects of environmental exposure to pesticides on the development of asthma and related respiratory symptoms in children. However, this **Chapter** cannot provide a comprehensive review of the effects of pesticide exposure on human health in Tanzania due to limited data and literature on the subject.

This thesis set out to investigate the effects of environmental exposure to pesticides and cleaning agents on the prevalence of asthma and allergic symptoms in adolescents who participated in the PIAMA. We observed no association between these environmental factors (environmental exposure to pesticides and cleaning agents) and the risk of asthma, related respiratory symptoms, and allergic symptoms in adolescents who participated in the PIAMA study. There is a need to develop a birth cohort study that will investigate the influence of

environmental exposure to pesticides and the use of cleaning agents on the development of asthma, allergic symptoms and lung function in children in developing countries.

Nederlandse Samenvatting

De prevalentie van astma en allergische klachten is gedurende de afgelopen decennia toegenomen. Er wordt gesuggereerd dat beroepsmatige blootstelling aan pesticiden geassocieerd is met een verhoogd risico op astma en gerelateerde luchtwegklachten bij volwassenen. Ook is er aangetoond dat volwassenen die regelmatige schoonmaakmiddelen gebruiken, dan wel voor werk of gebruik thuis, een verhoogd risico hebben. Daarnaast is het gebruik van bepaalde schoonmaakmiddelen in huishoudens mogelijk geassocieerd met een verhoogd risico op astma en allergische symptomen bij kinderen. Echter is de wetenschappelijke literatuur op het gebied van effecten van blootstelling aan pesticiden en schoonmaakmiddelen op kinderen/adolescenten nog beperkt. Daarom benadrukken steeds meer wetenschappelijke studies het belang van onderzoek naar de associatie tussen blootstelling aan pesticiden uit het milieu en het gebruik van schoonmaakmiddelen thuis en astma en gerelateerde symptomen gericht op kinderen.

Hoofdstuk 2 richtte zich op het in kaart brengen van blootstelling aan pesticiden uit het milieu voor deelnemers aan de PIAMAstudie met behulp van gegevens over velden gebruikt voor landbouwdoeleinden die waarschijnlijk behandeld zijn met pesticiden (PIAMA staat voor Preventie en Incidentie van Astma en Mijt Allergie). De nabijheid tot deze velden werd gebruikt als benadering voor de milieublootstelling aan landbouw-pesticiden op het woonadres. Slechts een kleine gedeelte van alle deelnemers bleek vlakbij (binnen een straal van 50 of 100 meter) velden te wonen die gebruikt worden voor de teelt van bepaalde gewassen die relevant zijn vanwege de toepassing van pesticiden (ongeveer 7 procent van de deelnemers woonde op minder dan 100 meter afstand hiervan). De resultaten toonden verder aan dat 40% van de PIAMA deelnemers binnen 500 meter afstand van deze velden woonden en 64% binnen 1000 meter afstand.

Hoofdstuk 3 had als doel om de mogelijke associatie tussen blootstelling aan landbouw-pesticiden op het woonadres en de prevalentie van astma bij adolescenten te onderzoeken. Ook werd bekeken of wonen in de nabijheid van velden met teelt van bepaalde gewassen die waarschijnlijk behandeld worden met pesticiden, geassocieerd was met astma en gerelateerde respiratoire symptomen bij PIAMA deelnemers op het moment van de follow-up op 14-jarige leeftijd. De resultaten leverden echter geen duidelijk bewijs dat wonen in de nabijheid van deze velden geassocieerd is met een verhoogd risico op astma en gerelateerde respiratoire symptomen.

Hoofdstuk 4 onderzocht mogelijke associaties tussen het gebruik van schoonmaakmiddelen in huishoudens en de prevalentie van astma, rinitis (een ontsteking van het neusslijmvlies) en eczeem bij adolescenten. In dit hoofdstuk wordt geconcludeerd dat er geen nadelige gevolgen konden worden aangetoond van het gebruik van schoonmaakmiddelen in het huishouden en de genoemde symptomen bij de PIAMA deelnemers op 14-jarige leeftijd.

Hoofdstuk 5 had als doel om een overzicht te geven, gericht op Tanzania, van de wetgeving, de huidige situatie en de weg voorwaarts voor het implementeren van onderzoeksbevindingen over de impact van blootstelling aan pesticiden zowel vanuit het milieu als beroepsmatig op humane gezondheid. Het merendeel van de gepubliceerde studies hierover in Tanzania, bleek betrekking te hebben op beroepsmatige blootstelling aan pesticiden en gezondheidseffecten bij boeren en landarbeiders. Epidemiologische studies naar de relaties tussen milieu-blootstelling aan pesticiden en respiratoire effecten bij kinderen in Tanzania zijn schaars, ondanks de intensieve toepassing van pesticiden. Daarom wordt in dit hoofdstuk het belang benadrukt voor onderzoek naar de effecten van milieu-blootstelling aan pesticiden en de ontwikkeling van astma en gerelateerde respiratoire symptomen bij kinderen. Dit hoofdstuk bevat niet een uitgebreid review van de effecten van blootstelling aan pesticiden op humane

gezondheid in Tanzania vanwege beperkingen aan beschikbare data en literatuur over dit onderwerp.

Dit proefschrift was gericht op het onderzoeken van de effecten van milieu-blootstelling aan pesticiden en schoonmaakmiddelen op de prevalentie van astma en allergische symptomen in adolescenten die deelnamen aan de PIAMAstudie. Binnen dit onderzoek konden geen associaties aangetoond worden tussen deze milieu-blootstellingen en het voorkomen van astma, gerelateerde respiratoire symptomen en allergische symptomen in adolescenten die deelnamen aan de PIAMAstudie. Het is belangrijk dat geboortecohort studies opgezet worden die gericht zijn op kinderen in ontwikkelingslanden om de invloed van milieu-blootstelling aan pesticiden en het gebruik van schoonmaakmiddelen op de ontwikkeling van astma, allergische symptomen en longfunctie te onderzoeken.

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List of Publications

BUKALASA, J. S., BRUNEKREEF, B., KOPPELMAN, G. H., WIJGA, A. H., VONK, J. M. & GEHRING, U. 2019. Use of cleaning agents at home and respiratory and allergic symptoms in adolescents: the PIAMA birth cohort study. *Environ Int*, 128, 63 -69.

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UNPUBLISHED WORK

BUKALASA, J. S. Environmental and Occupational Exposure to Pesticides and Human Health Effects in Tanzania: Current Understanding and Future Opportunities.

BUKALASA, J. S., OWISSO, R. D., MWEZI, R.J. Residential Exposure to Pesticides and Cleaning Detergents with increased Risk of Respiratory and Allergic Symptoms among Farm Workers in Northern Tanzania (Submitted to ISEE 2022 conference).

Curriculum Vitae

Joseph Stephen Bukalasa was born at the ocean road hospital in Dar es Salaam, Tanzania on August 28, 1979. He graduated from high school (Tosamaganga High School) in 2002. He obtained a Bachelor of Science degree in Environmental Science and Management at the Sokoine University of Agriculture, Tanzania in 2006. In 2006, he started to work with African Assay Laboratories Limited and SGS as Laboratory Chemist until 2007 whereby he joined the Local Government Authority to work with Ngorongoro District Council as Environmental Officer. In 2009, he started a Master of Science in Public Health at Umea University in Sweden. He graduated with a Master's degree in Public Health in 2011. After graduating with a Master of Science in Public Health, Joseph worked with World Vision Tanzania under the project called Kilindi – Maternal, New Born and Child Health (KMNBCH - Project) as Project Officer until 2012. In 2012, he shifted to Arusha and started to work with Tropical Pesticides Research Institute as Research Officer – Toxicology. In January 2015, he started his PhD at the Institute for Risk Assessment Science (IRAS), Utrecht University in The Netherlands. His research focused on the effects of environmental exposure to pesticides and cleaning agents on the prevalence of asthma, related respiratory symptoms and allergic symptoms in adolescents who participated in the PIAMA study. In 2019, Joseph resumed his work at the Tropical Pesticides Research Institute (TPRI) and he was appointed as Acting Registrar of Pesticides in Tanzania. He is mandated to deal with pesticide registration and control in the country. He is also responsible for the implementation of the Pesticides International code of conduct and other international guidelines, agreement and treats.

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