Occupational exposure to pesticides and respiratory health

Ali Mamane[1,2], Isabelle Baldi[1,2,3], Jean-François Tessier[2], Chantal Raherison[1,2,4] and Ghislaine Bouvier[1,2]

Affiliations: [1]ISPED – Laboratoire Santé Travail Environnement, INSERM U897, Université de Bordeaux, Bordeaux, France. [2]ISPED – Centre INSERM U897 – Epidémiologie-Biostatistique, Bordeaux, France. [3]Service de Médecine du Travail, CHU de Bordeaux, Bordeaux, France. [4]Service des Maladies Respiratoires, CHU de Bordeaux, Bordeaux, France.

Correspondence: Ali Mamane, ISPED – Laboratoire Santé Travail Environnement, INSERM U897, Université de Bordeaux, 146 rue Léo Saignat, Bordeaux 33076, France. E-mail: ali.mamane@isped.u-bordeaux2.fr

ABSTRACT This article aims to review the available literature regarding the link between occupational exposure to pesticides and respiratory symptoms or diseases. Identification of epidemiological studies was performed using PubMed. 41 articles were included, 36 regarding agricultural workers and five regarding industry workers.

Among the 15 cross-sectional studies focusing on respiratory symptoms and agricultural pesticide exposure, 12 found significant associations with chronic cough, wheeze, dyspnoea, breathlessness or chest tightness. All four studies on asthma found a relationship with occupational exposure, as did all three studies on chronic bronchitis. The four studies that performed spirometry reported impaired respiratory function linked to pesticide exposure, suggestive of either obstructive or restrictive syndrome according to the chemical class of pesticide.

12 papers reported results from cohort studies. Three out of nine found a significant relationship with increased risk of wheeze, five out of nine with asthma and three out of three with chronic bronchitis. In workers employed in pesticide production, elevated risks of chronic obstructive pulmonary disease (two studies out of three) and impaired respiratory function suggestive of an obstructive syndrome (two studies out of two) were reported.

In conclusion, this article suggests that occupational exposure to pesticides is associated with an increased risk of respiratory symptoms, asthma and chronic bronchitis, but the causal relationship is still under debate.

@ERSpublications
A review of occupational (agricultural and industry) exposure to pesticides and associated respiratory health effects http:///ow.ly/M09Gc

Introduction

Worldwide each year 4 million people die prematurely from chronic respiratory diseases [1], around 300 million people suffer from asthma and 210 million people suffer from chronic obstructive pulmonary disease (COPD) [2]. This situation has led stakeholders to advocate strengthening the fight against the major risk factors for respiratory diseases, including air pollution [3].

Chronic respiratory diseases affect the entire airway from the ear, nose and throat to the pulmonary alveoli, and are characterised by an inflammatory condition induced or aggravated by viruses, bacteria, fungi and environmental components [4, 5]. Among these, allergens, toxins, tobacco smoke, gaseous or

This article has supplementary material available from err.ersjournals.com

Received: July 30 2014 | Accepted after revision: Oct 07 2014

Conflict of interest: None declared.

Provenance: Submitted article, peer reviewed.

particulate air pollutants and a number of chemicals, including pesticides, can present a risk to the respiratory system [6–8].

The generic term "pesticides" covers over 1000 various chemical substances, and they have been increasingly used on crops and livestock since the 1950s. Pesticides can be classified according to their target within three main categories and their numerous chemical groups. 1) Insecticides: organochlorines, organophosphates, carbamates, pyrethroids and newer chemical groups such as neonicotinoids and phenylpyrazoles. 2) Herbicides: amides, chlorophenoxy, bipyridyls, dinitroanilines, triazines, urea herbicides and aminophosphonates. 3) Fungicides: inorganic, dithiocarbamates, anilides, dicarboximides, strobilurin, aromatic, (benz)imidazoles and conazoles. There are also other categories based on target organisms, *i.e.* nematicides, acaricides, rodenticides and fumigants [9]. However, the classification of pesticides remains difficult because a substance can belong to different chemical groups, have different targets and several modes of action. As for toxicity, most of the insecticides, but also some fungicides and herbicides, are neurotoxic, and some substances from various chemical groups can exert genotoxic, reprotoxic and other toxic effects separately and independently from their main effect on weeds, insects or fungal diseases. As a consequence, no worldwide accepted classification currently exists.

Occupational exposure to pesticides occurs directly during manufacture of the product, during transport and storage, and during preparation and spreading by the user, but also during re-entry into treated fields, harvest and equipment cleaning [10, 11]. In agriculture, most pesticides enter the body dermally, followed by respiratory and oral routes [11, 12]. Pesticide inhalation mainly occurs during fumigation, mixture preparation and/or application in closed environments (greenhouses and manufacturing plants). Occupational exposure of farmers, farm workers and pesticide manufacturing industry workers might be the most significant, and has been extensively studied, although para-occupational and residential exposure also deserve interest [13, 14].

A few *in vitro* and animal studies have assessed the toxicity of certain pesticides towards the respiratory system. The exposure of rats to hexachlorobenzene (aromatic fungicide) induced eosinophilic airway inflammation and methacholine bronchial hyperreactivity [5]. Bipyridyl herbicides (paraquat and diquat) are also well known lung toxicants *via* reactive oxygen species (ROS) production [15]. *In vitro* cytotoxicity of folpel (phthalimide fungicide) on human bronchial epithelial cells has also been observed, with a production of ROS in the first hour of exposure, suggesting that folpel exposure could be involved in the pathogenesis of acute or chronic inflammatory respiratory diseases [16].

Thus, the purpose of this article is to review the link between occupational exposure to pesticides and the occurrence of respiratory diseases or symptoms in epidemiological studies.

Methods

Our research was based on the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [17]. A comprehensive search of studies published up to December 2013 on pesticide exposure and respiratory health (chronic diseases, clinical symptoms and impairment in respiratory function) was conducted in the MEDLINE database of the US National Library of Medicine (accessed *via* PubMed). The following keywords were used: "(pesticides OR agrochemicals OR insecticides OR fungicides OR herbicides) and (respiratory disorders OR respiratory diseases OR lung diseases OR wheeze OR asthma OR cough OR bronchitis OR dyspnea) and (epidemiology OR epidemiologic study OR case-control OR cohort) not warfarin" with the following limits: "humans" and "English/French" language.

We retrieved 427 papers; 64 review articles that did not contain original data were excluded (fig. 1). Selection of articles was performed based on titles, then by reading the abstracts so as to rule out irrelevant papers. Three articles identified from the authors' references were added, leading to a total of 68 articles. Seven papers were excluded after reading the full text of the article: four dealt with overall mortality but did not specifically deal with respiratory diseases [18–21], two were toxicology studies [22, 23] and one investigated idiopathic pulmonary fibrosis without mentioning exposure to pesticides [24]. Thus, 61 articles were finally selected for review (fig. 1), 41 dealing with occupational exposures and 20 with environmental exposures. In this review, we will focus on occupational exposure and respiratory health effects.

A standardised reading form allowed us to collect the following information: first author, year of publication, location, study design, objectives, population, respiratory effect, exposure assessment, main results and conclusions.

Among the 36 articles involving agricultural professionals, 22 study designs were cross-sectional, two were case–control and 12 were longitudinal (cohorts). Five studies (one longitudinal (cohort) and four cross-sectional studies) examined exposure among workers in the pesticide industry.

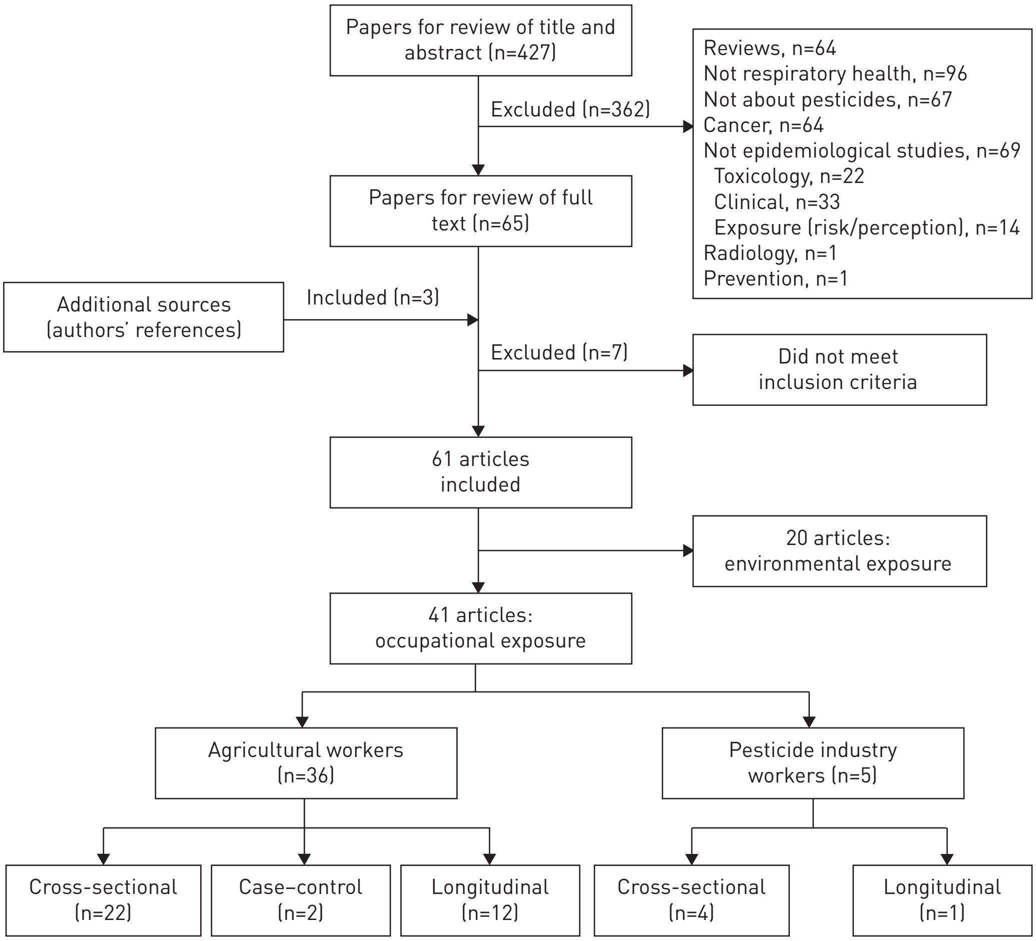

FIGURE 1 Flow chart for the identification and selection of included articles.

Results

Studies on agricultural workers

Cross-sectional and case–control studies

Among the 24 cross-sectional and case–control studies, 20 were based on self-reported symptoms or diagnoses (18 without and three with confirmation by a physician or general practitioner), and measurements of respiratory function were performed in four studies (table 1). Table S1 describes these cross-sectional and case–control studies.

Respiratory diseases: asthma and chronic bronchitis

Regarding respiratory diseases, asthma was studied in four studies [25–28] and chronic bronchitis or COPD were investigated in three studies [26, 27, 29].

Three cross-sectional studies have been conducted since the 1990s. A survey on 1939 male farmers from Saskatchewan (Canada) showed a significant association between self-reported asthma confirmed by a doctor and the use of carbamate insecticides (OR 1.8, 95% CI 1.01–3.01) over the past 5 years [25]. In 2006, a study focusing on 1499 Vietnam veterans who applied Agent Orange (the mixture of two equal parts of the herbicides 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)) showed a higher frequency of chronic respiratory diseases, such as chronic bronchitis, asthma, emphysema or tuberculosis (OR 1.62, 95% CI 1.28–2.05), compared with 1428 matched military employees who did not fight in Vietnam [26]. In the United Arab Emirates in 1999, 98 male agricultural workers were compared to 98 non-agricultural workers. Exposure was defined as having applied pesticides during the month preceding the study or working in close proximity to spreading areas (60% of agricultural workers). A higher prevalence of asthma (OR 1.8, 95% CI 1.01–3.01) and chronic bronchitis (OR 1.38, 95% CI 1.09–1.78) was observed [27].

Two case–control studies were conducted in Lebanon in 2006. Based on the subjects' responses, three types of exposure (occupational, para-occupational, and domestic or living next to a farm) were defined.

DOI: 10.1183/16000617.00006014

DOI: 10.1183/16000617.0006014

TABLE 1 Effects of pesticides on the respiratory health of agricultural workers

First author [ref.]	Country	Summary of method			Statistically significant main findings
		Population	Pesticide exposure	Health outcomes	
Respiratory diseases: asthma and bronchitis					
Senthilselvan [25]	Canada	1939 farmers	Organophosphate, organochlorine, carbamate insecticides	Self-reported respiratory symptoms	Increased asthma with carbamate insecticide use
Kang [26]	USA	1499 Vietnam veterans/ 1428 non-Vietnam veterans	Sprayed herbicides (Agent Orange)	Self-reported; chronic medical condition diagnosed by a doctor	Increased chronic bronchitis and asthma, elevated among Vietnam veterans who sprayed herbicides *versus* non-Vietnam veterans
Bener [27]	United Arab Emirates	98 farmers/98 controls	Pesticides (not specified)	Lifelong respiratory symptoms	Increased chronic cough and asthma in farmers *versus* controls
Salameh [28]	Lebanon	245 asthma cases/ 262 controls	Pesticides (not specified)	Confirmation of asthma by lung specialist	Increased asthma with any exposure to pesticides
Salameh [29]	Lebanon	110 chronic bronchitis cases/262 controls	Pesticides (not specified)	Confirmation of chronic bronchitis by lung specialist	Increased chronic bronchitis according to increase in intensity and/or duration of different levels of exposure to pesticides
Respiratory symptoms					
Zuskin [30]	Croatia	167 exposed/ 81 unexposed workers	Pesticides (not specified)	Lifelong respiratory symptoms	Increased chronic cough, dyspnoea and chest tightness in exposed females *versus* controls ($p<0.01$)
Zuskin [31]	Croatia	174 exposed/ 115 unexposed workers	Pesticides (not specified)	Pulmonary function measures (spirometry)	Increased chronic cough and chronic phlegm ($p<0.05$) in workers employed for >10 years
Castro-Gutiérrez [32]	Nicaragua	134 paraquat exposed/ 152 unexposed workers	Paraquat	Respiratory symptoms during the last 24 months	Increased episodic wheezing accompanied by shortness of breath among the more intensely exposed workers
Wilkins [33]	USA	1793 farmers	Pesticides (not specified)	Respiratory symptoms during the last 12 months	Increased chronic cough with lifetime tractor operations
Sprince [34]	USA	385 farmers	Agricultural pesticides (insecticides for crops and livestock, and herbicides)	Respiratory symptoms	Increased ever-wheezy chest due to applying pesticides to livestock
Beseler [35]	USA	761 farm operators and spouses	Agricultural pesticides (not specified)	History of respiratory disorders and symptoms	Increased wheeze with pesticide poisoning in current smokers
Masley [36]	Canada	511 males, 499 females and 393 children	Pesticides and fertilisers	Respiratory symptoms during life	Increase in one or more respiratory symptoms (cough, phlegm, wheeze or shortness of breath) with pesticide exposure
Schenker [37]	Costa Rica	219 farm workers/ 110 controls	Paraquat	Respiratory symptoms	Increased shortness of breath with wheeze with each unit increase in the total cumulative paraquat index

Continued

TABLE 1 Continued

First author [ref.]	Country	Summary of method			Statistically significant main findings
		Population	Pesticide exposure	Health outcomes	
Fieten [38]	Costa Rica	69 exposed/ 58 unexposed workers	Terbufos, chlorpyrifos, paraquat	Respiratory symptoms during past year	Increased wheeze with exposure to the organophosphate insecticides chlorpyrifos and terbufos in nonsmokers
Faria [39]	Brazil	1379 farmers	Organophosphates, pyrethroids and dithiocarbamates	Self-reported asthma and chronic respiratory diseases	Increased asthma symptoms and chronic respiratory disease symptoms with pesticide poisoning
Ejigu [40]	Ethiopia	82 farm workers/ 47 controls	Agricultural pesticides (not specified)	Lifelong respiratory symptoms	Increased prevalence of respiratory symptoms, including cough, phlegm and wheeze in farm workers *versus* controls ($p<0.05$)
Pathak [41]	India	108 pesticide sprayers/ 30 controls	Agricultural pesticides	Respiratory symptoms	Increased respiratory symptoms with tractor-mounted sprayers compared to controls
Ngowi [42]	Tanzania	133 coffee farm workers	Agricultural pesticides: fungicides, insecticides and herbicides	Respiratory symptoms during spraying and nonspraying seasons	No significant association
Jones [43]	USA	100 pilots (aerial spraying of pesticides)/ 100 controls	Agricultural pesticides	Respiratory symptoms	No significant association
Abu Sham'a [44]	Palestine	250 farmers	Agricultural pesticides not specified	Respiratory symptoms during the last 12 months	No significant association
Respiratory function					
Mekonnen [45]	Ethiopia	102 pesticide sprayers/ 69 non-sprayers	Pesticides on the farms: chlorpyrifos, diazinon and malathion	Pulmonary function measurements	Decreased lung volumes (reduced FVC and FEV_1) in the 15–24-year age group of pesticide sprayers compared to similarly aged non-sprayers
Hernández [46]	Spain	89 pesticide sprayers/ 25 unexposed farm workers	10 agricultural pesticides	Physical examination during the peak spraying season	Decreased $FEF_{25-75\%}$ with lifelong cumulative exposure to pesticides; decreased lung volumes (restrictive disease) with recent exposure to neonicotinoids
Chakraborty [47]	India	376 exposed/ 348 controls	Agricultural pesticides	Pulmonary function measurements	Decreased lung function in exposed workers compared to controls ($p<0.001$)
Cha [48]	South Korea	2508 paraquat applicators/ 374 non-paraquat applicators	Paraquat	Report of doctor-diagnosed symptoms/diseases: COPD and asthma; pulmonary function measurements	Decreased restrictive ventilatory defect with paraquat application

All the studies were cross-sectional except those of Salameh and co-workers [28, 29], which were case–control studies. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC; COPD: chronic obstructive pulmonary disease.

DOI: 10.1183/16000617.00006014

The first study included 245 asthmatics and 262 controls selected by a chest physician. A significant increase in the risk of asthma for any type of pesticide exposure was observed (OR 2.11, 95% CI 1.47–3.02) and occupational use showed the highest risk (OR 4.98, 95% CI 1.07–23.28) [28]. The second study included 110 subjects with chronic bronchitis confirmed by a lung specialist and 262 controls. The results of this study showed that chronic bronchitis was associated with exposure to pesticides (OR 2.46, 95% CI 1.53–3.94), particularly with occupational exposure (OR 15.92, 95% CI 3.50–72.41) [29].

Respiratory symptoms

15 cross-sectional studies investigated the link between agricultural work or pesticide exposure and various respiratory symptoms.

In Croatia in 1993, the respiratory health of 167 greenhouse workers was compared to 81 office workers. Chronic cough, dyspnoea and rhinitis were more frequent in exposed females, and rhinitis was more frequent in exposed males [30]. In 1997, 174 vineyard and orchard workers from Croatia were found to suffer more frequently from dyspnoea, chest tightness, chronic cough and chronic phlegm than unexposed workers employed in the food industry [31]. In 1997 in Nicaragua, symptoms of 134 applicators of paraquat on banana plantations were compared to 152 controls, *i.e.* nonsprayer plantation workers. They suffered more frequently from severe dyspnoea (least exposed: OR 2.8; most exposed: OR 4.6) and episodic breathlessness and wheezing (most heavily exposed: OR 2.9) [32].

A study dealing with cereal producers in Ohio, USA, in 1999 on 1793 male cereal producers showed an association between past life as a tractor driver and chronic cough (OR 3.34, 95% CI 1.30–10.8). It also revealed a link between the surface area of corn grown for silage or fodder and cough (OR 3.85, 95% CI 1.04–14.2). Direct contact with pesticides was not significantly associated with chronic cough and dyspnoea [33]. Insecticide use on livestock over the past 12 months was associated with a significantly increased risk of chronic phlegm (OR 1.91, 95% CI 1.02–3.57), wheezing (OR 3.92, 95% CI 1.76–8.72) and influenza-like symptoms (OR 2.93, 95% CI 1.69–5.12), whereas no association was observed for the use of insecticides or herbicides on crops in 385 male farmers in Iowa, USA [34]. In study from north eastern Colorado (USA), including 761 farmers and their spouses in 2009, pesticide intoxication was found to be significantly associated with cough (OR 2.18, 95% CI 1.03–4.64) and allergy (OR 1.95, 95% CI 1.08–3.53) among nonsmokers and with wheezing among smokers (OR 8.21, 95% CI 1.28–52.6) [35]. The PECOS (Prairie Echo) study, conducted in 2000 in rural Saskatchewan, showed an increased prevalence of bronchitis (OR 4.3, 95% CI 2.0–9.4) and respiratory symptoms (cough, chronic phlegm, wheezing and shortness of breath) (OR 2.4, 95% CI 1.1–5.2) among farmers' wives only [36]. In 2004, Schenker *et al.* [37] studied paraquat exposure on banana, coffee and oil palm tree plantations in male farm workers in Costa Rica. A cumulative index of exposure, taking into account the history of tasks and protective equipment, was calculated. For each unit increase of this index, the risk of chronic cough was almost doubled (OR 1.8, 95% CI 1.0–3.1) and was more than doubled for breathlessness and wheezing (OR 2.3, 95% CI 1.2–5.1) [37]. Another study by Fieten *et al.* [38] showed a higher incidence of wheezing in nonsmokers reporting use of chlorpyrifos (OR 6.7, 95% CI 1.6–28.0) or terbufos (OR 5.9, 95% CI 1.4–25.6) among 69 female Costa Rican plantain workers.

A study conducted in 2005 among 1379 Brazilian agricultural workers showed that a history of pesticide poisoning was associated with a higher prevalence of asthma symptoms (OR 1.54, 95% CI 1.04–2.58) and chronic respiratory disease symptoms (OR 1.57, 95% CI 1.08–2.28), the effect of these pesticide exposures on respiratory disease was stronger in females than males [39].

A study on 82 Ethiopian male farmers applying pesticides on corn, sesame, pepper, soy and wheat found a higher prevalence of chronic cough, phlegm and wheeze compared to 47 office workers [40].

The most recent study in 2011 was performed in India (north Uttar Pradesh) in 108 male pesticide applicators (42 backpack sprayers and 66 tractor-mounted sprayers) on cereals and vegetables. There was an increased risk of respiratory symptoms among applicators using a tractor-mounted sprayer (OR 5.14, 95% CI 1.0–29) and a nonsignificant increase for those using a backpack sprayer (OR 3.41, 95% CI 0.77–21) compared to control subjects [41].

Three cross-sectional studies reported no association between occupational exposure to pesticides or working in agriculture and respiratory health. In the 1990s, the frequency of respiratory symptoms reported by 133 farmers in Tanzanian coffee plantations was comparable between spraying and nonspraying periods of organophosphate insecticide [42]. In 2003, no difference in the frequency of respiratory symptoms was observed between 100 pilots performing aerial application of agricultural pesticides in the USA and 100 unexposed matched controls [43]. Finally, no significant association was found between exposure to organophosphate pesticides and reported respiratory symptoms among 250 Palestinian male farmers cultivating fruit and vegetables [44].

DOI: 10.1183/16000617.00006014

Respiratory function

Finally, only four cross-sectional studies performed respiratory function measurements. In 2004, a study was performed in Ethiopia in the Great Rift Valley among 102 pesticide sprayers on orchards, cereal and vegetable crops, and in a control group of 69 nonapplicator farm workers. Sprayers were backpack applicators of organophosphate insecticides (chlorpyrifos, diazinon and malathion). The 15–24-year age group of pesticide sprayers had significantly reduced forced expiratory vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) compared to a similarly aged group of nonsprayers [45]. In greenhouse truck farms in Andalusia, Spain, respiratory function was studied in 89 pesticide applicators and 25 nonapplicators. Recent exposure to cholinesterase inhibitors was associated with a decrease in FEV_1, and cumulative lifetime exposure to pesticides with a reduction in forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$); both are signs of obstructive airway syndrome. Recent use of neonicotinoid insecticides was associated with various impairments in lung function suggesting a restrictive syndrome, and use of bipyridilium herbicides with abnormal alveolar–capillary diffusion [46]. Chakraborty *et al.* [47] compared respiratory function of 376 nonsmoking male farmers in rural Bengal, India, who applied organophosphate and carbamate insecticides to rice, wheat and vegetable crops, and 348 nonagricultural workers. A significant reduction in lung function (FVC and FEV_1/FVC) was observed in the farmers [47]. A study conducted among South Korean farmers (2508 applicators of paraquat and 374 nonapplicators) found significantly lower FVC and FEV_1 in applicators with a dose–response relationship for duration of paraquat application (>30 years: OR 1.89, 95% CI 1.11–3.24; >150 days: OR 1.76, 95% CI 1.04–2.98) [48].

Finally, 12 out of 15 cross-sectional studies found a significant relationship between pesticide exposure and various respiratory symptoms; four studies out of four found a relationship with asthma and three studies out of three found a relationship with chronic bronchitis. Regarding the definition of respiratory health, all four studies measuring respiratory function showed impaired function (FEV_1, FVC and $FEF_{25–75\%}$ reduction) linked to pesticide exposure. To assess respiratory health symptoms or diseases, 16 studies used standardised, validated questionnaires either from the British Medical Research Council (MRC), the American Thoracic Society (ATS), the ATS Division of Lung Diseases or the European Community Respiratory Health Survey (ECRHS).

However, in some studies, pesticide exposure assessment was missing or very brief. Working in the agricultural sector was assumed to be equivalent to being exposed to pesticides. However, although only a few studies assessed lifelong pesticide use and calculated cumulative exposure indexes, they all found a dose–effect relationship [32, 37, 46, 48].

Longitudinal studies

Table 2 presents a summary of the longitudinal studies on respiratory health and occupational pesticide exposure. Table S2 describes these studies in detail.

Wheeze and asthma

Four cohorts have published results dealing with pesticide exposure and asthma or wheeze.

The main study, the Agricultural Health Study (AHS), is a cohort of 89 655 subjects who were included between 1993 and 1997 in Iowa and North Carolina (both USA) to explore the health effects of pesticides and other agricultural exposures in farm-based pesticide applicators (n=52 394), their spouses (n=32 345) and commercial pesticide applicators (n=4916). Participants were asked about the use of 50 pesticides among the most commonly used in the two states (frequency of use, number of years and number of lifetime application days). The average age was >40 years at baseline [61]. Several studies on occupational pesticide exposure and respiratory health effects have been conducted in the AHS cohort.

An association between wheeze and exposure to 11 pesticides was observed in 20 468 applicators who responded to the respiratory questionnaire, with higher risks for two herbicides (paraquat: OR 1.27, 95% CI 1.04–1.56; *S*-ethyl-dipropylthiocarbamate (EPTC): OR 1.32, 95% CI 1.05–1.65) and three organophosphate insecticides (parathion: OR 1.50, 95% CI 1.04–2.16; malathion: OR 1.50, 95% CI 1.02–1.28; chlorpyrifos: OR 1.12, 95% CI 1.01–1.25). A dose–response relationship was observed for wheeze and atrazine (>20 days per year: OR 1.53, 95% CI 1.21–1.95) [49].

Among farmers, seven of the 40 pesticides used in the previous year were significantly associated with the occurrence of wheeze over the past 12 months (herbicides: alachlor, atrazine, EPTC, petroleum oil and trifluralin; and insecticides: malathion and permethrin for animals) with odds ratios ranging between 1.13 and 1.37 (the highest value was for EPTC). For commercial applicators, three pesticides (herbicide: chlorimuron-ethyl; and insecticides: dichlorvos and phorate) were associated with higher risks than those observed in farmers, the highest being for dichlorvos (OR 2.48, 95% CI 1.08–5.66) and phorate (OR 2.35, 95% CI 1.36–4.06). A dose–response relationship was observed for chlorimuron-ethyl among

DOI: 10.1183/16000617.00006014

TABLE 2 Respiratory health of agricultural workers: longitudinal studies

First author [ref.]	Country	Summary of method			Statistically significant main findings
		Population	Pesticide exposure	Health outcomes	
Asthma and wheeze					
Hoppin [49]	USA	20 468 pesticide applicators (farmers) and 16 630 farmers in the AHS	40 specific pesticides	Self-reported wheeze	Increased wheezing with atrazine, chlorpyrifos and parathion
Hoppin [50]	USA	17 920 pesticide applicators and 2255 commercial pesticide applicators in the AHS	40 specific pesticides	Self-reported wheeze	Increased wheeze with five pesticides used in the past year in farmers; increased wheeze with chlorimuron-ethyl, dichlorvos, and phorate in commercial applicators
Hoppin [51]	USA	2255 commercial pesticide applicators in the AHS	40 specific pesticides	Self-reported wheeze, asthma (self-reported doctor-diagnosed)	Increased wheeze with eight herbicides; highest odds ratio was for application of chlorpyrifos for >40 days per year
Hoppin [52]	USA	25 814 female farm workers, including 702 cases of asthma and 25 112 control subjects in the AHS	50 specific pesticides	Self-reported doctor-diagnosed asthma after 19 years of age	Increased atopic asthma with seven insecticides, two herbicides and one fungicide; parathion use had the highest odds ratio (2.88); increased non-atopic asthma only with permethrin use on crops
Hoppin [53]	USA	19 704 farmers, including 441 cases of asthma and 19 263 control subjects in the AHS	50 specific pesticides	Self-reported doctor-diagnosed asthma after 19 years of age	Increased allergic asthma with ever-use of 12 pesticides and nonallergic asthma with four pesticides; for allergic asthma, the strongest association was with coumaphos (odds ratio 2.34), and for nonallergic asthma with DDT
Henneberger [54]	USA	926 adult pesticide applicators with active asthma in the AHS	36 specific pesticides	Exacerbation of asthma, self-reported visit to emergency room	Increased exacerbation of allergic asthma associated with pendimethalin and aldicarb
Beard [55]	Australia	1999 outdoor staff working as part of an insecticide application and 1984 outdoor workers not occupationally exposed to insecticides	Pesticides: arsenic, DDT and other chemicals	Ascertainment of vital status	Higher asthma mortality for applicators compared with the general Australian population; increased asthma mortality in subjects working with modern chemicals compared to other subjects
Baldi [56]	France	15 494 farmers, including 1246 cases of asthma in the AGRICAN study	Agricultural pesticides and farming activities	Self-reported doctor-diagnosed asthma	Increased allergic asthma in participants reporting a history of pesticide poisoning
Boers [57]	Netherlands, Italy, Finland and Bulgaria	248 workers exposed to pesticides and 231 non-exposed workers from the EUROPIT study	Ethylenebisdithiocarbamate and/or other pesticides	Self-reported asthma and respiratory symptoms	No significant association
Chronic bronchitis					
Hoppin [58]	USA	20 908 farmers, including 654 cases of chronic bronchitis in the AHS	50 specific pesticides	Self-reported doctor-diagnosed chronic bronchitis after 19 years of age	Increased chronic bronchitis with 11 pesticides; heptachlor use had the highest odds ratio (in the adjusted model)

Continued

DOI: 10.1183/16000617.00006014

TABLE 2 Continued

First author [ref.]	Country	Summary of method			Statistically significant main findings
		Population	Pesticide exposure	Health outcomes	
Valcin [59]	USA	21 541 nonsmoking female spouses of farm workers, including 583 cases of chronic bronchitis in the AHS	50 specific pesticides	Self-reported doctor-diagnosed chronic bronchitis after 19 years of age	Increased chronic bronchitis with five pesticides in nonsmoking spouses of farmers; paraquat use had the highest odds ratio
Tual [60]	France	14 441 farmers, including 1207 cases of chronic bronchitis	Agricultural pesticides and farming activities	Self-reported doctor-diagnosed chronic bronchitis after 20 years of age	Increased chronic bronchitis with exposure to pesticide poisoning and pesticide use in potato farmers

AHS: Agricultural Health Study; DDT: dichlorodiphenyltrichloroethane; AGRICAN: Agriculture and Cancer.

farmers and commercial applicators (>10 days of use per year: OR 1.39 (95% CI 1.03–1.88) and OR 1.97 (95% CI 1.34–2.90), respectively), and for chlorpyrifos among farmers and commercial applicators (>20 days of use per year: OR 1.48 (95% CI 1.00–2.19) and OR 1.96 (95% CI 1.05–3.66), respectively) [50]. Similar results were observed in 2255 commercial applicators in Iowa [51].

Among 25 814 female farmers in the AHS, 702 (2.7%) reported a diagnosis of asthma, including 282 allergic cases (with eczema or hay fever) and 420 nonallergic cases. Exposure to pesticides was associated with allergic asthma only (OR 1.46, 95% CI 1.14–1.87). 10 pesticides (seven insecticides, two herbicides and one fungicide) were significantly associated with allergic asthma, the highest risks were observed with parathion (OR 2.88, 95% CI 1.34–6.20), coumaphos (OR 2.19, 95% CI 1.02–4.69) and metalaxyl (OR 2.61, 95% CI 1.35–4.04). The use of permethrin on crops (OR 2.19, 95% CI 1.33–3.61) was the only pesticide associated with nonallergic asthma [52].

Among the 19 704 male farmers, 441 (2.2%) asthmatics (allergic: n=127; nonallergic: n=314) were identified. High exposure to pesticides, characterised by poisoning or injury, was associated with a doubling of the risk of asthma of both allergic (OR 1.98, 95% CI 1.30–2.99) and nonallergic origin (OR 1.96, 95% CI 1.49–2.56). 12 pesticides were associated with an increased risk of allergic asthma, with odds ratios >2 for coumaphos (OR 2.34, 95% CI 1.49 – 3.70), heptachlor (OR 2.01, 95% CI 1.30–3.11), parathion (OR 2.05, 95% CI 1.21–3.46) and fumigants (tetrachloride/carbon disulfide: OR 2.15, 95% CI 1.23–3.76; ethylene dibromide: OR 2.07, 95% CI 1.02–4.20). For nonallergic asthma, four pesticides (petroleum oil, dichorodiphenyltrichloroethane (DDT), malathion and phorate) were associated with an increased risk of asthma. The organochlorine DDT was the most strongly associated (OR 1.41, 95% CI 1.09–1.84) [53]. More recently, 926 pesticide applicators (farmers and commercial) with active asthma were studied to find a link between asthma exacerbation during the past 12 months (observed in 202 (22%) applicators) and the use of pesticides at inclusion. A positive link was observed only between allergic asthma exacerbation and the use of the herbicide pendimethalin (OR 2.1, 95% CI 1.1–4.1) and the insecticide aldicarb (OR 10.2, 95% CI 1.9–55) [54].

Other longitudinal studies have studied the link between asthma and pesticide occupational exposure. In Australia, a control programme against ticks in cattle was conducted between 1935 and 1995. Three types of pesticides were successively used: an arsenic derivative from 1935 to 1955, DDT from 1955 to 1986 and modern synthetic products from 1976. Mortality in 1999 Australian workers involved in this programme was compared to that of 1984 matched unexposed workers. Asthma mortality during the follow-up period was higher in subjects exposed to pesticides (standardised mortality ratio (SMR) 3.45, 95% CI 1.39–7.10) and the risk was greater by restricting the analysis to the period of synthetic pesticide use (SMR 6.44, 95% CI 1.33–18.8) [55].

In France, the first results in a 10% sample (n=14 441 farmers) of the AGRICAN (Agriculture and Cancer) cohort were published in 2013. A link was found between allergic asthma and the use of pesticides in pastures (OR 1.35, 95% CI 1.08–1.68), on vines (OR 1.43, 95% CI 1.15–1.77), for fruit growing (OR 1.58, 95% CI 1.20–2.09), on beets (OR 1.52, 95% CI 1.16–2.00), in greenhouses (OR 1.66, 95% CI 1.10–2.51) and for horse breeding (OR 1.35, 95% CI 1.02–1.80). Risks of allergic asthma were increased in participants reporting a history of pesticide poisoning (OR 1.97, 95% CI 1.43–2.73). For nonallergic

 DOI: 10.1183/16000617.00006014

asthma, the only significant association was observed in participants involved in pesticide use on beets (OR 1.47, 95% CI 1.03–2.10) [56].

The multicentre prospective EUROPIT study involved 248 farmers occupationally exposed to pesticides and 231 unexposed workers in various occupational sectors in the Netherlands, Italy, Finland and Bulgaria. No association was observed with the diagnosis of asthma (OR 1.19, 95% CI 0.93–1.52) or the occurrence of asthma attacks (OR 1.14, 95% CI 0.72–1.80) and urinary levels of ethylene thiourea, a metabolite of dithicarbamate fungicides [57].

Chronic bronchitis

Two cohorts, AHS and AGRICAN, studied the link between agricultural practices and chronic bronchitis.

Among 20 908 farmers and/or commercial applicators of pesticides from the AHS cohort (20 400 males and 508 females), 654 (3%) had chronic bronchitis (reported diagnosis of chronic bronchitis established by a doctor after the age of 19 years) [58]. Chronic bronchitis was significantly associated with 11 pesticides, with heptachlor (organochlorine insecticide) presenting the strongest association (OR 1.50, 95% CI 1.19–1.89). The prevalence of chronic bronchitis was also associated with a history of acute pesticide exposure (OR 1.85, 95% CI 1.51–2.25). In the 21 541 nonsmoking spouses of farmers, five pesticides were associated with chronic bronchitis: dichlorvos (OR 1.63, 95% CI 1.01–2.61), DDT (OR 1.67, 95% CI 1.13–2.47), carbofuran (carbamate insecticide) (OR 1.68, 95% CI 1.03–2.74), cyanazine (OR 1.88, 95% CI 1.00–3.54), and paraquat (OR 1.91, 95% CI 1.02–3.55). Growing up on a farm was associated with a decreased risk of chronic bronchitis (OR 0.81, 95% CI 0.68–0.97) [59].

In the AGRICAN cohort (n=14 441 farmers), the authors found a significant association between chronic bronchitis and two agricultural activities: livestock farming (OR 1.24, 95% CI 1.03–1.48) and potato production (OR 1.33, 95% CI 1.13–1.57) [60].

In summary, a total of nine out of the 12 papers from three cohorts focused on asthma/wheeze; three observed a significant relationship with increased risk of wheeze, and five with asthma. Only one cohort study did not find any relationship between asthma and exposure to one chemical group of fungicides. Three out of three articles found a significant relationship with chronic bronchitis. None of these longitudinal studies performed respiratory function measurements due to the study design and sample size. Moreover, the questionnaires were specific to the studies; however, questions referred to disease "diagnosed by a doctor" in eight articles.

Studies among workers in the pesticide manufacturing industry

19 Lebanese male workers packaging liquid pesticides (pyrethroid and carbamate insecticides) had a 5.6-fold higher risk of impaired respiratory function (abnormal FEV_1/FVC) and a 16.5-fold higher risk of an abnormal $FEF_{25\%}$, characteristic of an obstructive syndrome, compared to 43 workers from other factories not manufacturing pesticides [62].

Zuskin *et al.* [63] studied the respiratory health of 82 workers (30 females and 52 males) in a pesticide-manufacturing plant in Croatia. In females, a significant relationship between duration of work and $FEF_{25\%}$ was observed and duration of work was strongly associated with abnormalities in all lung function parameters in males [63].

In four states of the USA (Michigan, Illinois, Washington and Kansas), Ruder *et al.* [64] conducted a retrospective cohort among 2122 pentachlorophenol plant workers. All workers who had already worked in a pentachlorophenol-manufacturing plant and were registered in the National Institute for Occupational Safety and Health database were included. Causes of death between 1940 and 2005 were determined from the National Death Index of the National Center for Health Statistics. A significant excess of mortality was observed for COPD (63 deaths: SMR 1.38, 95% CI 1.06–1.77) but not for other diseases of the respiratory system (94 deaths: SMR 1.02, 95% CI 0.82–1.25).

Burns *et al.* [65] examined 496 employees in the Dow Chemical Company (Midland, MI, USA), working in the production of the organophosphate insecticide chlorpyrifos, and 911 unexposed matched workers in the same city. Health data were extracted from the company's medical records and a diagnosis of some respiratory diseases (acute respiratory infection, other diseases of the upper respiratory tract, COPD and pneumoconiosis) was more frequent in chlorpyrifos production workers. There was a strong association between exposure and acute respiratory infections (OR 1.49, 95% CI 1.8–2.5) [65].

A study conducted in New Jersey and Missouri (both USA) in 1991 involved 281 workers in units manufacturing the herbicide 2.4.5-T and its derivatives and 260 matched, unexposed people living in the same area. No significant association was observed between 2,3,7,8-tetrachlorodibenzo-p-dioxin blood levels (contaminant of 2.4.5-T production) and COPD (OR 1.58, 95% CI 0.59–4.25) [66].

DOI: 10.1183/16000617.00006014

In summary, these studies focused on respiratory function or COPD in pesticide industry workers. Two of them found impaired respiratory function, one found an excess of COPD disease and respiratory tract infections, and one found an excess of COPD mortality. The last study did not find any association with COPD. None of them studied asthma and wheeze. Table S3 describes these studies in detail.

Discussion

Since the 1950s, the desire to improve the yield of agricultural crops has led to widespread use of various kinds of products such as fertilisers, herbicides, fungicides and insecticides. The clinical observation of short-term and long-term respiratory symptoms in people using these substances or working in their manufacture or packaging has contributed to a growing awareness of the risks associated with the use of these products [4]. The objective of this article was to review the available literature regarding the potential respiratory risks of occupational and environmental pesticides. The literature search allowed 41 studies dealing with the occupational context to be selected.

We focused our review on respiratory symptoms, asthma and chronic bronchitis; the definition of COPD was not clear in some articles with only a few studies having performed a measure of respiratory function. Regarding the potential link between pesticides and lung cancer, which is an important question, we decided to exclude lung cancer from the scope of our review. Indeed, the question of the specific pattern of cancers in farmers (including lung cancer) has been addressed in a more general way in many reviews. While some pesticides have oncogenic properties in humans, farmers generally smoke less than the general population. The consequence is that the prevalence of lung cancer is generally lower in farmers than in nonfarmers, possibly even taking smoking into account. A recent review, conducted by Alavanja and Bonner [67] included a rather complete specific section on lung cancer. The authors concluded that a large number of studies noted associations between widely used classes of pesticides and lung cancer, with some specific exposure–response gradients [67].

It is clear from this review that the majority of epidemiological studies have convergent results, indicating that occupational exposure to pesticides and agricultural practices are associated with an increased risk of respiratory symptoms or diseases.

However, the question that arises is about the nature of the link observed in most of these studies. Hill [68] proposed the following criteria for determining a causal association: strength of association, consistency, specificity, temporality, dose–response link, biological plausibility, experimental evidence and analogy. Some of these criteria have been met in some of the studies reviewed, and suggest a causal relationship between occupational exposure to pesticides and respiratory health, although involved symptoms, respiratory function parameters and diseases are not always the same.

The health data collected in these studies were mostly based on the use of standardised questionnaires. The ATS questionnaire was used in 11 studies, the British MRC questionnaire in seven studies and the ECRHS questionnaire in one study. The AHS and AGRICAN cohorts had their own questionnaire, although based on the previous questionnaires, but for other studies the reliability of questionnaire items is unknown. Spirometric measurements were performed in only four studies, mainly cross-sectional studies, due to the time and cost preventing their use in a cohort study design. Pesticide exposure assessment was often scarce due to the type of work performed or the questionnaire used, which were mostly retrospective, and only a few authors calculated a cumulative index or assessed various parameters of exposure (type of pesticides, duration and frequency). Blood and urinary metabolites of pesticides were measured in three studies. Indeed, in most of the cases they are useful to assess recent, but not past, exposure to nonpersistent pesticides. Among agricultural workers, despite their limitations, data from cross-sectional studies are already making a case for the respiratory risk faced by workers who come into contact with pesticides. Most cross-sectional studies carried out among agricultural workers showed significant positive associations between pesticide exposure and the occurrence of respiratory health effects. Pesticide exposure was associated with a higher prevalence of respiratory symptoms (cough, wheeze, phlegm, breathlessness and chest tightness), impairments in lung function, and asthma and chronic bronchitis. Only three studies did not find any association, which may be partly explained by the short duration of exposure, use of personal protective equipment or agricultural practices, characteristics of the control group and small sample size.

In the case of occupational exposure to paraquat, there was a dose–response relationship with the risk of chronic cough or dyspnoea, breathlessness and wheezing [32, 37]. Among pesticide applicators, several studies showed impairments in respiratory function, especially with paraquat (reduction associated with the number of years of application) [48] and organophosphate, carbamate, neonicotinoid insecticides and bipyridylium herbicides, sometimes with a dose–effect relationship [46].

However, the most conclusive results come from longitudinal studies. The AHS cohort has given rise to a series of studies on exposure to specific pesticides and showed that numerous pesticides were significantly

 DOI: 10.1183/16000617.00006014

associated with allergic asthma [52], wheeze [49, 51] and chronic bronchitis [58]. It was also shown that accidental exposure or pesticide poisoning were associated with an increased risk of allergic and nonallergic asthma [59]. The more recent French AGRICAN cohort studied asthma and chronic bronchitis according to type of crop or cattle. Allergic asthma was associated with pesticide use on crops (grassland and vineyard) and pesticide poisoning, nonallergic asthma was associated with pesticide use on beets [56], and chronic bronchitis was associated with pesticide poisoning for those without healthcare [60].

Other interesting results concern early life on a farm and asthma risk [23, 53, 56]. The results suggest that growing up on a farm might modify the association between pesticide use and asthma risk.

A recent review of the literature on the link between asthma and exposure to pesticides focused on studies of the pathophysiological mechanisms. The originality of this work lies in the hypotheses that might explain the links demonstrated by epidemiological studies. According to this review, the main mechanism lies in the neurogenic inflammation induced by contact with pesticides in agricultural populations. In the case of asthma induced by organophosphates, the problem seems to be a dysfunction in muscarinic M2 receptors, which are normally used to limit the release of acetylcholine esterase by parasympathetic fibres [69].

With regard to subjects involved in the manufacture of pesticides, the majority of studies (four out of five) also found significant positive associations between pesticide exposure and respiratory symptoms or decreased lung function. These studies focused on the manufacture of pentachlorophenol [64] and chlorpyrifos [65], the packaging of liquid pesticides (pyrethroids and carbamates) [62] and various other pesticides [63]. No association was observed among workers in 2,4,5-T production in one study [66]. These results should lead to questions in regulations concerning the manufacture of pesticides in order to control the risks of such substances on the health of factory workers.

Numerous cross-sectional and longitudinal studies have found a positive association between agricultural work or exposure to pesticides in farmers and respiratory symptoms (such as chronic cough, wheeze and phlegm), self-reported asthma and chronic bronchitis, and, in several studies, impaired pulmonary function parameters. Unfortunately, at this time, there is no longitudinal study of pulmonary function among people occupationally exposed to pesticides. Moreover, COPD has been rarely studied, rather chronic bronchitis. In addition, there is no study that demonstrates a dose–effect relationship between exposure to pesticides and accelerated decline in FEV_1 after adjustment for smoking habits. It is the reason why, whatever the conclusions of the studies analysed, we finally consider that at this time it is has not been proved that occupational exposure to pesticides presents a risk of COPD. Regarding asthma, existing evidence is stronger. Nevertheless, it is uncertain whether pesticides cause asthma or act as a trigger for asthma exacerbation, or both. The main limitations of current evidence are the definition of asthma outcomes and the assessment of exposure. In several studies, asthma outcomes were self-reported, without any data on pulmonary function and/or bronchial responsiveness. In addition, assessment of exposure is also generally based on self-reports. However, some studies [37, 38, 44, 46, 47, 58] assessed cumulative lifetime exposure to pesticides, while others asked about specific pesticides used [32, 37, 64, 65] or specific crops [34, 56], allowing a more precise definition of exposure. Finally, even for asthma, it is difficult to establish a causal relationship with exposure to pesticides.

In conclusion, this review clearly demonstrates that occupational exposure to pesticides presents a risk to the respiratory tract. Only a few studies measured lung function parameters, but results always showed a decrease in some parameters in association with exposure to certain pesticides, suggestive of an obstructive or restrictive syndrome. It is also worth noting that in some studies, symptoms or diseases were self-reported by subjects, although it would be preferable to use validated questionnaires from lung specialists and respiratory societies, with questions referring to diseases diagnosed by a doctor or to measures of respiratory function. When possible, respiratory function measures and medical check-ups would be useful.

Regarding the sample size, larger groups of subjects are required in order to better highlight the risks associated with specific contexts and specific chemical classes of pesticides.

Further studies should particularly focus on pesticide exposure assessment (cumulative lifetime exposure) and specific pesticide identification, in order to determine possible dose–effect relationships, and finally assess the causal relationship.

References

1 Forum of International Respiratory Societies. Respiratory Diseases in the World. Realities of today – opportunities for tomorrow. Sheffield, European Respiratory Society, 2014.
2 World Health Organization. World Health Statistics. Geneva, WHO, 2008.
3 Schraunfnagel D. The world respiratory diseases report. *Int J Tuberc lung Dis* 2013; 17: 1517.
4 Dalphin JC. Pathologie respiratoire en milieu agricole [Respiratory pathology in the agricultural environment]. *Rev Prat* 1998; 48: 1313–1318.

5 Michielsen C, Zeamari S, Leusink-Muis A, *et al.* The environmental pollutant hexachlorobenzene causes eosinophilic and granulomatous inflammation and *in vitro* airways hyperreactivity in the Brown Norway rat. *Arch Toxicol* 2002; 76: 236–247.
6 Bessot JC, Blaumeiser M, Kopferschmitt MC, *et al.* L'asthme professionnel en milieu agricole [Occupational asthma in an agricultural setting]. *Rev Mal Respir* 1996; 13: 205–215.
7 Crinnion WJ. Do environmental toxicants contribute to allergy and asthma? *Alter Med Rev* 2012; 17: 6–18.
8 Hoppin JA, Umbach DM, London SJ, *et al.* Animal production and wheeze in the Agricultural Health Study: interactions with atopy, asthma, and smoking. *Occup Environ Med* 2003; 60: e3.
9 European Commission. Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides. *Off J Eur Union* 2009; L309: 71–86.
10 Maroni M, Fanetti AC, Metruccio F. Risk assessment and management of occupational exposure to pesticides in agriculture. *Med Lav* 2006; 97: 430–437.
11 Baldi I, Lebailly P, Rondeau V, *et al.* Levels and determinants of pesticide exposure in operators involved in treatment of vineyards: results of the PESTEXPO Study. *J Expo Sci Environ Epidemiol* 2012; 22: 593–600.
12 Dowling KC, Seiber JN. Importance of respiratory exposure to pesticides among agricultural populations. *Int J Toxicol* 2002; 21: 371–381.
13 Eskenazi B, Bradman A, Castorina R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ Health Perspect* 1999; 107: 409–419.
14 Sanborn MD, Cole D, Abelsohn A, *et al.* Identifying and managing adverse environmental health effects: 4. Pesticides. *CMAJ* 2002; 166: 1431–1436.
15 Vallyathan V, Shi X, Castranova V. Reactive oxygen species: their relation to pneumoconiosis and carcinogenesis. *Environ Health Perspect* 1998; 106: 1151–1155.
16 Canal-Raffin M, l'Azou B, Jorly J, *et al.* Cytotoxicity of folpet fungicide on human bronchial epithelial cells. *Toxicology* 2008; 249: 160–166.
17 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269.
18 Charles LE, Burchfiel CM, Fekedulegn D, *et al.* Occupational exposure to pesticides, metals, and solvents: the impact on mortality rates in the Honolulu Heart Program. *Work* 2010; 37: 205–215.
19 O'Malley M, Barry T, Ibarra M, *et al.* Illnesses related to shank application of metam-sodium, Arvin, California, July 2002. *J Agromedicine 2005*; 10: 27–42.
20 Gomes Do Espirito Santo ME, Marrama L, Ndiaye K, *et al.* Investigation of deaths in an area of groundnut plantations in Casamance, South of Senegal after exposure to Carbofuran, Thiram and Benomyl. *J Expo Anal Environ Epidemiol* 2002; 12: 381–388.
21 Cocco P, Blair A, Congia P, *et al.* Long-term health effects of the occupational exposure to DDT. A preliminary report. *Ann NY Acad Sci* 1997; 837: 246–256.
22 Payán-Rentería R, Garibay-Chávez G, Rangel-Ascencio R, *et al.* Effect of chronic pesticide exposure in farm workers of a Mexico community. *Arch Environ Occup Health* 2012; 67: 22–30.
23 Ohayo-Mitoko GJ, Kromhout H, Simwa JM, *et al.* Self reported symptoms and inhibition of acetylcholinesterase activity among Kenyan agricultural workers. *Occup Environ Med* 2000; 57: 195–200.
24 Awadalla NJ, Hegazy A, Elmetwally RA, *et al.* Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Egypt: a multicenter case-control study. *Int J Occup Environ Med* 2012; 3: 107–116.
25 Senthilselvan A, McDuffie HH, Dosman JA. Association of asthma with use of pesticides. Results of a cross-sectional survey of farmers. *Am Rev Respir Dis* 1992; 146: 884–887.
26 Kang HK, Dalager NA, Needham LL, *et al.* Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. *Am J Ind Med* 2006; 49: 875–884.
27 Bener A, Lestringant GG, Beshwari MM, *et al.* Respiratory symptoms, skin disorders and serum IgE levels in farm workers. *Allerg Immunol* 1999; 31: 52–56.
28 Salameh P, Waked M, Baldi I, *et al.* Respiratory diseases and pesticide exposure: a case-control study in Lebanon. *J Epidemiol Community Health* 2006; 60: 256–261.
29 Salameh PR, Waked M, Baldi I, *et al.* Chronic bronchitis and pesticide exposure: a case-control study in Lebanon. *Eur J Epidemiol* 2006; 21: 681–688.
30 Zuskin E, Schachter EN, Mustajbegovic J. Respiratory function in greenhouse workers. *Int Arch Occup Environ Health* 1993; 64: 521–526.
31 Zuskin E, Mustajbegovic J, Schachter EN, *et al.* Respiratory function in vineyard and orchard workers. *Am J Ind Med* 1997; 31: 250–255.
32 Castro-Gutiérrez N, McConnell R, Andersson K, *et al.* Respiratory symptoms, spirometry and chronic occupational paraquat exposure. *Scand J Work Environ Health* 1997; 23: 421–427.
33 Wilkins JR 3rd, Engelhardt HL, Rublaitus SM, *et al.* Prevalence of chronic respiratory symptoms among Ohio cash grain farmers. *Am J Ind Med* 1999; 35: 150–163.
34 Sprince NL, Lewis MQ, Whitten PS, *et al.* Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project. *Am J Ind Med* 2000; 38: 455–462.
35 Beseler CL, Stallones L. Pesticide poisoning and respiratory disorders in Colorado farm residents. *J Agric Saf Health* 2009; 15: 327–334.
36 Masley ML, Semchuk KM, Senthilselvan A, *et al.* Health and environment of rural families: results of a Community Canvass survey in the Prairie Ecosystem Study (PECOS). *J Agric Saf Health* 2000; 6: 103–115.
37 Schenker MB, Stoecklin M, Lee K, *et al.* Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure. *Am J Respir Crit Care Med* 2004; 170: 773–779.
38 Fieten KB, Kromhout H, Heederik D, *et al.* Pesticide exposure and respiratory health of indigenous women in Costa Rica. *Am J Epidemiol* 2009; 169:1500–1506.
39 Faria NM, Facchini LA, Fassa AG, *et al.* Pesticides and respiratory symptoms among farmers. *Rev Saude Publica* 2005; 39: 973–981.
40 Ejigu D, Mekonnen Y. Pesticide use on agricultural fields and health problems in various activities. *East Afr Med J* 2005; 82: 427–432.

 DOI: 10.1183/16000617.00006014

41 Pathak MK, Fareed M, Bihari V, *et al.* Cholinesterase levels and morbidity in pesticide sprayers in North India. *Occup Med (Lond)* 2011; 61: 512–514.
42 Ngowi AV, Maeda DN, Partanen TJ, *et al.* Acute health effects of organophosphorus pesticides on Tanzanian small-scale coffee growers. *J Expo Anal Environ Epidemiol* 2001; 11: 335–339.
43 Jones SM, Burks AW, Spencer HJ, *et al.* Occupational asthma symptoms and respiratory function among aerial pesticide applicators. *Am J Ind Med* 2003; 43: 407–417.
44 Abu Sham'a F, Skogstad M, Nijem K, *et al.* Lung function and respiratory symptoms in male Palestinian farmers. *Arch Environ Occup Health* 2010; 65: 191–200.
45 Mekonnen Y, Agonafir T. Lung function and respiratory symptoms of pesticide sprayers in state farms of Ethiopia. *Ethiop Med J* 2004; 42: 261–266.
46 Hernández AF, Casado I, Pena G, *et al.* Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects. *Inhal Toxicol* 2008; 20: 839–849.
47 Chakraborty S, Mukherjee S, Roychoudhury S, *et al.* Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of 16 agricultural workers in India. *J Occup Health* 2009; 51: 488–497.
48 Cha ES, Lee YK, Moon EK, *et al.* Paraquat application and respiratory health effects among South Korean farmers. *Occup Environ Med* 2012; 69: 398–403.
49 Hoppin JA, Umbach DM, London SJ, *et al.* Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. *Am J Respir Crit Care Med* 2002; 165: 683–689.
50 Hoppin JA, Umbach DM, London SJ, *et al.* Pesticides and adult respiratory outcomes in the agricultural health study. *Ann NY Acad Sci* 2006; 1076: 343–354.
51 Hoppin JA, Umbach DM, London SJ, *et al.* Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study. *Am J Epidemiol* 2006; 163: 1129–1137.
52 Hoppin JA, Umbach DM, London SJ, *et al.* Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study. *Am J Respir Crit Care Med* 2008; 177: 11–18.
53 Hoppin JA, Umbach DM, London SJ, *et al.* Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. *Eur Respir J* 2009; 34: 1296–1303.
54 Henneberger PK, Liang X, London SJ, *et al.* Exacerbation of symptoms in agricultural pesticide applicators with asthma. *Int Arch Occup Environ Health* 2013; 87: 423–432.
55 Beard J, Sladden T, Morgan G, *et al.* Health impacts of pesticide exposure in a cohort of outdoor workers. *Environ Health Perspect* 2003; 111: 724–730.
56 Baldi I, Robert C, Piantoni F, *et al.* Agricultural exposure and asthma risk in the AGRICAN French cohort. *Int J Hyg Environ Health* 2014; 217: 435–442.
57 Boers D, van Amelsvoort L, Colosio C, *et al.* Asthmatic symptoms after exposure to ethylenebisdithiocarbamates and other pesticides in the Europit field studies. *Hum Exp Toxicol* 2008; 27: 721–727.
58 Hoppin JA, Valcin M, Henneberger PK, *et al.* Pesticide use and chronic bronchitis among farmers in the Agricultural Health Study. *Am J Ind Med* 2007; 50: 969–979.
59 Valcin M, Henneberger PK, Kullman GJ, *et al.* Chronic bronchitis among nonsmoking farm women in the agricultural health study. *J Occup Environ Med* 2007; 49: 574–583.
60 Tual S, Clin B, Levêque-Morlais N, *et al.* Agricultural exposures and chronic bronchitis: findings from the AGRICAN (AGRIculture and CANcer) cohort. *Ann Epidemiol* 2013; 23: 539–545.
61 Alavanja MC, Sandler DP, McMaster SB, *et al.* The Agricultural Health Study. *Environ Health Perspect* 1996; 104: 362–369.
62 Salameh P, Waked M, Baldi I, *et al.* Spirometric changes following the use of pesticides. *East Mediterr Health J* 2005; 11: 126–136.
63 Zuskin E, Mustajbegovic J, Schachter EN, *et al.* Respiratory function in pesticide workers. *J Occup Environ Med* 2008; 50: 1299–1305.
64 Ruder AM, Yiin JH. Mortality of US pentachlorophenol production workers through 2005. *Chemosphere* 2011; 83: 851–861.
65 Burns CJ, Cartmill JB, Powers BS, *et al.* Update of the morbidity experience of employees potentially exposed to chlorpyrifos. *Occup Environ Med* 1998; 55: 65–70.
66 Calvert GM, Sweeney MH, Morris JA, *et al.* Evaluation of chronic bronchitis, chronic obstructive pulmonary disease, and ventilatory function among workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Am Rev Respir Dis* 1991; 144: 1302–1306.
67 Alavanja MC, Bonner MR. Occupational pesticide exposures and cancer risk: a review. *J Toxicol Environ Health B Crit Rev* 2012; 15: 238–263.
68 Hill AB. The environment and disease: association or causation?: *Proc R Soc Med* 1965; 58: 295–300.
69 Hernández AF, Parrón T, Alarcón R. Pesticides and asthma. *Curr Opin Allergy Clin Immunol* 2011; 11: 90–96.