WORKING FOR A HEALTHY FUTURE

Strategic Consulting Report: P603-09535
February 2011

A systematic review of literature on asthma prevalence and exacerbation and other respiratory diseases in association with pesticide exposure

FINAL REPORT

DEFRA Contract: PS2619

Contract value: £54,138

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EXECUTIVE SUMMARY

Aims
The aim of this systematic review was to identify any associations between exposure to pesticides and the incidence or prevalence of respiratory symptoms in those exposed to pesticides; in particular the occurrence of asthma. Furthermore the review aimed to identify evidence gaps in the existing knowledge base and make recommendations on future areas and content of research.

Methodology
In total, 4,390 publications were initially identified from the searches carried out. After initial title and abstract screening this was reduced to 524 publications. At this stage duplicate publications were also removed resulting in 348 screened abstracts for consideration. Papers which did not fulfil the inclusion criteria (e.g. language, date of publication etc.) were removed (195 papers). Further papers were rejected during full paper review and quality assessment as they did not meet the inclusion criteria and a total of 44 papers were included. These were evaluated for quality and data were extracted. A decision was made to remove the studies graded as negative (i.e., not meeting quality standards) during quality assessment as this would impact on the overall quality of the review, therefore, a total of 25 papers were included.

Results
Results from the systematic review suggest that exposure to pesticides may be associated with existing asthma, however methodological issues with the papers, such as cross-sectional/case-control design, measurements of exposure and asthma symptoms and adjustments for confounders; limit the strength of the evidence base in this area. The association between pesticide exposure and asthma appears to be more evident and consistent in children than in adults.

The systematic review suggests that exposure to pesticides may be associated with COPD/chronic bronchitis however, the strength of evidence with regards to the association is weaker than the association with asthma, with fewer studies and a lack of studies using lung function to identify COPD: a disease defined on lung function parameters.

Limitations
The main shortcomings of the included studies were: most studies were cross-sectional in nature; relatively few employed pulmonary function testing; a lack of research on individual agents; the use of surrogate measures of exposure; and failure to adjust for potential confounding, especially socio-economic status. In addition, most, if not all, of the reported studies assume that any adverse effect is a consequence of the active pesticide constituent. Therefore we are unable to exclude the possibility that any reported adverse health effect of a pesticide may in reality be an adverse effect of co-formulant(s) in commercial pesticide preparations.

Recommendations for future research
A number of recommendations can be made including longitudinal studies with improved prospective exposure measurement/assessment. There are some issues with farm environments and co-exposures, therefore studies that are designed to minimise co-exposures and agricultural dust are desirable, but may not be easily achievable. Cross shift studies of changes in lung function and inflammatory markers in exposed workers with concurrent measurement of exposures would be appropriate.

Continued research into the potential mechanisms and genetic susceptibility is also recommended.

1 INTRODUCTION

The IOM was commissioned to carry out a systematic review of epidemiological studies of groups exposed to pesticides including those exposed at work (agriculture or manufacture) and the general public. The aim of the review was to identify any associations between exposure to pesticides and the incidence or prevalence of respiratory symptoms in those exposed to pesticides; in particular the occurrence of asthma. The objectives of the review were to:

1. Identify published epidemiological studies of individuals exposed, occupationally or non-occupationally, to pesticides to determine the relationship, if any, between pesticide exposure and respiratory ill health;

2. Review the strength of evidence linking pesticide exposure to respiratory ill health in individual studies, taking account of the characteristics of the exposure;

3. If sufficient data exist, to identify specific pesticides or groups of chemically related pesticides that may be linked to respiratory ill health;

4. If warranted by the quality of data, to undertake a meta-analysis to determine the overall strength of evidence linking specific groups of pesticides to respiratory ill health;

5. Review the biological plausibility and assess the evidence for causality of any apparent relationships between respiratory ill health and specific pesticides/groups of pesticides;

6. Advise on the current strength of evidence linking pesticide exposure to respiratory ill health

Furthermore the review aimed to identify evidence gaps in the existing knowledge base and make recommendations on future areas of research and the content of such research.

2 METHODOLOGY

A search strategy was developed including search terms, search engines used and inclusion/exclusion criteria. A copy of the search strategy is presented in Appendix A. Search terms were developed from expertise within the research team. This included the identification of the population (both occupational and on-occupational). Initial search terms for different pesticides were collated from the paper by Dick *et al* (2010) on the development of a task-exposure matrix for pesticide use (Dick *et al.,* 2010). This was further refined by expertise within the research team. Respiratory outcomes were collated by the research team and further terms were input by team experts in respiratory medicine.

Titles and abstracts were stored using Ref Works. Figure 1 presents the screening and reviewing process. On completion of the searches, title and abstract screening were carried out independently by two researchers and results were compared. Where there was disparity, this was discussed and a consensus reached. On receipt of the full papers, a second screening was carried out which resulted in the removal of papers

that did not meet the inclusion criteria (English language, published after 1990, peer-reviewed, exposure not through diet). After this, paper quality assessment was carried out using the criteria presented in Appendix C which were based on those published by the Scottish Intercollegiate Guidelines Network[1].

2.1 LABELLING AND DIAGNOSIS OF RESPIRATORY CONDITIONS

The diagnosis of lung disease can be based, depending upon the type of disease, on lung function testing, symptoms (e.g. via questionnaire) or X-rays/scans or combinations of all three. For airway disease such as asthma and chronic obstructive pulmonary disease (COPD) although the diagnosis is usually made on the basis of lung function testing and symptoms, more specialised tests such as bronchial provocation studies (asthma) and cross sectional imaging (emphysema) are usually reserved for specialists and/or diagnostically challenging cases. Symptoms of lung disease are few – breathlessness, wheeze, cough, sputum and chest pain and it is therefore not surprising that there is overlap in symptoms between different respiratory diseases and between respiratory and cardiovascular diseases in the context of breathlessness and chest pain.

Where there is no absolute diagnostic criterion for a condition then there is considerable scope for differences in diagnosis of a particular condition in the clinical setting. In airways disease, bronchitis and asthma are often diagnosed differently by different individual clinicians; particularly in children. The use of structured and validated questionnaires reduces the potential bias from diagnostic differences, however the choice of questions and which single questions or combination of questions are used can be left open to the researchers which again allows the potential for labelling bias. The situation is further complicated when considering environmental exposures and respiratory responses which may be acute and transient (e.g. following pesticide spraying) or persistent or of long standing following repeated exposures. The difference between exacerbation of existing disease and development for the first time of disease is important to dissect out as each situation has different implications. Transient airway narrowing associated with acute exposure may well be a problem acutely but is not an issue in the long term. However, if repeated exposures result in the development of an asthmatic or bronchitic state, then that clearly is much more important in terms of health outcome.

One further aspect is that of competing diagnosis. For instance it is often very difficult to distinguish acute wheezing illness in children from genuine asthma, particularly below the age of 2 when viral infections are so common. Consequently, use of wheezing rather than an attempted diagnostic label may be the right approach for specific situations when trying to determine causal associations.

Asthma is defined by the presence of variable airflow obstruction, the airways contracting and relaxing either spontaneously or as a result of treatment due to inflammation of the airways. This variability in airflow can be captured by lung function tests over time or before and after a bronchodilator (tube opening) drug or by measuring the irritability of the airways using tests of bronchial hyper-responsiveness. Consequently, the diagnosis of asthma in epidemiological terms has been the matter of much debate. Some authorities accept a positive answer to the question “Has a doctor ever told you, you have asthma?”, others accept a positive response to a question on

[1] SIGN, 2008, SIGN 50: A guideline developers handbook. Scottish Intercollegiate Guidelines Network, Edinburgh. http://www.sign.ac.uk/pdf/sign50.pdf

repeated episodes of wheeze while others require the presence of relevant symptoms plus positive bronchial responsiveness. No studies in the literature reviewed here used bronchial responsiveness testing and the questionnaires used were often not identifiable as validated and accepted asthma questionnaires. However, if the pattern of associations of an exposure in relation to asthma and to questions of wheeze coheres across different studies then this adds to the likelihood of a causal relationship.

COPD is the all encompassing name being used for what used to be called chronic bronchitis and emphysema. It covers a number of different disease processes but the net result is that these individuals have narrow bronchial tubes, the narrowing being largely irreversible unlike the situation in asthma where airway calibre can potentially increase to normal. Diagnosis of COPD is based on lung function tests with clearly defined criteria but it is equally possible that 'early COPD' can be present pathologically without fulfilling the lung function requirements for formal definition as COPD. COPD is currently diagnosed by measurement of post bronchodilator lung function (spirometry) usually following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines but these guidelines constrain definition of COPD to specific changes in lung function parameters. Changes can occur in lung function without the GOLD definition being achieved and so, if pesticide exposure is associated with the development of COPD, earlier changes in lung function might also be expected.

Farmer's lung (extrinsic allergic alveolitis due to a sensitivity to thermophilic bacteria in mouldy hay) also adds to the confusion in an agricultural setting. Again the main symptoms are breathlessness, cough and wheeze but those affected are, likely as not, exposed to pesticides. We found one paper which specifically addressed this condition and which examined pesticides and other agricultural factors associated with self-reported farmer's lung. High pesticide exposure events (OR = 1.75, 95% CI 1.39-2.21), and ever having used organochlorines (OR = 1.34, 95% CI 1.04-1.74) or carbamate pesticides (OR = 1.32, 95% CI 1.03-1.68) were associated with farmer's lung in mutually adjusted models (Hoppin *et al.,* 2009). However, the inter-relationship between the causal agents of Farmer's lung, pesticide exposure and symptoms are so inter-related that we feel no conclusions can be drawn in terms of deciding whether pesticides do in fact contribute to worsening of disease in this condition. We have therefore not considered this issue further.

3 RESULTS

3.1 RESULTS OF THE SEARCHES

In total, 4,390 publications were initially identified from the searches carried out. After initial title and abstract screening this was reduced to 524 publications. At this stage duplicate publications were also removed resulting in 348 screened abstracts for consideration.

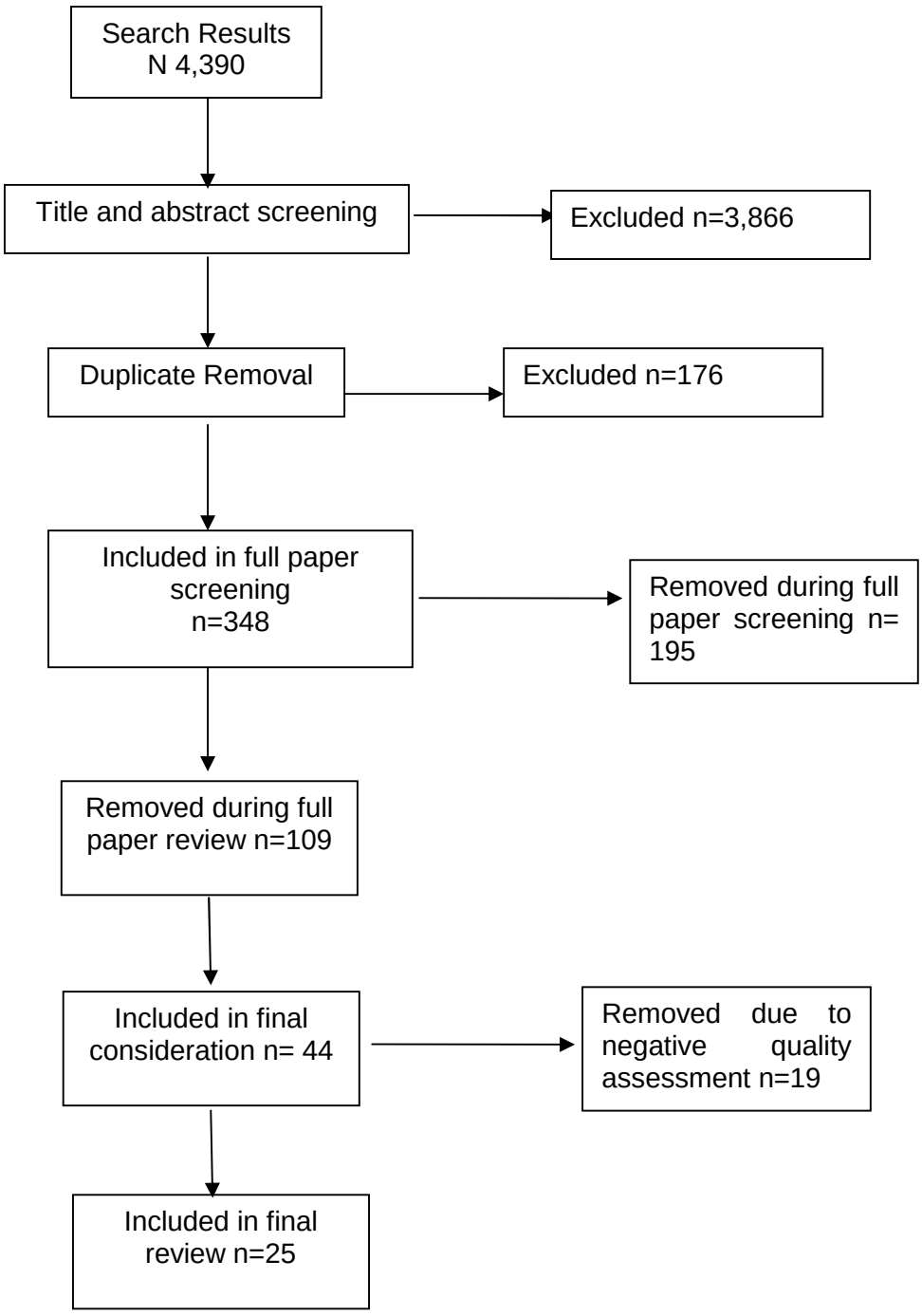

Figure 1. Breakdown of searches

3.2 EVIDENCE REVIEW

3.2.1 Types of Studies

As noted in section 2 above, papers which did not fulfil the inclusion criteria (e.g. language, date of publication etc) were removed (195 papers). Further papers were rejected during full paper review and quality assessment. The reasons for the

exclusions of those papers are summarised in Appendix C and are related to issues including papers on acute pesticide poisonings, case studies, non-systematic reviews, military exposure (which is atypical of and considerably higher than occupational/bystander exposure) and non-English articles.

A total of 44 papers met the inclusion criteria for the review. These were evaluated for quality and data were extracted. A decision was made at this point to remove the studies graded as negative in terms of quality (-, at high risk of bias) as this would impact on the overall quality of the review and any subsequent meta-analysis. A summary of the removed papers is presented in Appendix E. The papers included in the review are presented in Appendix D.

A total of 25 papers were included within the review. The majority of studies were cross-sectional with 15 cross-sectional, one retrospective cross-sectional and one stratified two-stage cluster design; 2 case-control studies including one nested case-control study; three birth cohort studies, two of which were longitudinal; one historical cohort study, one retrospective cohort study and one systematic review. It should be noted that several of the papers arose from one large prospective study (the Agriculture Health Study) of Iowa and North Carolina pesticide applicators and their spouses. The study enrolled over 52,000 licensed private pesticide applicators, mostly farmers, from 1993 to 1997, representing more than 82% of applicators in both states.

The evidence review below is set out by health end-point: asthma; wheeze; bronchitis and COPD; lung function; and lower respiratory tract infections. In addition to discussing the results of the papers, the limitations of the studies are also considered. As papers often cover more than one health end-point (e.g. asthma and wheeze), the consideration of the limitations only appears in the health end-point where the paper is first discussed and is not repeated.

In most of the studies the pesticide exposures were based on descriptive information such as job title or self-reported use of pesticides. Inevitably in all studies there is either other risk factors for respiratory ill-health, such as working in an general agricultural environments with a range of allergens and dusts, or in specific work situations where there are known associations between prevalent exposures and asthma or other respiratory disease, for example dust exposure in poultry houses.

3.2.2 The Evidence for Association of Pesticide Exposure with Asthma

Eighteen papers were identified within the review that included asthma or asthma-related symptoms as a health outcome (Beard *et al.,* 2003, Boers *et al.,* 2008, Chakraborty *et al.,* 2009, Faria *et al.,* 2005, Hoppin *et al.,* 2008, Hoppin *et al.,* 2009, Huang *et al.,* 1995, Jones *et al.,* 2009, Nriagu *et al.,* 1999, Salam *et al.,* 2004, Salameh *et al.,* 2003, Schenker *et al.,* 2004, Sunyer *et al.,* 2005, Sunyer *et al.,* 2006, Sunyer *et al.,* 2010, Weselak *et al.,* 2007, Yemaneberhan *et al.,* 1997, Zhang *et al.,* 2002). These are summarised below.

Mortality Studies in Adults

Beard *et al* (2003) carried out a study of 1,999 outdoor workers who worked with pesticides compared to a group of 1,984 workers who worked outside but were not occupationally exposed to pesticides and to the general Australian population between 1935 and 1996. Exposure assessment was carried out by examining the recorded use of pesticides including arsenic use (1935-1955), DDT use (1955-1962), early period of

modern chemical use including coumaphos, carbophenothion, carbaryl, chlorpyrifos, bromophos ethyl, dioxothion, ethion, chlordimeform and cymayazole (1962-1986) and modern chemical use including amitraz, promacyl, cupermethrin, chorfenvinphos and flumethrin (1976 – present time). This was a mortality study but follow-up was also carried out for 1,533 people via postal questionnaire. The survey identified that, when compared with Australia data, self-reported asthma was significantly increased (OR=1.59, 95% CI 1.05-2.43) in the study group. The mortality component of the study also identified that mortality from asthma was increased in the study population when compared with the general Australian population (SMR=3.45, 95% CI 1.39-7.10) based on 7 deaths in the exposed group and 2 deaths in the comparison group. Analysis of the mortality data by time period identified significantly increased mortality rates for asthma during the modern chemical period (SMR=6.44, 95% CI 1.33-18.22) but no significant associations were found for the arsenic period or the DDT period of study. However, no further analysis was carried out to examine links to exposures to specific pesticides. A notable weakness of this study is the ascertainment of the outcomes of bronchitis, asthma and emphysema, whilst self-reported it is not clear whether these were doctor diagnosed conditions or merely what subjects with respiratory symptoms considered themselves to have. Although adjustment was made for possible confounding by cigarette smoking, on balance it seems likely that subjects with what might be considered to be COPD nowadays were misclassified as asthma. Moreover the clinical diagnostic criteria for asthma have changed during the 60 year time span encompassed by the study. Additionally, asthma mortality is a poor indicator of asthma prevalence and is confounded by misclassification bias as deaths from COPD may be registered as deaths from asthma; leading to over-estimation of asthma mortality (British Thoracic Association 1984; Sears *et al.,* 1986).

Jones *et al* (2009) carried out a systematic review and meta-analysis of mortality in crop protection production workers. The review identified 21 references that reported on 37 different mortality cohorts. The analysis of results identified that the SMR for bronchitis, emphysema and asthma was 1.08, 95% CI 0.86-1.35 based on 23 studies. Further analysis was carried out for studies where individuals were exposed to phenoxy herbicides. The SMR for this group was calculated as 1.06, 95% CI 0.81-1.38 based on analysis of 16 studies. The systematic review did not identify clear evidence of an increased risk of death due to asthma, emphysema and bronchitis; no further analysis of the individual disorders was carried out. As this was a mortality study, the SMRs were not included in Table 3, which relates to ORs.

Studies of Asthma Prevalence in Adults

Beard *et al* (2003) carried out a study of 1,999 outdoor workers who worked with pesticides compared to a group of 1,984 workers who worked outside but were not occupationally exposed to pesticides and to the general Australian population between 1935 and 1996. Exposure assessment was carried out by examining the recorded use of pesticides including arsenic use (1935-1955), DDT use (1955-1962), the early period of modern chemical use including coumaphos, carbophenothion, carbaryl, chlorpyrifos, bromophos ethyl, dioxothion, ethion, chlordimeform and cymayazole (1962-1986) and modern chemical use including amitraz, promacyl, cupermethrin, chorfenvinphos and flumethrin (1976 – present time). This was a mortality study but follow-up was also carried out for 1,533 people via postal questionnaire. The survey identified that, when compared with Australian data, self-reported asthma was significantly increased (OR=1.59, 95% CI 1.05-2.43) in the study group. The limitations of the study are discussed above.

Boers *et al* (2008) carried out a prospective case control study to examine asthmatic symptoms after exposure to ethylenebisdithiocarbamates and other pesticides. The study group included 248 workers across four countries (Netherlands, Italy, Finland and Bulgaria) who were compared with 231 non-exposed workers. Measures used in the study included a self-administered questionnaire (with validated questions) and urine samples to test for exposure to ethylenebisdithiocarbamates. The analysis found a non-significant inverse relationship between pesticide exposure and self-reported asthma diagnosis (OR=0.41, 95% CI 0.15-1.11) while for urinary metabolites, a positive association was identified with asthma (OR=1.19, 95% CI 0.93-1.53). However this also was not significant and the study suggests that there is not an association between exposure to these pesticides and self-reported asthma. The relatively small study size with power to detect only a doubling of the risk of asthma raises the possibility that the negative associations reported in this study may have arisen as a consequence of a Type II error. The authors suggest that inverse associations reported between pesticide exposure and respiratory outcomes may reflect a healthy worker effect with those individuals with severe respiratory disease likely to avoid any chemical exposures..

Chakraborty *et al* (2009) measured lung function and respiratory symptoms in agricultural workers exposed to organophosphate and carbamate pesticides in West Bengal, India. The study compared 376 non-smoking agricultural workers with 348 age and sex matched controls. Exposure to pesticides was assessed using self-reports of frequency and duration of spraying and was split into regular sprayers (at least an hour a day, 5 days a month for the past 5 years) and those spraying less than this who were considered occasional sprayers. The chemicals included in the paper were methyl parathion, phosphamidon, carbofuran, dichlorvos, monocrotophos, carbaryl, chlorpyrifos and dimethoate. Cholinesterase inhibition was measured using blood samples. Within the study 3.7% of agricultural workers reported doctor diagnosed asthma (3.6% of occasional sprayers and 3.9% of regular sprayers). A significant association was found between doctor diagnosed asthma and exposure to pesticides (OR=1.34, 95% CI 1.09-1.79) where those who had less than 50% cholinesterase inhibition were the reference group and those with more than 50% inhibition were the exposed group. However, more that 50% cholinesterase inhibition is marked inhibition and the adverse association may be a consequence of symptomatic bronchoconstriction induced by organophosphate poisoning.

Faria *et al* (2005) carried out a cross-sectional survey of 1,379 farmers in Brazil. Respiratory symptoms were assessed using an adapted American Thoracic Society questionnaire. Pesticide exposure was assessed using an interview which identified the main chemical groups used, their usage and frequency of use. The main chemicals identified were fenthion, dimethoate, trichlorfon, methyl parathion, methamidophos, deltamethrin, cypermethrin, atrazine, simazine, nancozeb, maneb, captan, dodine, benzimidazole, glyphosate and paraquat. From this a collective environmental exposure was estimated by collecting data from the whole farm including fertilizers. From the sample, 12.2% reported asthma symptoms defined as two or more episodes of wheezing with shortness of breath at any time in their lifetime Further associations identified that symptoms of asthma were significantly associated with pesticide application of more than 3 days per month (OR=2.11, 95% CI 1.14-3.92); equipment cleaning more than two days per month (OR=2.06, 95% CI 1.13-3.77) and self-reported pesticide poisoning (OR=1.64, 95% CI 1.04-2.58). Further analysis of the data investigated exposure to different types of pesticides in relation to asthma symptoms. However, no significant associations were found. Although suitable adjustment was made for confounding exposures/factors the very broad definition of

asthma symptoms with the potential to encompasses childhood wheezing symptoms is a significant weakness, moreover with this definition of asthma the reported adverse association could reflect aggravation of pre-existing asthma.

Hoppin *et al* (2008, 2009) examined asthma symptoms as part of the Agricultural Health Study in the US. Hoppin *et al* (2008) examined adult-onset atopic and non-atopic asthma in farm women in the Agricultural Health Study. The study of 25,814 women identified that 702 women reported doctor diagnosed adult onset asthma, of which 282 were atopic and 420 non-atopic asthma cases. Data collected from the women included a complete health history and personal use of 50 specific pesticides. Results from the study showed that there was little evidence for an association between all asthma (atopic and non-atopic combined) and pesticide use (personal communication from Prof Jane Hoppin June 2011) but that use of any pesticide was associated with atopic asthma but not with non-atopic asthma. Particular pesticides were also found to be associated with atopic asthma including herbicides generally, 2,4-D, and glyphosate. Insecticides were also associated with atopic asthma including insecticides generally, carbamates generally and carbaryl specifically. From organophosphate chemicals a significant association was found for malathion, parathion and phorate. The use of permethrin in animals was also found to be significantly associated with atopic asthma; this was not found for use with crops. For fungicides, metalaxyl was significantly associated with adult onset atopic asthma. The authors suggested that pesticides may be contributing to adult onset atopic asthma in farm women.

Table 1: Associations between pesticides and allergic asthma in women (Hoppin *et al* 2008)

Exposure	Controls (n = 25,112)		Atopic patients with Asthma (n = 282)		95% Confidence Interval		
	n	%	n	%	Odds Ratio	Lower Limit	Upper Limit
Any pesticide	14,346	57	181	64	1.46	1.14	1.87
Herbicides	9,394	38	122	44	1.43	1.12	1.83
2,4-D	3,745	15	52	19	1.53	1.12	2.10
Alachlor	1,058	4	10	4	0.95	0.50	1.79
Atrazine	1,142	5	12	4	1.06	0.59	1.91
Butylate	352	1	5	2	1.45	0.59	3.55
Chlorimuron-ethyl	424	2	4	2			
Cyanazine	725	3	6	2	0.84	0.37	1.90
Dicamba	1,014	4	11	4	1.11	0.60	2.05
Glyphosate	8,468	34	106	39	1.31	1.02	1.67
Imazethapyr	767	3	3	1			
Metolachlor	830	3	8	3	0.98	0.48	2.00
Metribuzin	449	2	4	2			
Paraquat	286	1	6	2	1.90	0.83	4.34
Pendimethalin	606	2	4	2			
Petroleum oil	894	4	11	4	1.20	0.65	2.22
Trifluralin	1,347	6	15	6	1.14	0.67	1.94
Insecticides	10,052	40	132	47	1.43	1.12	1.81
Carbamates	7,953	32	110	39	1.46	1.14	1.86
Carbaryl	7,776	31	106	38	1.41	1.10	1.80
Carbofuran	463	2	9	3	1.92	0.98	3.77
Organophosphates	6,592	26	91	33	1.45	1.12	1.87
Chlorpyrifos	1,003	4	14	5	1.36	0.79	2.33
Coumaphos	319	1	7	3	2.19	1.02	4.69

Dichlorvos	666	3	9	3	1.35	0.69	2.66
Diazinon	2,542	10	33	12	1.23	0.85	1.77
Fonofos	468	2	8	3	1.80	0.88	3.68
Malathion	5,004	20	76	28	1.60	1.22	2.10
Parathion	240	1	7	3	2.88	1.34	6.20
Phorate	481	2	10	4	2.14	1.07	3.88
Terbufos	732	3	11	4	1.52	0.82	2.81
Organochlorines	1,950	8	31	11	1.27	1.07	2.31
Aldrin	206	1	2	1			
Chlordane	1,056	4	16	6	1.43	0.85	2.38
DDT	920	4	16	6	1.79	1.06	3.03
Heptachlor	198	1	1	0			
Lindane	380	2	8	3	1.92	0.94	3.92
Pyrethroids	1,222	5	18	7	1.46	0.90	2.37
Permethrin (animals)	891	4	15	6	1.71	1.01	2.91
Permethrin (crops)	491	2	7	3	1.30	0.61	2.78
Fungicides	1,208	5	18	7	1.41	0.87	2.30
Captan	550	2	8	3	1.33	0.65	2.70
Chlorothalonil	237	1	5	2	1.93	0.79	4.75
Maneb	382	2	8	3	1.93	0.94	3.98
Metalaxyl	366	2	10	4	2.61	1.35	5.04
Fumigants**	441	2	5	2	1.02	0.42	2.50
80/20 mix	133	1	1	0			
Methyl bromide	301	1	3	1			

† Models adjusted for age, state, smoking status, body mass index, and ‘‘grew up on farm;’’ ORs not reported if fewer than five exposed cases.

** Fumigant category is based on use of any fumigant; only those pesticides with five or more exposed cases are presented.

Hoppin *et al* (2009) examined pesticide use and adult onset asthma in male farmers. The study involved 17,920 farmers and 2,255 pesticide applicators. Adult onset asthma was defined as doctor diagnosed asthma after the age of 20. Pesticide exposure was assessed by identifying lifetime pesticide use for 50 different pesticides and from this lifetime pesticide use, lifetime days of use and intensity adjusted days of use were calculated. The results identified that 2.2% of the sample reported adult onset asthma; 127 defined as allergic asthma and 314 as non-allergic asthma. Further analysis of the data showed a significant association between high pesticide exposure events and allergic asthma (OR=1.98, 95% CI 1.30-2.99) and non-allergic asthma (OR=1.96, 95% CI 1.49-2.56). Eight individual pesticides were also found to be associated with allergic asthma, heptachlor, lindane, coumaphos, diazinon, parathion, captan, 80/20 mix carbon tetrachloride/carbon disulfide and ethylene dibromide. These results are presented in Table 2. Non-allergic asthma was associated with DDT exposure. It was suggested that current farming activities including handling animals did not confound these results.

In both studies Hoppin et al (2008, 2009) there was no adjustment for confounding by socio-economic status, a factor associated with asthma and likely to be associated with pesticide exposure.

Table 2: Associations between pesticides and allergic asthma in male farmers adjusted for age, US state, smoking, high pesticide exposure events and body mass index (Hoppin *et al* 2009)

Exposure	Controls (N=19,263)		Allergic asthma (N=127)				
	n	%	n	%	Odds Ratio*	95% Confidence Interval	
Herbicides						Lower limit	Upper limit
2,4,5-T	3564	19	38	31	1.44	0.96	2.14
2,4,5-TP	925	5	13	11	1.91	1.06	3.44
2,4-D	15054	79	110	87	1.56	0.91	2.69
Alachlor	10219	56	69	57	0.93	0.64	1.34
Atrazine	14034	73	94	75	0.95	0.63	1.45
Butylate	5058	27	42	33	1.23	0.84	1.81
Chlorimuron-ethyl	6124	32	45	36	1.21	0.83	1.75
Cyanazine	7842	43	58	49	1.14	0.77	1.70
Dicamba	9607	53	71	59	1.19	0.78	1.81
EPTC	3611	20	35	29	1.61	1.06	2.43
Glyphosate	14788	77	104	82	1.37	0.86	2.17
Imazethapyr	8042	45	52	44	0.97	0.64	1.48
Metolachlor	8624	47	58	48	0.99	0.69	1.44
Metribuzin	7179	38	55	44	1.16	0.79	1.70
Paraquat	3068	16	28	22	1.67	1.05	2.65
Pendimethalin	7104	38	44	35	0.94	0.64	1.36
Petroleum Oil	3933	21	33	27	1.28	0.85	1.92
Trifluralin	9964	55	62	53	0.79	0.54	1.16
Insecticides							
Carbamates							
Aldicarb	1508	8	7	6	0.79	0.35	1.79
Carbaryl	8089	43	63	50	1.26	0.85	1.85
Carbofuran	5266	29	42	35	1.10	0.75	1.61
Organochlorines							
Aldrin	3247	17	33	27	1.19	0.77	1.86
Chlordane	3592	19	42	34	1.77	1.19	2.63
DDT	4344	23	47	37	1.42	0.93	2.17
Dieldrin	704	4	10	8	1.47	0.75	2.90
Heptachlor	2289	12	34	27	2.01	1.30	3.11
Lindane	2528	14	28	23	1.57	1.01	2.41
Toxaphene	2156	11	18	15	1.06	0.63	1.78
Organophosphates							
Chlorpyrifos	8037	42	60	48	1.26	0.89	1.80
Coumaphos	1646	9	24	21	2.34	1.49	3.70
Diazinon	3891	21	38	30	1.57	1.05	2.35
Dichlorvos	2092	12	21	18	1.47	0.90	2.39
Fonofos	4079	23	37	31	1.43	0.95	2.16
Malathion	12150	64	87	69	1.08	0.74	1.59

Exposure	Controls (N=19,263)	Allergic asthma (N=127)				
Parathion	1501	8	19	16	2.05	1.21	3.46
Phorate	5776	31	48	39	1.23	0.84	1.81
Terbufos	7224	40	51	43	1.05	0.72	1.53
Pyrethroids							
Permethrin (animals)	2365	13	21	18	1.51	0.92	2.45
Permethrin (crops)	2328	13	20	18	1.52	0.93	2.48
Fungicides							
Benomyl	1519	8	10	8	0.97	0.49	1.94
Captan	1951	11	22	19	1.83	1.15	2.94
Chlorothalonil	1427	7	6	5	0.64	0.27	1.51
Maneb/Mancozeb	1530	8	13	11	1.40	0.74	2.67
Metalaxyl	3695	20	26	21	1.26	0.77	2.06
Fumigants							
80/20 mix (carbon tetrachloride/carbon disulfide)	818	4	15	12	2.15	1.23	3.76
Aluminum phosphide	641	3	6	5	1.34	0.58	3.06
Ethylene dibromide	818	4	10	8	2.07	1.02	4.20
Methyl bromide	2838	15	16	13	0.86	0.46	1.60

* No p-values shown as they were unavailable in the paper for allergic asthma only (values were only available when both allergic and non-allergic asthma ORs were significant)

Huang *et al* (1995) looked at respiratory symptoms in those involved in chlorothalonil (TCPN) production. In this small study of 28 individuals and 18 reference workers, lung function tests were carried out and an interview with an occupational physician. Data were collected using the Japanese version of the MRC questionnaire on respiratory symptoms. The results identified that the participants reported more symptoms of wheezing, shortness of breath, chest tightness at work along with chronic cough, chronic phlegm, eye and nasal irritation ($P<0.05$) when compared to the reference group. This was confirmed in the results for the lung function tests with the exposed workers having reduced FEV1 and FEV1 as a percentage of predicted. These associations could be considered to be consistent with chlorothalonil's recognised classification as a respiratory irritant. No OR was available; therefore this study was not included in table 3. Although no multivariate analyses were conducted; the exposed and control subjects were very similar in terms of age, height, weight, and smoking status, no mention was made of socio-economic status.

Nriagu *et al* (1999) examined asthma and respiratory symptoms in domestic environments in South Africa. The study used a modified version of the WHO questionnaire for asthma studies in an interview format. A total of 213 households were interviewed including 693 adults and 367 children. From the survey, 12% of the adults and 10% of the children reported having doctor diagnosed asthma. Further analysis of this data found that the use of pump spray insecticides in the home was significantly associated with asthma (OR=3.67, 95% CI 1.19-11.3) in adults but not children, and pump spray insecticide use was not associated with wheezing symptoms. Whilst multivariate analyses were reported to have been conducted, the variables included in these analyses were not made clear.

Schenker *et al* (2004) examined pulmonary function in 219 paraquat handlers compared to 100 non-handlers in Costa Rica. The study aimed to find out whether chronic low level paraquat exposure caused restrictive lung function and gas transfer impairment and is reported fully in section 3.2.4. Data were collected via an interviewer-administered questionnaire, pulmonary function and exercise tests and a measure of cumulative paraquat exposure. Although the study reported a non-significant association between asthma and cumulative paraquat exposure (OR=1.6, 95% CI 0.9-3.0) this was not supported by pulmonary function testing. Furthermore, the reported association between cumulative paraquat exposure and shortness of breath with wheeze in the absence of an association with wheeze raises the possibility of misdiagnosis with symptoms arising from restrictive disease being diagnosed erroneously as asthma. Further modelling of the data showed no association between increases in the cumulative paraquat index and having a diagnosis of asthma.

Yemaneberhan *et al* (1997) carried out a survey of 9,844 urban and 3,032 rural Ethiopian participants to examine asthma and atopy prevalence in Ethiopia. Data were collected by trained field workers using a translated International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire. Exposure was assessed by questions regarding insecticide use which was reported as being common in the urban group. The study included data from males, females and children. The percentages reporting asthma were 3.6% of the urban participants and 1.3% of the rural participants. The study found that self-reported asthma was significantly lower in the rural group than in the urban group (OR=0.35, % CI 0.25-0.49) after adjustment for smoking. The time of onset of asthma was also asked about within the study and the onset for 95% of participants who could recall this was approximately 10 years before the study date. Use of malathion and/or DDT in the home as an insecticide was included in an exploratory analysis attempting to identify exposures contributing to the observed rural/urban difference. The likelihood of asthma and wheezing symptoms was not associated with insecticide use, however any home insecticide, and malathion use in the home, but not DDT, was associated with atopic sensitisation to house dust mite. In Ethiopia insecticides are used to protect against mosquitoes and not house dust mites (i.e. insecticide is not used as an acaricide), it seems highly unlikely that the association with insecticide is confounded by an association with the insect/pest.

Zhang *et al* (2002) examined respiratory symptoms in China. Using a self-reported questionnaire of symptoms and insecticide exposure, 22,258 adults completed the survey. The questionnaire was carried out as an interview by village doctors using questions on bronchial symptoms and further questions from the American Thoracic Society (ATS). Additional questions were asked on smoking and environmental and occupational exposure to chemicals, dust, insecticides and fertilisers. In total 3.1% of the sample had been exposed to insecticides and 17.5 % had been exposed to other chemicals. Further analysis after adjustment for smoking, age , sex and county of residence identified that having an asthma attack was significantly associated with insecticide exposure (OR=1.9, 95% CI 1.3-2.9). However, it is notable that the prevalence of symptoms was low amongst the workers exposed to insecticides (wheeze; 3.5%) and that whereas asthma attacks and chronic cough and phlegm were associated with insecticide exposure use of asthma medication was not associated and diagnosed asthma not reported at all. This pattern of associations with symptoms and not more reliable indices of diagnosed asthma is less suggestive of an association with asthma and could be in keeping with associations with chronic bronchitis/COPD. Further weaknesses include a lack of objective measurements on both health outcomes and exposure assessment and failure to adjust for the possible confounding effects of socio-economic status.

Table 3: Odds Ratios for Pesticide Exposure and Asthma in Adults

Author	Asthma definition	Exposure metric	Co-exposures	Odds ratio	Lower limit	Upper limit
Beard *et al* (2003)	Self-reported asthma	Board of Tick Control records estimating type of chemical and duration of exposure estimates	Agricultural environment, cattle	1.59	1.05	2.43
Boers *et al* (2008)	Self-reported doctor diagnosed	Job history of exposure to pesticides (Y/N)	Agricultural environment (for some participants)	0.41	0.15	1.12
		Urinary Markers		1.19	0.93	1.53
Chakraborty *et al* (2009)	Self-reported doctor diagnosed	Split into regular sprayers (at least an hour a day, 5 days per month for 5 years) or occasional sprayers	Agricultural environment	1.34	1.05	1.71
Faria *et al* (2005)	Symptoms of asthma	Apply pesticides > 3 days per month vs no exposure	Agricultural environment, cattle, birds, horses	2.11	1.14	3.91
Hoppin *et al* (2008)	Self-reported doctor diagnosed adult-onset asthma	Use of any pesticide, lifetime total years of pesticide use and frequency	Agricultural environment	Atopic Asthma		
				1.46	1.14	1.87
				Non-atopic Asthma		
				1.00	0.82	1.22
Hoppin *et al* (2009)	Self-reported doctor diagnosed adult-onset asthma	History of High Pesticide Exposure Events	Agricultural environment	Atopic Asthma		
				1.98	1.30	2.99
				Non-atopic Asthma		
				1.96	1.49	2.56
Nriagu *et al* (1999)	Self-reported doctor diagnosed asthma	Use of insecticides in the home	Unknown	3.67	1.19	11.3
Schenker *et al* (2004)	Self-reported	Paraquat exposure using a cumulative paraquat exposure index	Agricultural environment (Banana, coffee and palm oil)	1.60	0.9	3.0
Yemaneberhan *et al* (1997)	Self-reported	Self-reported use of insecticides urban vs rural exposure	Unknown	0.35	0.25	0.49
Zhang *et al* (2002)	Self-reported asthma attack	Self-reports of insecticide exposure	Outdoor agricultural worker, biomass fuel burning	1.9	1.3	2.9

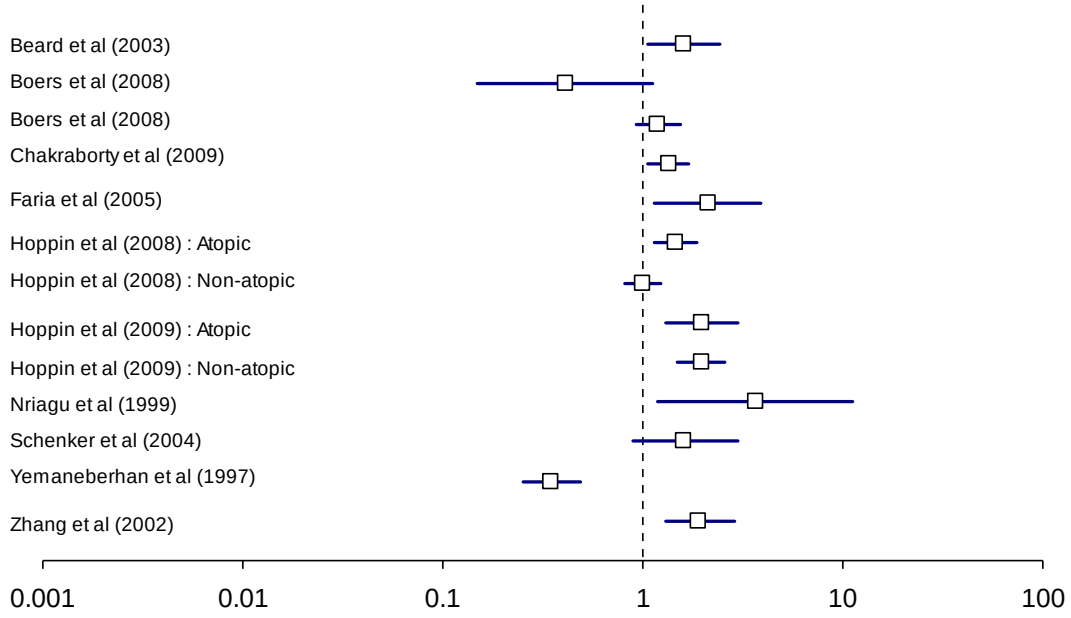

Figure 2: Odds ratios for asthma in adults. Please note that odds ratios refer to different exposure metrics – see table 3 and please read section 3.2.2 for details of the underlying studies

Studies of pesticide exposure in relation to childhood asthma

Weselak *et al* (2007) examined *in utero* pesticide exposure as part of the Ontario Farm Family Health Study. The participants were 2,964 parents who had 5,853 pregnancies. Data were collected via postal questionnaire one to the farm operator; including information on chemicals used, one to the male parent and one to the female parent. From this retrospective study, no significant associations were found between the use of pesticides by either parent during pregnancy and asthma in the children.

Sunyer *et al* (2005) reported on a Menorcan prospective birth cohort of 482 recruited children recruited in utero to the study, of whom 468 were successfully followed up at age 4 and follow-up to age 6 Sunyer *et al* (2006). Sunyer *et al* (2005) collected blood samples from 405 of the study children at birth and from 285 at age four years. Although cord serum DDE levels were positively associated with wheezing symptoms at age four (OR=1.32, 95% CI 1.13-1.54), no significant association was identified between levels of DDE at birth and doctor diagnosed asthma at age four. The associations were reported after extensive adjustment was made for potentially confounding factors including socio-economic status and that only 1.9% of children had a diagnosis of asthma at age four, reflecting the diagnostic uncertainty that exists for wheezing symptoms in young children.

Sunyer *et al* (2006), in a follow-up study of the cohort with the participants aged 6.5 years, the authors defined asthma as the presence of wheezing on one or more occasion in the previous year or doctor diagnosed asthma reported by parents. Further data was collected included BMI, skin prick testing from 308 children and breastfeeding patterns. Results for asthma are presented here and those for wheeze

are presented in section 3.2.6. Results showed that doctor diagnosed asthma at age 6.5 years was associated with serum levels of DDE at birth (OR=1.18, 95% CI 1.01-1.39) but not with DDE at aged 4. However, children who were formula fed rather than breast fed were found to have lower levels of DDE and DDT in blood samples. Furthermore, breastfeeding was found to have a protective effect against diagnosed asthma (OR=0.33, 95% CI 0.08-0.87) in all the children studied. The investigators used an appropriate strategy to adjust for potential confounding factors that included consideration of socio-economic status. The study suggests that there is evidence for an effect of DDE on asthma levels in children; however there were no environmental exposure measurements made as part of this work, but it was noted that there are no known environmental releases of DDE in this community.

Salam *et al* (2004) reported on early life environmental risk factors for asthma in the Children's Health Study which is a birth cohort of 6,259 children from southern California. From the cohort, two nested case control groups were obtained, the first 338 cases of asthma and 579 controls followed by 279 cases and 412 controls. Data were collected retrospectively from the biological mother who provided a detailed history on health, demographics and exposures via a telephone interview. Assessment was also made of confounders including smoking, socio-economic status, education and race. The results of the study showed that there was a significant association between diagnosed asthma and being exposed to pesticides in the first year and later (OR=2.39, 95% CI 1.17-4.89) and between early persistent asthma and being exposed to pesticides in the first year (OR=3.58, 95% CI 1.59-8.06). However, this association was not found for children not exposed in the first year. Similar results were found for herbicide and pesticide exposure where those exposed in the first year and later were more at risk of any asthma (OR=2.53, 95% CI 1.26-5.09) and early persistent asthma (OR=3.78, 95% CI 1.70-8.41). Although the study highlights a number of significant associations, and a suitable strategy was employed to adjust for potential confounding factors including socio-economic status, the study is weakened by its reliance on retrospective recall on date of asthma diagnosis and early life exposures with consequent potential for recall bias. In addition there were no objective measurements of exposure.

Salameh *et al* (2003) used a questionnaire survey to evaluate health in school children aged between 5 and 16 years in Lebanon. The survey was designed for completion by the parents and included questions from the American Thoracic Society on respiratory diseases. A total of 3,291 questionnaires were completed and exposure to pesticides was subdivided into residential, domestic, para-occupational and any exposure. Residential exposure was described as living near a treated field; domestic exposure as use of pesticides by a household member either in the house or garden and para-occupational exposure was described as the occupational use of pesticides by one of the household members. Doctor-diagnosed asthma was found to be significantly associated with residential use of pesticides (OR=2.10, 95% CI 1.01-4.42), domestic use of pesticides (OR=1.99, 95% CI 1.00-3.99), para-occupational use of pesticides (OR=4.61, 95% CI 2.06-10.29) and any exposure to pesticides (OR=1.73, 95% CI 1.02-2.97). Although the investigators extensively adjusted for potentially confounding factors including socio-economic status and parental reports of asthma were confirmed by a doctor the study could have been affected by bias in relation to living in different areas of the country, recall bias by parents and differential responses from the schools. No further breakdown of types of pesticides was available.

Table 4: Odds Ratios for Pesticide Exposure and Asthma in Children

Author	Asthma definition	Exposure metric	Co-exposures	Odds ratio	Lower limit	Upper limit
Salam *et al* (2004)	Doctor Diagnosed	Self-reported farm related exposures to crops, dusts, animals, herbicides and pesticides in first year of life	Crops, dusts, animals	2.39	1.17	4.89
Salameh *et al* (2003)	Self-reported doctor diagnosed	Any exposure to pesticides	Dust, animals	1.73	1.02	2.97
Sunyer *et al* (2005)	Doctor diagnosed asthma at 4 years	Cord blood and blood samples	Unknown	RR 1.46	0.92	2.32
Sunyer *et al* (2006)	Doctor diagnosed asthma at age 6.5	Cord blood and blood samples aged 4	Unknown	1.18	1.01	1.39
Weselak *et al* (2007)	Self-reported doctor diagnosed	Any exposure to pesticides during pregnancy	Farm environment	1.00	0.71	1.40

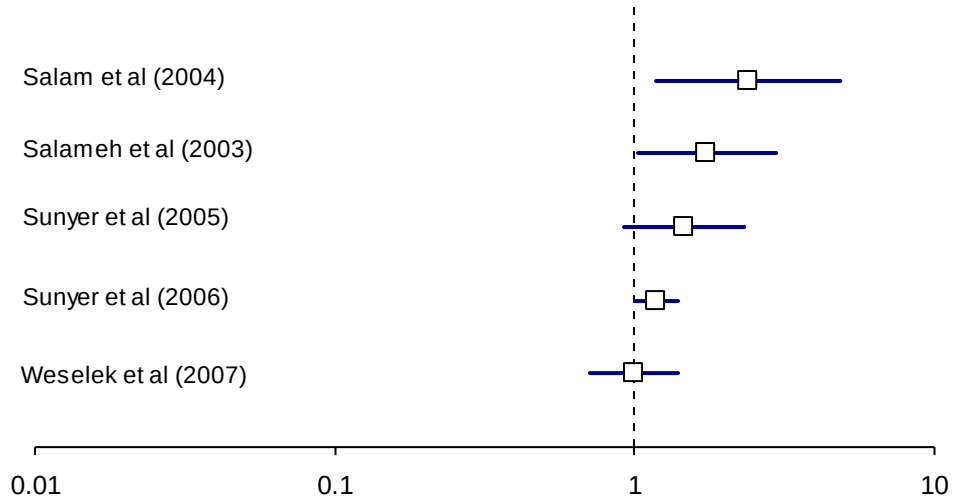

Figure 3: Odds ratios for asthma in children. Please note that odds ratios refer to different exposure metrics – see table 4 and please read section 3.2.2 for details of the underlying studies

Studies of Rhinitis prevalence

The airway commences at the nose and mouth and continues into the lung, consequently the effects of any exposure on the lung airways is often preceded or associated with effects on the nose. Inflammation of the nasal airway (rhinitis) is closely

associated with the presence of similar inflammation in the small airways of the lungs that manifests as asthma. Five studies examined associations between pesticide exposure and rhinitis (Chakraborty *et al.,* 2009, Hoppin *et al.,* 2007, Hoppin *et al.,* 2009, Huang *et al.,* 1995, Nriagu *et al.,* 1999, Weselak *et al.,* 2007)

Chakraborty *et al* (2009) examined a number of symptoms in agricultural workers exposed to organophosphate and carbamate pesticides in eastern India. The study compared 376 workers with 348 matched controls. To assess rhinitis, the questionnaires based on the MRC and ATS respiratory questionnaires were employed using an investigator to interview the participants. Overall, both those involved in occasional spraying and regular spraying of pesticides reported runny or stuffy nose significantly more frequently than the control group; 44.4% versus 20.1% ($P<0.01$). However, more that 50% cholinesterase inhibition is marked inhibition and the adverse association may be a consequence of symptomatic bronchoconstriction induced by organophosphate poisoning.

(Hoppin *et al.,* 2007) as part of the Agricultural Health Study, examined a number of different symptoms in relation to farmers lung and pesticide exposure. Using self-administered questionnaires, data were available from 21393 applicators (mainly farmers) and 30242 spouses. Overall, 74% of applicators who had had farmers' lung had rhinitis compared to 67% of those who did not report farmers' lung. No data were available for the spouses in relation to rhinitis. **Hoppin *et al* (2009)** again as part of the Agricultural Health Study, reported on data examining adult onset asthma and pesticide use. The study of 19,704 farmers identified that 66% of the control group reported a runny nose in the past year, 88% of those with allergic asthma reported the same and 74% of individuals with non-allergic asthma.

Huang *et al* (1995) looked at respiratory symptoms in those involved in chlorothalonil (TCPN) production. In this small study of 28 individuals, nose irritation was reported significantly more frequently in the chlorothalonil workers (46.4%), than in the reference group (5.6%), ($p<0.001$). The limitations of this study are outlined above along with chlorothalonil's classification as a respiratory irritant.

Nriagu *et al* (1999) examined asthma and respiratory symptoms in domestic environments in South Africa. The study used a modified version of the WHO questionnaire for asthma studies and was used in an interview format. A total of 213 households were interviewed including 693 adults and 367 children. When asked, 44% of adults and 50% of children within the sample reported frequent blocked runny noses. Further analysis on the reporting of constant runny noses was not carried out within this paper as the study did not relate the prevalence of rhinitis to pesticide exposure.

The evidence that pesticide exposure was linked to rhinitis was limited but there is a suggestion that nasal symptoms are related to pesticide exposure. These could be interpreted as either symptoms of irritancy or true chronic rhinitis.

Studies rated as negative for quality

During the quality assessment process, the ten studies cited were graded as negative (-) after quality assessment (Bener *et al.,* 1999, Dahlgren *et al.,* 2003, Fieten *et al.,* 2009, Garry *et al.,* 1994, Jones *et al.,* 2003, Radon *et al.,* 2002, Salameh *et al.,* 2006, Senthilselvan *et al.,* 1992, Senthilselvan *et al.,* 1992, Strong *et al.,* 2004, Zuskin *et al.,* 1997). They were excluded from the review as there was concern that their inclusion could potentially bias the results of the review.

The reasons for the negative quality assessment were based on:

- No pesticide agents being identified (Bener *et al.,* 1999, Jones *et al.,* 2003, Radon *et al.,* 2003, Salameh *et al.,* 2006, Senthilselvan *et al.,* 1992, Senthilselvan *et al.,* 2000, Zuskin *et al.,* 1997) no confounders being taken into account (Bener *et al.,* 1999, Strong *et al.,* 2004) inadequate adjustment for smoking (Dahlgren *et al.,* 2003, Strong *et al.,* 2004) participants taking part in a class action and research funded by a law firm (Dahlgren *et al.,* 2003)co-exposures were common so could not identify the pesticide (Fieten *et al.,* 2009) high dropout rate in the study (Jones *et al.,* 2003) no medical outcomes measured (Garry *et al.,* 1994) self-reported un-validated method (Salameh *et al.,* 2006).

3.2.3 The evidence for association with Wheeze

Seventeen papers were found that examined associations between wheeze and pesticide exposure (Boers *et al.,* 2008, Chakraborty *et al.,* 2009, Faria *et al.,* 2005, Hoppin *et al.,* 2002, Hoppin *et al.,* 2006a, Hoppin *et al.,* 2006b, Hoppin *et al.,* 2007, Hoppin *et al.,* 2009, Huang *et al.,* 1995, Nriagu *et al.,* 1999, Salameh *et al.,* 2003, Schenker *et al.,* 2004, Sprince *et al.,* 2000, Sunyer *et al.,* 2005, Sunyer *et al.,* 2006, Yemaneberhan *et al.,* 1997, Zhang *et al.,* 2002)

Exposure Studies in Adults

Boers *et al* (2008) carried out a prospective case control study to examine asthmatic symptoms after exposure to ethylenebisdithiocarbamates and other pesticides. The study group included 248 workers across 4 countries (Netherlands, Italy, Finland and Bulgaria) who were compared with 231 non-exposed workers. A fuller description of the methodology is available in section 3.2.2. The analysis of the survey data (adjusted for all confounders) did not find a significant association with wheeze and exposure to pesticides (OR=0.56, 95% CI 0.32-0.98), rather a significantly lower occurrence of wheeze in those exposed. Analysis of the urine samples showed no association between wheeze and exposure to pesticides (OR=0.99, 95% CI 0.87-1.13).

Chakraborty *et al* (2009) studied respiratory symptoms in agricultural workers exposed to organophosphate and carbamate pesticides in eastern India. The study compared 376 non-smoking agricultural workers with 348 age and sex matched controls. A fuller description of the methodology is reported in section 3.2.2. Overall, 19.4% of the sprayer group reported wheeze compared with 9.8% of the control group ($p<0.01$). This could be broken down into 18.4% of the occasional sprayer group and 20.9% of the regular sprayer group. The researchers further analysed the data in relation to cholinesterase inhibition and comparisons identified that wheeze was significantly associated with having more than 50% cholinesterase inhibition (OR=2.9, 95% CI 2.1-4.2). As noted previously, more that 50% cholinesterase inhibition is marked inhibition and the adverse association may be a consequence of symptomatic bronchoconstriction induced by organophosphate poisoning.

Faria *et al* (2005) carried out a cross-sectional survey of 1,379 farmers in Brazil. Respiratory symptoms were assessed using an adapted American Thoracic Society questionnaire. Pesticide exposure was assessed using an interview which identified the main chemical groups used, their usage and frequency of use. The main chemicals identified were fenthion, dimethoate, trichlorfon, methyl parathion, methamidophos, deltamethrin, cypermethrin, atrazine, simazine, nancozeb, maneb,

captan, dodine, benzimidazole, glyphosate and paraquat. From this a collective environmental exposure was estimated by collecting data from the whole farm including fertilizers. From the sample, 17.9% reported wheezing and shortness of breath. Further associations identified that symptoms of asthma (defined as two or more episodes of wheezing with shortness of breath) were significantly associated with pesticide application of more than 3 days per month (OR=2.11, 95% CI 1.14-3.92); equipment cleaning more than two days per month (OR=2.06, 95% CI 1.13-3.77) and self-reported pesticide poisoning (OR=1.64, 95% CI 1.04-2.58). Further analysis of the data investigated exposure to different types of pesticides in relation to asthma symptoms. However, no significant associations were found.

Hoppin *et al* (2002) examined the association between wheeze and pesticide use in 20,468 pesticide applicators as part of the Agricultural Health Study. The study used self-administered questionnaires and asked about 40 currently used pesticides. Wheeze was defined in the questionnaire as wheezing or whistling in the chest and the number of episodes in the past 12 months were identified. Pesticide exposure was assessed using information on pesticide type, frequency of application, total pesticide use and lifetime years of application. In total, 19% of participants reported wheeze in the previous 12 months. After adjustments for confounders (notably not including socio-economic status), wheeze was found to be significantly associated with exposure to the herbicides alachlor (OR=1.24, 95% CI 1.09-1.42), atrazine (OR=1.20, 95% CI 1.07-1.42), chlorimuron ethyl (OR=1.14, 95% CI 1.02-1.29), paraquat (OR=1.27, 95% CI 1.04-1.56), petroleum oil (OR=1.28, 95% CI 1.11-1.48) and trifluralin (OR=1.12, 95% CI 1.00-1.25). The full results are presented in Table 5. It was not possible to calculate an OR for 'exposure to any pesticide' compared to no pesticide exposure as all participants in this study were exposed to at least one pesticide due to their occupation, therefore this study is not included in Table 6.

Table 5: Associations between wheeze and pesticide exposure in male and female applicators (Hoppin *et al* 2002)

Chemical	Wheeze (*n = 3,838*) % exposed	No Wheeze (*n = 16,630*) % exposed	Adjusted OR*	95% CI	p Trend
Herbicides					
2,4-D	62.4	64.7	0.99	(0.88, 1.11)	0.46
Alachlor	21	17.6	1.24	(1.09, 1.42)	<0.01
Atrazine	54.6	53.2	1.20	(1.07, 1.34)	<0.01
Butylate	1.6	1.2	1.23	(0.86, 1.77)	0.29
Chlorimuron ethyl	16.4	14.5	1.14	(1.02, 1.29)	<0.01
Cyanazine	15.5	15.8	1.03	(0.90, 1.18)	0.17
Dicamba	30.8	32.3	1.06	(0.95, 1.19)	0.22
EPTC	4	3.4	1.32	(1.05, 1.65)	0.01
Glyphosate	68.1	64.9	1.05	(0.95, 1.17)	0.04
Imazethapyr	34.2	35.8	1.06	(0.95, 1.17)	0.02
Metolachlor	27.4	27	1.07	(0.97, 1.19)	0.26
Metribuzin	6.7	6.4	1.13	(0.94, 1.37)	0.03
Paraquat	5	3.6	1.27	(1.04, 1.56)	<0.01
Pendimethalin	18.3	17	1.04	(0.93, 1.17)	0.05
Petroleum oil	10.3	7.9	1.28	(1.11, 1.48)	<0.01
Trifluralin	29.3	28.3	1.12	(1.00, 1.25)	0.03
Insecticides					
Organophosphates					
Chlorpyrifos	24.2	22	1.12	(1.01, 1.25)	0.01
Coumaphos	3.5	3.1	0.95	(0.75, 1.20)	0.63
Diazinon	8	6.1	1.04	(0.88, 1.23)	0.52
Dichlorvos	3.2	3	1.14	(0.90, 1.44)	0.30
Fonofos	5.4	5.3	1.08	(0.89, 1.31)	0.38
Malathion	34.7	30.7	1.14	(1.02, 1.28)	0.01
Parathion	1.4	0.8	1.50	(1.04, 2.16)	0.01
Phorate	3.8	3.5	1.06	(0.84, 1.34)	0.72
Terbufos	16.8	16.7	1.09	(0.96, 1.23)	0.21
Trichlorfon	0.2	0.1	1.93	(0.69, 5.41)	—
Carbamates					
Aldicarb	3.8	3.1	0.97	(0.78, 1.20)	0.89
Carbaryl	20.1	16.3	1.13	(0.98, 1.30)	0.01
Carbofuran	3.6	3.2	1.11	(0.86, 1.42)	0.51
Other insecticides					
Lindane	1.4	1.5	0.82	(0.58, 1.16)	0.80
Permethrin (crops)	6.4	5	1.13	(0.95, 1.35)	0.07
Permethrin (poultry)	5.8	5.1	1.26	(1.06, 1.51)	<0.01
Fungicides					
Benomyl (also carbamate)	2.4	2	1.03	(0.79, 1.35)	NA
Captan	7.2	6.7	1.01	(0.86, 1.19)	NA
Chlorothalonil	4	3.5	0.93	(0.75, 1.16)	NA
Maneb	3	2.3	1.16	(0.91, 1.48)	NA
Metalaxyl	11	7.8	1.19	(1.02, 1.38)	NA
Ziram	0.3	0.2	1.02	(0.48, 2.16)	NA
Fumigants					
Aluminum phosphide	0.5	0.6	0.67	(0.39, 1.18)	NA
Brom_O_Gas	5.7	4.2	1.11	(0.90, 1.35)	NA

* Odds ratios adjusted for age, state, past smoking, current smoking, and asthma/atopy. Comparison group is those who never reported using the pesticide.
NA - not applicable: trend test not performed for fumigants and fungicides, owing to the few days of usage/year.

For insecticides, Hoppin *et al* (2002) identified a significant association between the organophosphates chlorpyrifos (OR=1.12, 95% CI 1.01-1.25), malathion (OR=1.14, 95% CI 1.02-1.28) and parathion (OR=1.50, 95% CI 1.04-2.16). A positive association with wheeze was found with one fungicide which was metalaxyl (OR=1.19, 95% CI 1.02-1.38). One further insecticide, permethrin used on poultry was also found to be associated with wheeze (OR=1.26, 95% CI 1.06-1.51). However, in a subsequent paper the same authors concluded that animals and animal related exposures were important triggers for wheeze among adult farmers, and poultry related exposures were more important predictors of wheeze than other animal exposures (Hoppin et al, 2003).

The study also examined dose-response trends and positive trends were identified for atrazine, chlorpyrifos and parathion. The odds ratio for an association between those applying atrazine 20 or more days per year and wheeze was OR=1.53, (95% CI 1.21-1.95) compared to those who had never used the pesticide; for parathion wheeze was associated with 5 or more application days per year (OR=1.72, 95% CI 1.10-2.68).

(Hoppin *et al.,* 2006a) as part of the Agricultural Health Study examined health outcomes in 17,920 farmers and 2,225 commercial applicators to examine respiratory health outcomes. In this study, a similar methodology was used as in Hoppin *et al* (2002). The results identified that for farmers pesticides significantly associated with wheeze were the herbicides alachlor (OR=1.23, 95% CI 1.06-1.41), atrazine (OR=1.18, 95% CI 1.05-1.32), EPTC (OR=1.37, 95% CI 1.08-1.73), petroleum oil (OR=1.26, 95% CI 1.09-1.47). Malathion use by farmers was also associated with wheeze (OR=1.13, 95% CI 1.00-1.27). For the commercial applicators, chlorimuron-ethyl was associated with wheeze (OR=1.62, 95% CI 1.25-2.10) as was dichlorvos (OR=2.48, 95% CI 1.08-5.66) and phorate (OR=2.35, 95% CI 1.36-4.06). A dose response effect for wheeze among the sample was noted for chlorpyrifos for commercial applicators (OR=1.48, 95% CI 1.00-2.19) and farmers (OR=1.96, 95% CI 1.05-3.66) for exposure of at least 20 days per annum. It was not possible to calculate an OR for 'exposure to any pesticide' compared to no pesticide exposure as all participants in this study were exposed to at least one pesticide due to their occupation, therefore this study is not included in Table 6.

(Hoppin *et al.,* 2006b) reported on further analysis examining wheeze in commercial pesticide applicators. This study included 2,255 US applicators enrolled in the Agricultural Health Study. The results showed that the herbicide chlorimuron-ethyl and current use was associated with wheeze (OR=1.62, 95% CI 1.26-2.10). An association was also found with glyphosate (OR=1.38, 95% CI 1.03-1.86), imazethapyr (OR=1.35, 95% CI 1.05-1.75), metolachlor (OR=1.37, 95 % CI 1.05-1.78), metribuzin (OR=1.42, 95% CI 1.05-1.92), pendimethalin (OR=1.38 95% CI 1.07-1.79) and petroleum oil (OR=1.47, 95% CI 1.08-2.01). Associations were also found for the organophosphates chlorpyrifos (OR=1.47, 95% CI 1.09-1.99), dichlorvos (OR=2.48, 95% CI 1.09-5.64), fonofos (OR=1.78, 95% CI 1.07-2.98), phorate (OR=2.87, 95% CI 1.70-4.84) and terbufos (OR=1.66, 95% CI 1.09-2.53). It was not possible to calculate an OR for 'exposure to any pesticide' compared to no pesticide exposure as all participants in this study were exposed to at least one pesticide due to their occupation, therefore this study is not included in Table 6.

Further research by **(Hoppin *et al.,* 2009)** examined pesticides and other agricultural factors associated with self-reported farmer's lung. Within this sample 481 farmers reported this disorder. High pesticide exposure events (OR = 1.75, 95% CI 1.39-2.21), and ever use of organochlorine (OR = 1.34, 95% CI 1.04-1.74) and carbamate

pesticides (OR = 1.32, 95% CI 1.03-1.68) were associated with farmer's lung in mutually adjusted models. Because this paper addresses farmers' lung and not asthma it has not been included in the table below.

Hoppin *et al* (2009) examined the relationship between pesticides and adult-onset asthma in male farmers. The study of 19,704 farmers identified that 17% of the control group reported wheeze, 84% of those with allergic asthma reported the same and 70% of individuals with non-allergic asthma.

Huang *et al* (1995) looked at respiratory symptoms in those involved in chlorothalonil (TCPN) production and a full description of the methodology is available in section 3.2.2. The survey of 28 workers identified that 6 participants reported wheezing at work versus none in the reference group. However, this was a small study and confounders were not adjusted for within the analysis.

Nriagu *et al* (1999) examined asthma and respiratory symptoms in domestic environments in South Africa. The study used a modified version of the WHO questionnaire for asthma studies and was used in an interview format. A total of 213 households were interviewed including 693 adults and 367 children and when asked, 40% of adults and 37% of children reported having a "wheezy chest". Associations between reported wheeze and various factors were identified including use of insect coils in the house (OR=2.52, 95% CI 1.19-5.34).

Schenker *et al* (2004) examined pulmonary function in 219 paraquat handlers compared to 100 non-handlers in Costa Rica; a more complete summary of the methodology is available in section 2.3.4. Persistent wheeze was not found to be significant for the paraquat handlers in this study (OR=1.1, 95% CI 0.7-1.6).

Sprince *et al* (2000) examined associations between agricultural exposures and respiratory symptoms in Iowa. The study group of 385 participants completed a questionnaire that covered respiratory symptoms, demographic information and smoking information. Exposure was assessed by indicating whether they applied insecticides and herbicides to crops and livestock. Further assessment was made on whether such chemicals got on to hands or arms. In total, 10% of the sample reported being ever wheezy with 4% reporting a work-related chest wheeze. For farmers applying pesticides to livestock this was significantly associated with "chest ever wheezy" (OR=3.92, 95% CI 1.76-8.72). The use of conventional vertical silos was also associated with increased odds of chest ever being wheezy (OR=2.75, 95% CI 1.23-6.12). This is a small survey using a cross-sectional design that only adjusted for the potential confounding effects of smoking and age, failing to adjust for socio-economic status and diagnosed asthma, thus care must be taken in its interpretation.

Yemaneberhan *et al* (1997) carried out a survey of 9,844 urban and 3,032 rural Ethiopian participants to examine asthma and atopy prevalence in Ethiopia. Section 3.2.2 contains a fuller description of the methodology used. The percentage reporting wheeze was 3.7% of the urban participants and 1.2% of the rural participants. Analysis of the data found that self-reported wheeze was significantly lower in the rural group than in the urban group (OR=0.31, 95% CI 0.22-0.43) after adjustment for smoking. Results from this paper have been omitted from Table 6 due to the absence of any specific measures of exposure.

Zhang *et al* (2002) examined respiratory symptoms in a rural population in China exposed occupationally and environmentally to insecticides. Using a self-reported

questionnaire of symptoms and insecticide exposure, 22,258 adults completed the survey; a fuller description of the methodology is available in section 3.2.2. In total, 3.1% of the sample had been exposed to insecticides and 17.5 % had been exposed to other chemicals. Results identified that wheeze was significantly associated with insecticide exposure (OR=1.8, 95% CI 1.2-2.6) after adjustments for age, sex, smoking and county as well as the interaction between smoking and chemical exposure. The study had a number of limitations within its design and should be treated with caution as no particular chemicals were identified.

Table 6: Odds Ratios for Pesticide Exposure and Wheeze in Adults

Author	Wheeze definition	Exposure metric	Co-exposures	Odds ratio	Lower limit	Upper limit
Boers *et al* (2008)	Self-reported	Job history of exposure to pesticides (Y/N)	Agricultural environment (for some subjects)	0.56	0.32	0.98
		Urinary Markers		0.99	0.87	1.13
Chakraborty *et al* (2009)	Self-reported	≥50 cholinesterase inhibition	Agricultural environment	2.9	2.1	4.2
Faria *et al* (2005)	Symptoms of asthma	Apply pesticides > 3 days per ,month vs no exposure	Agricultural environment, cattle, birds, horses	2.11	1.14	3.91
Nriagu *et al* (1999)	Self-reported "having a wheezy chest"	Use of insecticides in the home	Unknown	2.52	1.19	5.34
Schenker *et al* (2004)	Self-reported persistent wheeze	Paraquat exposure using a cumulative paraquat exposure index	Agricultural environment (Banana, coffee and palm oil)	1.1	0.7	1.6
Sprince *et al* (2000)	Self reported "ever being wheezy"	Self-reports of applying pesticides to livestock	Agricultural environment	3.92	1.76	8.72
Zhang *et al* (2002)	Self-reported wheeze	Self-reports of insecticide exposure	Outdoor agricultural worker, biomass fuel burning	1.8	1.2	2.6

Exposure Studies in Children

Salameh *et al* (2003) used a questionnaire survey to evaluate health in school children in Lebanon. The survey was designed for completion by the parents and included questions from the American Thoracic Society on respiratory diseases. A total of 3,291 questionnaires were completed and exposure to pesticides was subdivided into residential, domestic, para-occupational and any exposure. In the analysis, recurrent wheezing was found to be associated with any exposure to pesticides (OR=2.10, 95% CI 1.39-3.18) as was ever wheezing (OR=1.99, 95% CI 1.43-2.78).

Sunyer *et al* (2005) reported on a birth cohort that included 482 recruited to the study and 468 who completed data collection up to age 4 and follow-up to age 6. Sunyer *et al* (2005) collected cord blood samples in 405 infants and 285 children aged 4 years and the analysis identified associations between persistent wheeze and levels of DDE

(RR=1.31; 95% CI 1.09-1.58). In non-atopic children, a significant association between levels of DDE and the presence of wheezing was found (RR=1.37, 95% CI 1.06-1.79).

Sunyer *et al* (2006), in a follow-up study of the cohort with the participants aged 6.5 years, defined asthma as the presence of wheezing on one or more occasion in the previous year and doctor diagnosed asthma. Further data was collected included BMI, skin prick testing from 308 children and breastfeeding patterns. The analysis of results identified that persistent wheezing was associated with levels of DDE at birth and at age 6.5 (wheeze, OR=1.13, 95% CI 1.03-1.39) but not with DDE at aged 4. However, children who were formula fed rather than breast fed were found to have lower levels of DDE and DDT in blood samples. However, breastfeeding was found to have a protective effect against wheeze (OR=0.53, 95% CI 0.34-0.82) in all the children studied.

Table 7: Odds Ratios for Pesticide Exposure and Wheeze in Children

Author	Asthma definition	Exposure metric	Co-exposures	Odds ratio	Lower limit	Upper limit
Salameh *et al* (2003)	Self-reported recurrent wheezing	Any exposure to pesticides	Dust, animals	2.10	1.39	3.18
Sunyer *et al* (2005)	Wheeze at 4 years	Cord blood and blood samples in non-atopic children	Unknown	RR 1.37	1.06	1.79
Sunyer *et al* (2006)	Wheeze at age 6.5	Cord blood and blood samples aged 4	Unknown	1.13	1.03	1.39

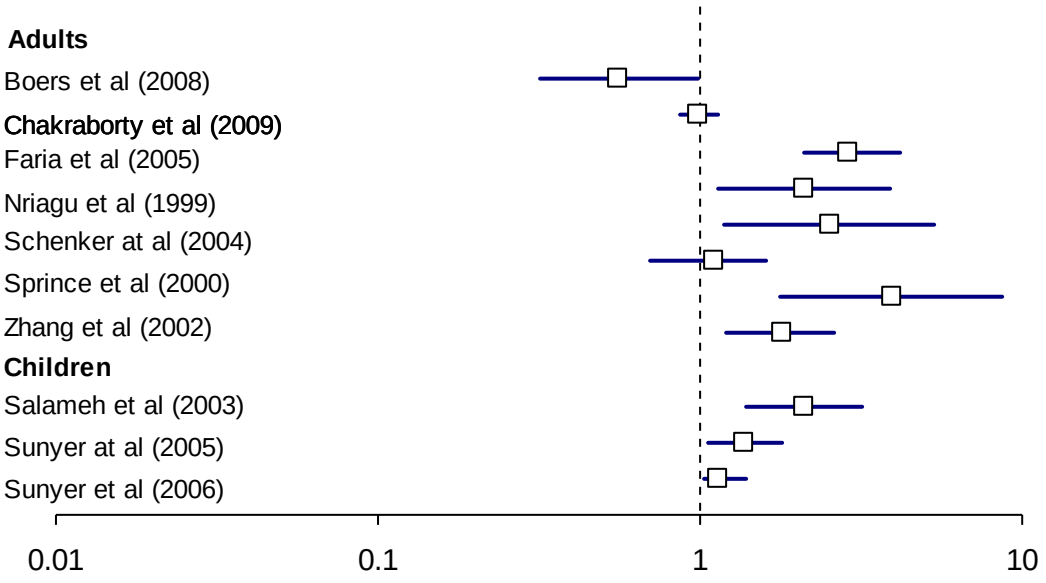

Figure 4: Odds ratios for wheeze. Please note that odds ratios refer to different exposure metrics – see tables 6 and 7 and section 3.2.3 for details

Studies rated as negative for quality

One study was removed after quality assessment (Bener *et al.,* 1999). The negative assessment was due to a lack of confounding variables being taken into account.

3.2.4 The Evidence for Association with Bronchitis and COPD

Six papers examined associations between bronchitis or chronic obstructive pulmonary disease (COPD) and pesticide exposure (Beard *et al.,* 2003, Chakraborty *et al.,* 2009, Faria *et al.,* 2005, Hoppin *et al.,* 2007, Jones *et al.,* 2009, Salameh *et al.,* 2003, Schenker *et al.,* 2004) The papers are summarised below.

Studies in Adults

Jones *et al* (2009) carried out a systematic review and meta-analysis of mortality in crop protection production workers. The review identified 21 references that reported on 37 different mortality cohorts. The analysis of results identified that the SMR for bronchitis, emphysema and asthma was 1.08, 95% CI 0.86-1.35 was based on 23 studies. One of the difficulties with this study is that it did not break down the data into bronchitis as a separate outcome and is therefore not included in table 9.

Beard *et al* (2003) carried out a study of 1,999 outdoor workers who worked with pesticides compared to a group of 1,984 workers who worked outside but were not occupationally exposed to pesticides and to the general Australian population between 1935 and 1996. Exposure assessment was carried out by examining the recorded use of pesticides including arsenic, DDT use, and modern chemical use. This was a mortality study but follow-up was also carried out for 1,533 people via postal questionnaire. In relation to bronchitis, the self-reported outcome component of the research identified that there was no significant association between bronchitis and exposure (OR=1.32, 95% CI 0.87-2.01).

Chakraborty *et al* (2009) studied respiratory symptoms in Indian agricultural workers exposed to organophosphate and carbamate pesticides. The study compared 376 non-smoking agricultural workers with 348 age and sex matched controls. The age range of the samples was 24-53 years and included non-smokers, non-chewers of tobacco and being apparently healthy. Chronic bronchitis (self reported as the presence of cough and expectorations on most of the days for at least 3 months in a year for two consecutive years or more) was reported significantly more by those involved in spraying, 19.1% compared to 6% in the control group ($P<0.05$) and more frequently in those who worked as regular sprayers with 26.8% reporting this ($p<0.01$). Further analysis of this data was carried out to examine cholinesterase inhibition among the work force and a positive association was found between chronic bronchitis and those with more than 50% cholinesterase inhibition (OR= 4.1, 95% CI 2.2-6.3). However organophosphate poisoning includes the symptoms of cough, bronchospasm and bronchorrhea so this may reflect a misdiagnosis.

The Chakraborty study also examined COPD and used spirometric measurements from the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) method. COPD was diagnosed in 18% of the sample compared to 6.9% of the control group ($p<0.001$). This was broken down into mild COPD (Gold Stage 1) in 9% compared with 4% of the control group ($p<0.006$); moderate COPD (stage IIA) in 5% of the sample compared with 2.3% of the controls; severe COPD (stage IIB) was identified in 2.9% of the sample compared to 0.5% of the controls ($p<0.001$) and very severe (stage III) was

found in 0.5% of the sample but not in the controls. Further analysis showed a positive association between COPD prevalence and AchE (cholinesterase) inhibition (OR=1.59, 95% CI 1.32-2.28) after adjustment for education and income.

Faria *et al* (2005) carried out a cross-sectional survey of 1,379 farmers in Brazil. Respiratory symptoms were assessed using an adapted American Thoracic Society questionnaire which was used as an interview. A fuller description of methods is available in section 3.2.2. Self-reports of chronic respiratory disease (presence of at least one of the following symptoms of cough and phlegm during most days of the week for three or more months per year, recurrent wheezing most days and nights or two or more episodes of wheezing with shortness of breath) were found to be positively associated with working on two or more farms (OR=1.92, 95% CI 1.08-3.41), mixing of pesticides more than 2 days per month (OR=1.85, 95% CI 1.18-2.91), washing of work clothes more than 2 days per month (OR=1.78, 95% CI 1.15-2.75) and pesticide poisoning (OR=1.57, 95% CI 1.08-2.28). Although the data were adjusted for a number of relevant sociodemographic factors such as age, sex, education, smoking, civil status, and agricultural area, the results are based on self-report of chronic respiratory disease.

Hoppin *et al* (2007b) examined chronic bronchitis as part of the Agricultural Health Study in the US. Responses from 20,400 male applicators and 508 female applicators who completed two questionnaires (40% of the licensed pesticide applicators and their spouses in two states) were analysed. Individuals with self-reported doctor diagnosed chronic bronchitis were identified from the second questionnaire. Exposure assessment to pesticides was carried out by obtaining detailed information on use of 50 pesticides, the total days and years use of each pesticide used and whether they had experienced a high pesticide exposure event (HPEE). The results identified that 3% of the sample had a history of doctor-diagnosed bronchitis since reaching 20 years of age. Associations were identified between reporting chronic bronchitis and having a high pesticide exposure event or HPEE (OR=1.85, 95% CI 1.51-2.25).

Sixteen further pesticides in the Hoppin *et al* (2007b) were identified as having an association with chronic bronchitis (see Table 8 for details).

Table 8: Associations between pesticide exposure and chronic bronchitis (Hoppin *et al* 2007b)

Exposure	Cases (n=654)	Controls (n=20,254)		95% Confidence Interval	
	%	%	Odds Ratio*	Lower Limit	Upper Limit
High Pesticide Exposure Event	21	14	1.83	1.50	2.24
Insecticides					
Carbamates					
Aldicarb	8	8	1.01	0.74	1.38
Carbaryl	56	43	1.43	1.20	1.70
Carbofuran	36	29	1.41	1.19	1.67
Organochlorines					
Aldrin	22	17	1.19	0.97	1.47
Chlordane	28	19	1.37	1.14	1.65
Dieldrin	6	4	1.25	0.88	1.78
DDT	37	23	1.43	1.19	1.73
Heptachlor	20	12	1.71	1.37	2.13
Lindane	18	13	1.40	1.13	1.73
Toxaphene	17	11	1.40	1.13	1.75
Organophosphates					
Chlorpyrifos	41	42	1.13	0.96	1.32
Coumaphos	13	9	1.42	1.11	1.83
Diazinon	30	21	1.47	1.22	1.76
Dichlorvos	13	11	1.36	1.06	1.73
Fonofos	22	23	1.10	0.90	1.36
Malathion	75	64	1.66	1.38	1.99
Parathion	12	8	1.33	1.03	1.73
Phorate	32	30	1.15	0.96	1.38
Terbufos	37	40	1.04	0.88	1.25
Pyrethroids					
Permethrin (animals)	13	13	1.37	1.07	1.75
Permethrin (crop)	15	13	1.26	1.00	1.59
Herbicides					
2,4-D	78	78	1.10	0.90	1.35
2,4,5-T	28	19	1.51	1.25	1.81
2,4,5-TP	9	5	1.69	1.26	2.25
Alachlor	55	56	1.06	0.89	1.25
Atrazine	68	72	0.97	0.81	1.17
Butylate	25	27	0.99	0.82	1.20
Chlorimuron-ethyl	33	32	1.21	1.02	1.44
Cyanazine	41	43	1.06	0.88	1.27
Dicamba	48	53	1.00	0.83	1.21
EPTC	20	20	1.12	0.91	1.39
Glyphosate	77	77	0.99	0.82	1.19
Imazethapyr	36	44	0.87	0.72	1.06
Metolachlor	43	47	0.99	0.84	1.18

Exposure	Cases (n=654)	Controls (n=20,254)		95% Confidence Interval	
Metribuzin	36	38	1.09	0.91	1.30
Paraquat	19	16	1.17	0.94	1.46
Pendimethalin	34	37	0.95	0.80	1.12
Petroleum oil	24	21	1.25	1.04	1.52
Trifluralin	50	54	0.98	0.82	1.16
Fumigants					
80/20 mix	7	4	1.29	0.93	1.78
Aluminum phosphide	3	3	1.03	0.65	1.62
Ethylene dibromide	5	4	1.02	0.70	1.46
Methyl bromide	17	15	0.91	0.72	1.17
Fungicides					
Benomyl	10	8	0.98	0.74	1.31
Captan	12	11	1.09	0.84	1.40
Chlorothalonil	8	7	0.87	0.64	1.19
Maneb/mancozeb	12	8	1.19	0.91	1.56
Metalaxyl	21	19	1.00	0.81	1.24
Ziram	1	1	1.48	0.59	3.69

*Odds Ratios adjusted for age, state, gender, and pack years

There was evidence of a dose-response effect for some pesticides (carbaryl, DDT, dichlorvos, malathion, permethrin), but little evidence for monotonic increases over all dose levels. Using solvents as pesticide additives and pesticide use off the farm were associated with chronic bronchitis (OR=1.39; 95% CI 1.07-1.79), and those who applied pesticides to animals were more likely to report chronic bronchitis (OR=1.39, 95% CI 1.18-1.64) than those who did not. Results from analyses excluding individuals with asthma were similar to those for the whole sample.

Shenker *et al* (2004) examined pulmonary function in 219 paraquat handlers compared to 100 non-handlers in Costa Rica. The methodology is further described in sections 3.2.2 and 3.2.4. This study reported a non-significant association between self-reported bronchitis and cumulative paraquat exposure (OR=1.3, 95% CI 0.9-2.0).

Table 9: Odds Ratios for Pesticide Exposure and Bronchitis or COPD in Adults

Author	Bronchitis Definition	Exposure metric	Co-exposures	Odds ratio	Lower limit	Upper limit
Beard *et al* (2003)	Self-reported bronchitis	Board of Tick Control records estimating type of chemical and duration of exposure estimates	Agricultural environment, cattle	1.32	0.87	2.01
Chakraborty *et al* (2009)	Self-reported bronchitis with >50% cholinesterase inhibition	Split into regular sprayers (at least an hour a day, 5 days per month for 5 years) or occasional sprayers	Agricultural environment	4.1	2.2	6.3
Chakraborty *et al* (2009)	COPD using GOLD method and more than 50% cholinesterase inhibition	Split into regular sprayers (at least an hour a day, 5 days per month for 5 years) or occasional sprayers	Agricultural environment	1.59	1.32	2.28
Faria *et al* (2005)	Self-reported chronic respiratory disease	Apply pesticides > 2 days per ,month vs no exposure	Agricultural environment, cattle, birds, horses	1.05	0.74	1.51
Hoppin *et al* (2007b)	Self-reported doctor diagnosed	High Pesticide Exposure Event	Agriculture environment	1.85	1.51	2.25
Schenker *et al* (2004)	Self-reported	Paraquat exposure using a cumulative paraquat exposure index	Agricultural environment (Banana, coffee and palm oil)	1.30	0.9	2.0

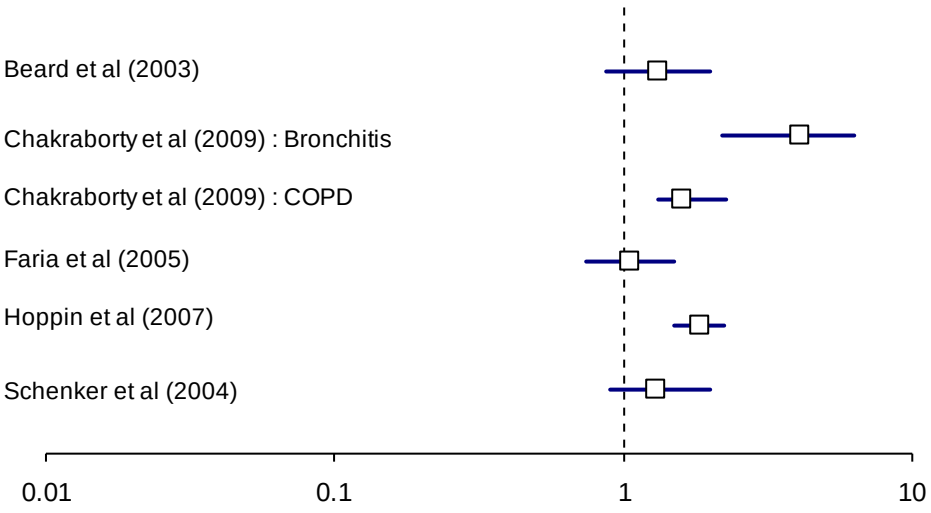

Figure 5: Odds ratios for bronchitis or COPD in adults. Please note that odds ratios refer to different exposure metrics – see table 9 and please read section 3.2.4 for details of the underlying studies

Studies rated as negative for quality

Eight studies were removed from the review as they were rated negatively (-) during the quality assessment. (Bener *et al.,* 1999, Beseler *et al.,* 2009, Beseler *et al.,* 2009, Burns *et al.,* 1998, Castro-Gutierrez *et al.,* 1997, Dahlgren *et al.,* 2003, Jones *et al.,* 2003) The studies were removed for a number of reasons including:

> No particular agents being identified (Bener *et al.,* 1999, Beseler *et al.,* 2009, Jones *et al.,* 2003); no confounding factors taken into account (Bener *et al.,* 1999, Beseler *et al.,* 2009, Castro-Gutierrez *et al.,* 1997, Jones *et al.,* 2003); no analysis of differences between cases and controls presented (Burns *et al.,* 1998, Castro-Gutierrez *et al.,* 1997) and inadequate adjustment for smoking (Dahlgren *et al.,* 2003).

Additionally, Salameh *et al*, 2003 was not included in this section of the report as there were concerns regarding the validity of chronic bronchitis symptoms in a paediatric population. The papers findings on asthma and wheeze in children are still included in this report.

3.2.5 The evidence for Association with Lung Function

Lung function measures were used as an outcome measure in four studies (Chakraborty *et al.,* 2009, Huang *et al.,* 1995, Schenker *et al.,* 2004, Senanayake *et al.,* 1993).

Chakraborty *et al* (2009) measured lung function in agricultural workers exposed to organophosphate and carbamate pesticides in eastern India. The study compared 376 non-smoking agricultural workers with 348 age and sex matched controls. The lung function results showed that both regular sprayers (defined as spraying for at least an hour a day, 5 days per month for the past 5 years or more) and occasional sprayers (those spraying less than the defined regular sprayers) had significantly reduced lung function when compared to the control group and the results are presented in Table 10. When occasional sprayers were compared with regular sprayers, the measure of FEV_1/FVC (%) was found to be significantly lower in regular sprayers (p=0.027).

Table 10: Spirometric measures (Chakraborty *et al* 2009)

Spirometric Measures	Control Group n=348, median age = 40 (25-53)	Agricultural Workers n=376, median age = 41 (24-52)		
		Overall n=376	Occasional Sprayer n=223	Regular Sprayer n=153
FVC (l)	2.58 ± 0.83	2.23 ± 0.9 *	2.24 ± 0.9	2.21 ± 0.9
FEV_1 (l)	2.36 ± 0.9	1.94 ± 0.8 *	1.98 ± 0.5	1.87 ± 0.9
FEV_1/FVC	91.5 ± 14.1	87.0 ± 15.5 *	88.2 ± 15.1	84.6 ± 16.1 **
$FEF_{25-75\%}$ (l/s)	2.81 ± 1.4	2.25 ± 1.2 *	2.27 ± 1.1	2.22 ± 1.3
PEFR (l/s)	2.73 ± 0.3	2.04 ± 1.4 *	2.06 ± 1.3	2.01 ± 1.6

* p< 0.0001, ** p< 0.027

FVC = forced vital capacity, FEV_1 = forced expiratory volume at 1 second, $FEF_{25-75\%}$ = forced expiratory flow at 25-75%, PEFR = peak expiratory flow rate

Huang *et al* (1995) carried out a cross-sectional survey of 28 workers involved in production of chlorothalonil (TCPN). The study examined a number of symptoms but

included lung function measures. The results indicated that there was a significant reduction in FEV_1, 3.39, versus 3.56 ($P<0.05$) and %FEV 72.8 versus 83.7 ($p<0.01$) when the results were compared with the reference group. Measured lung function values rather than predicted values were used. However, there were no significant differences in age, height, weight, and smoking habits between the case and referent groups (mean age: cases: 25.6 yrs; referents 24.8 yrs).

Senanayake *et al* (1993), examined tea plantation workers exposed to paraquat. The study involved 85 male sprayers who were compared with matched controls including 76 factory workers and 79 general workers. Lung function measures were carried out and the results showed no significant differences between the study and control groups.

Schenker *et al* (2004) examined pulmonary function in 219 paraquat handlers compared to 100 non-handlers in Costa Rica. The study aimed to find out whether chronic low level paraquat exposure caused restrictive lung function and gas transfer impairment. Data were collected via an interviewer-administered questionnaire, pulmonary function and exercise tests and a measure of cumulative paraquat exposure. Exposure was assessed using biological monitoring data and weighting for the type of crop and use of PPE. A work history was also collected that included handling of paraquat, length of employment and use of PPE. Lung function and maximal cardiopulmonary tests were also carried out on the sample. No significant differences were identified in lung function measures or exercise measures between the study and control group.

Studies rated as negative for quality

During the quality assessment of the papers, four studies were rated as negative (-) (Abu Sham'a *et al.,* 2010, Konieczny *et al.,* 1999, Peiris-John *et al.,* 2005, Senthilselvan *et al.,* 2000) The reasons for the negative quality assessment included no specific agents being identified (Abu Sham'a *et al.,* 2010, Peiris-John *et al.,* 2005, Senthilselvan *et al.,* 2000) and no confounding factors taken into account (Konieczny *et al.,* 1999)

3.2.6 The evidence for association with Lower Respiratory Tract Infections (LRTIs)

There has long been discussion as to whether viral respiratory infections are factors in the development of asthma. Viruses, notably rhino-viruses, are well recognised as exacerbators of asthma but the evidence to suggest that they may initiate asthma is less strong. We found one paper which considered LRTIs in children and pesticide exposure.

Sunyer *et al* (2010) examined both lower respiratory tract infections and asthma in a birth cohort in Spain. Using dichlorodiphenyldicholoroethylene (DDE) as a marker from mother's blood during the first trimester of pregnancy, a total of 584 women took part in interviews when their children were 6 and 14 months (Sunyer *et al.,* 2010) Within the analysis, 13% of babies had recurrent lower respiratory tract infections in the first 14 months of life. The analysis of results identified that DDE (83-149 ng/g) was the only organochlorine that had an association with lower respiratory tract infections at 6 months (RR=1.68, 95% CI 1.06-2.69) and 14 months (RR=1.59, 95% CI 1.09-2.34). Confounders were taken into account within the model. Further analysis with increased DDE levels (>149.53 ng/g) found a relative risk of 1.64, 95% CI 0.97-1.47) at

6 months and RR=1.68, 95% CI 1.11-2.53 at 14 months. The authors suggest that exposures during the prenatal period can have an effect on the development of the immune and respiratory system.

Due to the presence of only one paper that studied the link between LRTIs and pesticides, and as the link between LRTIs and the development of asthma is unclear, this end point is not considered further.

3.3 META-ANALYSIS OF DATA SETS

We considered the possibilities of carrying out meta-analyses of the studies available for each of the main health endpoints. Within each health endpoint, there were several studies which expressed quantitatively the relationship between exposure to pesticides and occurrence of the endpoint, often in the form of Odds Ratios for those exposed compared to those not exposed. However, as can be seen in the summary tables and text in the previous sections, the exposure metrics considered within the different studies varied considerably, and it was not appropriate to summarise across them (e.g. it was not appropriate to combine an odds ratio referring to "ever exposed to pesticides" with an odds ratio for "use of insecticides in the home" or an odds ratio for "applying pesticides more than 3 days per month"). No meta-analyses were therefore carried out.

4 DISCUSSION

4.1 THE AIM OF THE REVIEW

The aim of this systematic review was to determine if there was a relationship between pesticide exposure (both occupational and non-occupational) and respiratory ill health. In carrying out the review process, a number of factors were identified in relation to the difficulties in making conclusive evidence statements in relation to the research base. These difficulties are discussed in the following sections.

4.2 STUDY LIMITATIONS

This systematic review identified 44 papers which met the inclusion criteria for review but only 25 papers were graded as + or ++, (low or minimal risk of bias) and so were deemed of a quality to be included in the review.

The main shortcomings of the included studies were:

- Most studies were cross-sectional in nature
- Relatively few employed pulmonary function testing.
- A lack of research on individual agents
- The use of surrogate measures of exposure.
- Failure to adjust for potential confounding, especially socio-economic status

When exploring an association between an occupational or environmental exposure and a health outcome robust exposure measurements increase the likelihood of detecting an association, should one exist. Ideally biomonitoring for the agent/metabolite or biological effect monitoring would be employed. While this is possible for acute exposure to some pesticides (e.g. organophosphates, carbamates) only organochlorine insecticides have long term biomarkers of exposure. As a consequence, historical cohort studies and case control studies typically rely on

exposure surrogates such as ever/never exposed, years of exposure, job title (an imprecise exposure surrogate in agricultural work) (MacFarlane *et al.,* 2009), or qualitative estimates of pesticide exposure generated by a job or task exposure matrix (Dick 2010).

Many of the reviewed studies were affected by limitations in the exposure metrics employed; often relying on exposure surrogates such as self-reported exposure and/or imprecise exposure categories such as ever/never exposed to pesticides (Salam et al. 2004). Most studies relied on questionnaires to characterise likely exposures; an approach which can be vulnerable to recall bias and exposure misclassification. Relatively few studies employed biomonitoring to measure pesticide exposure (Sunyer *et al.,* 2010) or biological effect monitoring (Chakraborty 2009). A particular issue arose for those studies in agricultural settings where self-reports were used of pesticide exposure but often co-exposures to other agricultural respiratory hazards (e.g. grain dust, animal dander, endotoxins) were not evaluated. This was compounded by small sample sizes in further papers; however the samples sizes were restricted to those who were actually exposed to particular pesticides rather than a range of agents.

A notable feature of many of the studies in adult populations was the use of reports of wheezing by subjects as an asthma symptom in preference to the more accepted and rigorous outcome of doctor diagnosed asthma or even more preferably lung function and/or measures of airway hyper-reactivity. Even in those studies in adults that reported associations with doctor diagnosed asthma it is difficult to be entirely confident in those that report associations with doctor diagnosed asthma but not with wheezing symptoms, moreover it is possible that doctors may be more likely to diagnose asthma if he/she is aware of their occupational exposure. Given the likely association between socio-economic status and pesticide exposure and the well recognised association between socio-economic status and asthma it is critical that any study of pesticides and asthma adjusts for the potentially confounding effects of socio-economic status. Failure to adjust for socio-economic status is likely to introduce a systematic bias in favour of an adverse association between pesticide exposure and asthma and wheezing symptoms. The failure to adjust for socio-economic status is a notable weakness of many studies reporting associations between pesticides and asthma in adults. Whilst many/most of the reported studies in adult populations are likely to be biased it is notable that one longitudinal birth cohort study in children is of high quality, employing a prospective design, objective exposure assessment, ascertainment of best available paediatric asthma outcome and conducted rigorous adjustment for potentially confounding factors.

Seven of the papers included were based on the Agricultural Health Study (AHS). There are a number of difficulties associated with using the AHS. These include failure to suitably adjust for socio-economic status and the transferability of its findings to other settings. Furthermore, the studies involve multiple analyses of the same data-set and this results in significant overlap where exposure to one agent is highly correlated with exposure to another agent. Although the study population was large within the AHS, the exposure measurement was based on exposure to multiple agents. Thus a broad picture of potential associations can be viewed but little further knowledge is available as to particular agents or groups of chemicals. However, the review has been balanced with the use of smaller studies which may be methodologically weaker but can focus on particular agents.

Additionally, some papers studied pesticides that are no longer used in the UK, e.g. DDT and heptachlor; therefore those results will not be as relevant to the UK as studies

using pesticides currently approved. Most if not all of the reported studies assume that any adverse effect is a consequence of the active pesticide constituent, consequently one of the limitations of this review is the inability to exclude the possibility that any reported adverse health effect of a pesticide may in reality be an adverse effect of co-formulant(s) in commercial pesticide preparations.

4.3 MECHANISMS OF DISEASE

When considering the potential for pesticides to be causally implicated in lung disease, an understanding of the mechanisms involved in the pathogenesis of these conditions is needed. Asthma is characterised by immunologically mediated airway inflammation. It is well established that T-cells of the immune system can be simplistically divided into mutually exclusive Th1 and Th2 types. Th2 cells play a critical role in initiating and perpetuating the inappropriate immune response characteristic of asthma whereas Th1 cells are important in combating infection and in autoimmune diseases. Th2-cells are defined by the secretion of Th2 mediators such as interleukin (IL)-4, IL-5 and RANTES that are immuno-regulatory molecules that drive the inflammatory responses seen in asthma. Th1 cells are characterised by the secretion of the Th1 mediator interferon (IFN)-γ. Insight into the potential for pesticides to influence the immunological pathways that ultimately manifest as asthma can be obtained by investigating the potential for pesticides to promote the development of Th2 immune responses and inhibit the development of Th1 responses.

COPD is a lung disease that is also associated with airway inflammation; however, in contrast to asthma the airway inflammation of COPD is mediated by inflammatory cells known as neutrophils. The physiological function of neutrophils is to fight infection and they normally do this by ingesting organisms and killing them using enzymes and toxic molecules generated from oxygen known as reactive oxygen species. In COPD neutrophils are attracted from the bloodstream into the lung airways by inflammatory mediators such as IL-8 that are generated in areas of inflammation. Once in the airways the neutrophils are activated, and in doing so, release toxic mediators such as enzymes and reactive oxygen molecules that cause further inflammation and tissue damage. Insight into the potential for pesticides to influence the development of COPD can be obtained by investigated whether pesticides can influence the neutrophil mediated inflammation characteristic of COPD.

Potential mechanisms for pesticide-induced asthma

The biological plausibility of an association between pesticide exposure and an increase likelihood of asthma and atopic disease is supported by immunological studies that suggest that pesticide exposure favours Th2 biased immune responses associated with asthma and allergy. Blood levels of the Th2 mediators IL-5 and RANTES have been reported to be elevated in children exposed to chlordane in the residential setting (Phillips, 2000). In an occupational setting, blood levels of DDT and DDE have been associated with elevated levels of the Th2 mediator IL-4 and decreased levels of the Th1 mediator IFN-γ (Daniel *et al.,* 2002). Similarly in an occupational setting increasing blood levels of hexachlorobenzene were associated with reduced IFN-γ secretion by mitogen stimulated T-cells (Daniel *et al.,* 2001). In subjects who have suffered lindane poisoning in an occupational setting, blood levels of IL-4 have been reported to be elevated and IFN-γ decreased (Seth *et al.,* 2005). Although the organochlorine agents investigated in these studies are no longer approved for use in the UK, the reported associations suggest biological plausibility; clearly further research is required.

Early life exposure to pesticides is potentially particularly relevant to the development of asthma because this is the time when the first critical interactions between the immune system and allergens occurs, furthermore it has also been demonstrated that development of the immune system into broadly Th1 and Th2 patterns occurs in most children before the age of 5 years (Yabuhara *et al.,* 1997).

Potential mechanisms for pesticide-induced COPD

The potential for some pesticides to induce the neutrophilic airway inflammation typical of COPD and chronic bronchitis is illustrated by the results of studies demonstrating that pesticides induce neutrophil activation and stimulate the release of the pro-inflammatory mediator IL-8 and toxic reactive oxygen species. Organochlorine compounds have been reported to induce neutrophil activation in rat models and exposure of rats to 60 days of the pyrethroid permethrin has been show to markedly increase the generation of toxic reactive oxygen molecules by rat neutrophils with a 33 fold increase in toxic superoxide anion production (Gabbianelli *et al.,* 2009, Olivero *et al.,* 2002). In humans in vitro administration of the organochlorine toxaphene to neutrophils results in neutrophil activation and the release of the reactive oxygen molecule superoxide (Gauthier *et al.,* 2001). In vitro incubation of human lung alveolar cells with paraquat induces the release of toxic reactive oxygen molecules and the activation of genes coding for the inflammatory mediators IL-1A, IL-6, IL-8 that correlate with increased secretion of pro-inflammatory mediators such as IL-6 and IL-8 (Mitsopoulos *et al.,* 2010). In humans, the organochlorine insecticide dieldrin has been reported to increase human neutrophil reactive oxygen molecule production and the secretion of the proinflammatory mediator IL-8. Using a murine air pouch model, the same investigators reported that dieldrin induces neutrophilic inflammation (Pelletier *et al.,* 2001). In children exposed to chlordane in the residential setting blood levels of the IL-8 have been reported to be elevated (Phillips, 2000).

Cholinesterase inhibition

A number of pesticides inhibit acetyl cholinesterase which results in humans in the inhibition of a number of autonomic receptors both in the peripheral and central nervous systems. In particular in the context of respiratory symptoms, inhibition of peripheral muscarinic receptors will result in mucus hyper-secretion and potentially airway smooth muscle contraction. This will result in breathlessness, cough and wheeze which could occur in high dose in normal individuals (albeit reversibly) but will likely be a cause of greater reaction in those with pre-existing conditions such as asthma or COPD. Whilst approved use should not result in clinically significant systemic inhibition of acetyl cholinesterase, the possibility of local effects on pulmonary autonomic function remains.

4.4 EPIDEMIOLOGY

4.4.1 Initiation or Exacerbation?

As outlined above, asthma and COPD are characterised by airway inflammation albeit of differing patterns and aetiologies. Once airway inflammation is established exposures that induce further superimposed inflammation can be associated with acute exacerbations in the lung disease. It is important to differentiate exposures that initiate the development of airway inflammation and disease from those exposures that can trigger exacerbations. In some cases the exposures that initiate and exacerbate lung

disease are the same, for example allergens and asthma, smoking and COPD, however it is also clear that some factors are important in disease initiation and some in exacerbation, for example viral infections do not initiate COPD or asthma but are well recognised causes of exacerbations.

4.4.2 Mortality

Death from asthma is very uncommon and epidemiological studies of this endpoint are frequently hampered by small numbers. Furthermore, death certificates citing asthma are subject to misclassification with deaths from COPD being registered as deaths from asthma, leading to over-estimation of asthma mortality (British Thoracic Association 1984; Sears 1986) which increases with increasing age (Sears 1986). The evidence that pesticide exposure was a risk factor for asthma deaths in adults was limited. The two mortality studies reviewed (Beard 2003, Jones 2009) gave conflicting results with an Australian cohort study (Beard 2003) showing an elevated SMR in two of 16 analyses of pesticide exposure and asthma deaths. In contrast, a meta-analysis of 23 studies of mortality in pesticide manufacturers (Jones 2009) failed to show a significant effect of pesticides on asthma mortality. However, the latter study used a composite endpoint of death due to asthma, emphysema or bronchitis which may have obscured an association, if one existed, between pesticide exposure and asthma deaths.

With respect to the association between pesticide exposure and COPD mortality, similar problems exist. The main cause of COPD is smoking; therefore it is difficult to be sure about attribution of deaths to pesticides.

4.4.3 Asthma

Prevalent asthma in adults

A statistically significant association was found between prevalent asthma in adults (self-reported or doctor diagnosed) in seven of the 10 studies reviewed, although the effect sizes were generally small. Many of these studies involved agricultural workers and while some studies adjusted for co-exposures to allergens such as animal dander or crops these may not have been adequately controlled for where the prevalence of such co-exposures was high. Only one study in adults employed pesticide biomonitoring (Boers 2008) and that study, of ethylenebisdithiocarbamate exposed workers, failed to find an association with asthma.

Several studies (Chakraborty 2009, Faria 2005, Hoppin 2008, Hoppin 2009) identified an association between exposure to organophosphate pesticides, such as parathion and malathion, and asthma. Interestingly, the study by Chakraborty *et al* (2009) found that workers with greater than 50% cholinesterase inhibition were more likely to have doctor diagnosed asthma than the reference group who had less than 50% cholinesterase inhibition. One of the effects of acute organophosphate poisoning is bronchospasm (Eddleston *et al.,* 2008) raising the possibility that the observed association reflects acute organophosphate pesticide poisoning rather than a chronic effect.

Hoppin *et al* (2009) found that a history of a high pesticide exposure event (defined as an incident which gave the individual an unusually high pesticide exposure) was associated with a near doubling of the risk of both atopic and non-atopic asthma in the Agricultural Health Study. However, the agents associated with these high pesticide exposure events were not specified. Such high pesticide exposure events might reflect worker behaviour whereby those heavily exposed to pesticides may also be heavily

exposed to aeroallergens such as crop dusts. An alternative explanation is recall bias such that asthma sufferers are more likely to recall such high pesticide exposure events than non-asthmatics. A Japanese study of 28 workers manufacturing chlorothalonil found that exposed workers had significantly more asthma-like symptoms than a comparison group of unexposed workers from the same plant (Huang *et al* 1995). Although bronchial challenge testing was not undertaken the results are consistent with the known respiratory irritant effects of chlorothalonil .

Prevalent asthma in children

As regards the five studies of pesticides and asthma in children (Wesselak 2007; Sunyer 2005; Sunyer 2006; Salam 2004; Salameh 2003) four of the five studies found elevated odds ratios or relative risks, three of them significantly so (Sunyer 2005; Sunyer 2006; Salameh 2003). A notable study is that of Sunyer et al who conducted a well design prospective birth cohort study with objective measures of exposure (serum levels) prior to the development of disease, furthermore there was minimal attrition during follow up and the best available outcome parameters in a young children were ascertained and multivariate analyses included adjustment for confounders including socio-economic status. This Spanish (Menorca) cohort study measured 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene (DDE), the major metabolite of the organochlorine insecticide dichlorodiphenyltrichloroethane (DDT), in cord blood and blood samples and reported that doctor diagnosed asthma in children was positively associated with serum DDE levels at birth and at age 6.5 years (OR 1.18, 95%CI 1.01-1.39) but not at age 4 (RR 1.46, 95%CI 0.92-2.32). The source of DDE exposure in the children was from their mother's because there are no known environmental releases of DDE in the community from which this cohort was recruited.

Wheeze

The findings for wheeze in adults showed that 5 out of the 7 studies showed significant associations of pesticide exposure with wheeze, 4 of which had ORs of more than 2. There is therefore some consistency between the asthma findings and the wheeze findings which would support, at least in some settings, a causal relationship between pesticide exposure and asthma. In children, all three of the included studies showed significant associations of pesticide exposure and wheeze, one of which had an OR of more than 2.

Summary of findings in relation to asthma

The number of studies excluded on methodological grounds limits the strength of the evidence base in this area and even those included can in almost every case be criticised at one level or another. Specifically, direct or indirect measurement of exposure to pesticides was rarely reported, and objective measurement of asthma through bronchial responsiveness or serial peak flow measurements has never been undertaken. Separation of symptoms soon after exposure, when awareness of symptoms might be higher (especially if the subjects were aware of the purpose of the study) from repeated symptoms whose pattern was initially induced by exposure cannot be done with any certainty using cross sectional or case control studies which leaves open the possibility that these associations may not be due to true asthma. Equally, in many cases, confounders, notably allergen exposures were inadequately dealt with making conclusions of true causation difficult.

Nevertheless, even though the differences in methodological approach prevented formal meta-analysis, the pattern suggests that exposure to pesticides could be associated with prevalent asthma. When considering Bradford Hill's framework for assessing causation (Bradford-Hill, 1965) a number of the components can be

satisfied. The higher ORs were seen where reported exposures or their surrogates were higher (strength and dose-response) while in those studies of organophosphate exposure mechanistic evidence would support an effect on the airways both pharmacologically through mucus hypersecretion and smooth muscle contraction and immunologically through airway inflammation (biological plausibility). Temporality can only accurately be assessed in longitudinal studies which are absent from the evidence base but the findings are broadly consistent and cohere across different markers (e.g. asthma diagnosis and wheeze).

Consequently, these findings suggest that exposure to pesticides may be associated with prevalent asthma in both adults and children although some caution needs to be exercised when making this judgment, particularly in adults.

4.4.4 COPD and chronic bronchitis

Prevalent COPD/Chronic bronchitis

Of the six papers identified that explored chronic bronchitis and COPD (Beard *et al.,* 2003, Chakraborty *et al.,* 2009, Faria *et al.,* 2005, Hoppin *et al.,* 2007, Jones *et al.,* 2009, Salameh *et al.,* 2003, Schenker *et al.,* 2004), three showed a significant association, and a fourth (Schenker *et al,* 2004) showed a marginally non-significant positive association. Three papers identified significant associations with organophosphate exposure (Chakraborty *et al,* 2009, Faria *et al,* 2005, Hoppin *et al,* 2007) although one of these papers (Hoppin *et al,* 2007) identified multiple pesticide associations with chronic bronchitis including organophosphates, organochlorines, carbamates and herbicides. It seems unlikely that such a diverse range of agents would all induce COPD: to what extent residual confounding (perhaps by agricultural co-exposures such as other pesticides, animal dander, crop dusts, endotoxin or diesel exhaust) might explain these associations is unclear.

Lung function

Few studies employed lung function testing (Chakraborty *et al*, 2009; Huang *et al*, 1995; Schenker *et al*, 2004, Senanayake *et al,* 1993) when exploring pesticide related impacts on respiratory health and only one used objective diagnostic criteria (Chakraborty *et al*, 2009) - the GOLD criteria (Pauwels *et al.,* 2001) - so reducing the comparability of those studies which relied on self-reported symptoms. That study (Chakraborty *et al*, 2009) found an association between reduced lung function and work as a sprayer and evidence of an exposure response relationship with occasional sprayers having higher FEV1/FVC ratios than regular sprayers. Two studies (Schenker *et al*, 2004, Senanayake *et al*, 1993) examined paraquat exposed workers and their lung function and both failed to show any significant differences in lung function between study and control groups.

Summary

In summary, while the quality of most papers in this report are open to criticism, there is sufficient evidence to suggest that exposure to pesticides (or its surrogate) may be associated with a greater prevalence of asthma and asthma symptoms especially in children. In adults the evidence is suggestive but less convincing and the evidence for pesticides contributing to COPD also suggestive at best. Nevertheless, there is sufficient evidence to suggest that pesticide exposure constitutes a probable risk to the respiratory tract especially in children.

5 CONCLUSIONS

Summary of findings
Results from the systematic review suggest that exposure to pesticides may be associated with prevalent asthma. However, methodological issues with the papers, such as cross-sectional/case-control design, measurements of exposure and asthma symptoms and adjustments for confounders, limit the strength of the evidence base in this area. The association between pesticide exposure and asthma appears to be more evident and consistent in children than in adults. A single high quality prospective cohort study with objective assessment of exposure and little loss to follow up suggests that antenatal DDT exposure may increase the likelihood of childhood asthma.

The systematic review suggests that exposure to pesticides may be associated with COPD/chronic bronchitis however, the strength of evidence with regards to the association is weaker than the association with asthma with fewer studies and a lack of studies using lung function to identify COPD: a disease defined on lung function parameters.

Associations between specific pesticide exposure and asthma and COPD are mechanistically plausible with pesticide agents being reported to influence the immunological and neutrophilic inflammatory processes characteristic of asthma and COPD respectively.

Gaps in evidence / limitations
The majority of papers studied occupational exposures that are tightly regulated in the EU and workers have the opportunity to protect themselves from the exposure. A possibly worrying concern is the possible adverse effects of more widespread bystander and non-occupational pesticide exposure (e.g. ingestion). Given the different natures of occupational and non-occupational exposure (e.g. lower dose non-occupational) it is not possible to translate the associations reported in occupational studies to the general population. However, possible adverse effects of non-occupational exposures cannot be easily dismissed, it should be noted that Sunyer et al 2005 reported an association between non-occupational exposure and childhood wheeze/asthma.

In addition, most, if not all, of the reported studies assume that any adverse effect is a consequence of the active pesticide constituent; consequently we are unable to exclude the possibility that any reported adverse health effect of a pesticide may in reality be an adverse effect of co-formulant(s) in commercial pesticide preparations. Furthermore, the exposure measures used in many of the studies included were poor.

The results of the Agricultural Health Study were used often within this report. There is a danger of overusing the results and there is significant overlap in the study where exposure to one agent is highly correlated with another.

Conclusion
There is limited evidence from this systematic literature review that the use of pesticides products, in particular those based on older organophosphates, carbamates and organochlorines, causes or exacerbates airways diseases such as asthma and bronchitis.

Recommendations for future research

1 Longitudinal studies with improved prospective exposure measurement/assessment. However, longitudinal studies can be expensive and individual recall of exposure may be the best possible data that can be obtained. Reporting methods could be improved upon by the use of diaries for pesticide usage rather than recall alone. It may be possible to use existing cohorts rather than only develop new ones. There are some issues with farm environments and co-exposures, therefore it would be good to have studies that are designed to minimise co-exposures and agricultural dust, although this will be difficult to achieve.

2 Cross shift studies of changes in lung function and inflammatory markers in exposed workers with measurement of exposures with extensive study on mechanisms and potential study of genetic susceptibility.

6 REFERENCES

Abu Sham'a F, Skogstad M, Nijem K, Bjertness E, Kristensen P. (2010). Lung Function and Respiratory Symptoms in Male Palestinian Farmers. Archives of Environmental and Occupational Health; 65: 191-200.

Beard J, Sladden T, Morgan G, Berry G, Brooks L, McMichael A. (2003). Health impacts of pesticide exposure in a cohort of outdoor workers. Environmental Health Perspectives; 111: 724-730.

Bener A, Lestringant GG, Beshwari MM, Pasha MA. (1999). Respiratory symptoms, skin disorders and serum IgE levels in farm workers. Allergie Et Immunologie; 31: 52-56.

Beseler CL, Stallones L. (2009). Pesticide poisoning and respiratory disorders in Colorado farm residents. Journal of Agricultural Safety and Health; 15: 327-334.

Boers D, van Amelsvoort L, Colosio C, Corsini E, Fustinoni S, Campo L, Bosetti C, La Vecchia C, Vergieva T, Tarkowski M, Liesivuori J, Steerenberg P, van Loveren H. (2008). Asthmatic symptoms after exposure to ethylenebisdithiocarbamates and other pesticides in the Europit field studies. Human & Experimental Toxicology; 27: 721-727.

British Thoracic Association Research Committee (1984). Accuracy of death certificates in bronchial asthma. Thorax; 39: 505-509.

Burns CJ, Cartmill JB, Powers BS, Lee MK. (1998). Update of the morbidity experience of employees potentially exposed to chlorpyrifos. Occupational and Environmental Medicine; 55: 65-70.

Castro-Gutierrez N, McConnell R, Andersson K, Pacheco-Anton F, Hogstedt C. (1997). Respiratory symptoms, spirometry and chronic occupational paraquat exposure. Scandinavian Journal of Work, Environment & Health; 23: 421-427.

Chakraborty S, Mukherjee S, Roychoudhury S, Siddique S, Lahiri T, Ray MR. (2009). Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India. Journal of Occupational Health; 51: 488-497.

Dahlgren J, Warshaw R, Thornton J, Anderson-Mahoney CP, Takhar H. (2003). Health effects on nearby residents of a wood treatment plant. Environmental Research; 92: 92-98.

Daniel V, Huber W, Bauer K, Suesal C, Conradt C, Opelz G. (2002). Associations of dichlorodiphenyltrichloroethane (DDT) 4.4 and dichlorodiphenyldichloroethylene (DDE) 4.4 blood levels with plasma IL-4. Archives of Environmental Health: An International Journal; 57: 541-547.

Daniel V, Huber W, Bauer K, Suesal C, Conradt C, Opelz G. (2001). Associations of blood levels of PCB, HCHS, and HCB with numbers of lymphocyte subpopulations, in vitro lymphocyte response, plasma cytokine levels, and immunoglobulin autoantibodies. Environmental Health Perspectives; 109: 173.

Dick FD, Semple SE, Van Tongeren M, Miller BG, Ritchie P, Sherriff D, Cherrie JW. (2010). Development of a Task-Exposure Matrix (TEM) for Pesticide Use (TEMPEST). Annals of Occupational Hygiene; 54: 443-452.

Eddleston M, Buckley NA, Eyer P, Dawson AH. (2008). Management of acute organophosphorus pesticide poisoning. The Lancet; 371: 597-607.

Faria NM, Facchini LA, Fassa AG, Tomasi E. (2005). Pesticides and respiratory symptoms among farmers. Revista De Saude Publica; 39: 973-981.

Fieten KB, Kromhout H, Heederik D, van Wendel de Joode B. (2009). Pesticide exposure and respiratory health of indigenous women in Costa Rica. American Journal of Epidemiology; 169: 1500-1506.

Gabbianelli R, Falcioni ML, Nasuti C, Cantalamessa F, Imada I, Inoue M. (2009). Effect of permethrin insecticide on rat polymorphonuclear neutrophils. Chemico-Biological Interactions; 182: 245-252.

Garry VF, Kelly JT, Sprafka JM, Edwards S, Griffith J. (1994). Survey of health and use characterization of pesticide appliers in Minnesota. Archives of Environmental Health; 49: 337-343.

Gauthier M, Roberge CJ, Pelletier M, Tessier PA, Girard D. (2001). Activation of human neutrophils by technical toxaphene. Clinical Immunology; 98: 46-53.

Hoppin JA, Umbach DM, Kullman GJ, Henneberger PK, London SJ, Alavanja MC, Sandler DP. (2007). Pesticides and other agricultural factors associated with self-reported farmer's lung among farm residents in the Agricultural Health Study. Occupational and Environmental Medicine; 64: 334-341.

Hoppin JA, Umbach DM, London SJ, Alavanja MC, Sandler DP. (2002). Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. American Journal of Respiratory and Critical Care Medicine; 165: 683-689.

Hoppin JA, Umbach DM, London SJ, Henneberger PK, Kullman GJ, Alavanja MC, Sandler DP. (2008). Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study. American Journal of Respiratory and Critical Care Medicine; 177: 11-18.

Hoppin JA, Umbach DM, London SJ, Henneberger PK, Kullman GJ, Coble J, Alavanja MC, Beane Freeman LE, Sandler DP. (2009). Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology; 34: 1296-1303.

Hoppin JA, Umbach DM, London SJ, Lynch CF, Alavanja MC, Sandler DP. (2006a). Pesticides and adult respiratory outcomes in the agricultural health study. Annals of the New York Academy of Sciences; 1076: 343-354.

Hoppin JA, Umbach DM, London SJ, Lynch CF, Alavanja MC, Sandler DP. (2006b). Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study. American Journal of Epidemiology; 163: 1129-1137.

Huang J, Aoyama K, Ueda A, Matsushita T. (1995). Respiratory effects and skin allergy in workers exposed to tetrachloroisophthalonitrile. Bulletin of Environmental Contamination and Toxicology; 55: 320-324.

Jones DR, Sutton AJ, Abrams KR, Fenty J, Warren F, Rushton L. (2009). Systematic review and meta-analysis of mortality in crop protection product manufacturing workers. Occupational and Environmental Medicine; 66: 7-15.

Jones SM, Burks AW, Spencer HJ, Lensing S, Roberson PK, Gandy J, Helm RM. (2003). Occupational asthma symptoms and respiratory function among aerial pesticide applicators. American Journal of Industrial Medicine; 43: 407-417.

Konieczny B, Kossmann S, Makuch M. (1999). Impaired respiratory muscle function in chemical plant workers producing chlorfenvinphos. Annals of Agricultural and Environmental Medicine : AAEM; 6: 21-25.

MacFarlane E, Benke G, Del Monaco A, Sim M. (2009). Cancer incidence and mortality in a historical cohort of Australian pest control workers. Occupational and Environmental Medicine; 66: 818-823.

Mitsopoulos P, Suntres ZE. (2010). Cytotoxicity and gene array analysis of alveolar epithelial A549 cells exposed to paraquat. Chemico-Biological Interactions;

Nriagu J, Robins T, Gary L, Liggans G, Davila R, Supuwood K, Harvey C, Jinabhai CC, Naidoo R. (1999). Prevalence of asthma and respiratory symptoms in south-central Durban, South Africa. European Journal of Epidemiology; 15: 747-755.

Olivero J, Bezdecny SA, Ganey PE. (2002). A molecular motif required for the activation of rat neutrophil phospholipase A2 by organochlorine compounds. Chemical Research in Toxicology; 15: 153-159.

Pauwels RA, Buist AS, Calverley P, Jenkins CR, Hurd SS. (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. American Journal of Respiratory and Critical Care Medicine; 163: 1256.

Peiris-John RJ, Ruberu DK, Wickremasinghe AR, van-der-Hoek W. (2005). Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. Respiratory Medicine; 99: 1319-1324.

Pelletier M, Roberge CJ, Gauthier M, Vandal K, Tessier PA, Girard D. (2001). Activation of human neutrophils in vitro and dieldrin-induced neutrophilic inflammation in vivo. Journal of Leukocyte Biology; 70: 367.

Phillips TM. (2000). Assessing environmental exposure in children: immunotoxicology screening. Journal of Exposure Science and Environmental Epidemiology; 10: 769-775.

Radon K, Monso E, Weber C, Danuser B, Iversen M, Opravil U, Donham K, Hartung J, Pedersen S, Garz S, Blainey D, Rabe U, Nowak D. (2002). Prevalence and risk factors for airway diseases in farmers--summary of results of the European Farmers' Project. Annals of Agricultural and Environmental Medicine : AAEM; 9: 207-213.

Radon K, Winter C. (2003). Prevalence of respiratory symptoms in sheep breeders. Occupational and Environmental Medicine; 60: 770-773.

Salam MT, Li YF, Langholz B, Gilliland FD, Children's Health Study. (2004). Early-life environmental risk factors for asthma: findings from the Children's Health Study. Environmental Health Perspectives; 112: 760-765.

Salameh P, Waked M, Baldi I, Brochard P, Saleh BA. (2006). Respiratory diseases and pesticide exposure: a case-control study in Lebanon. Journal of Epidemiology and Community Health; 60: 256-261.

Salameh PR, Baldi I, Brochard P, Raherison C, Abi Saleh B, Salamon R. (2003). Respiratory symptoms in children and exposure to pesticides. The European

Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology; 22: 507-512.

Schenker MB, Stoecklin M, Lee K, Lupercio R, Zeballos RJ, Enright P, Hennessy T, Beckett LA. (2004). Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure. American Journal of Respiratory and Critical Care Medicine; 170: 773-779.

Sears MR, Hiller HH, de Boer G, Beaglehole R, Gillies AJD, Holst PE, O'Donnell TV, Rothwell RPG. (1986). Accuracy of certification of deaths due to asthma. American Journal of Epidemiology; 124: 1004-1011.

Senanayake N, Gurunathan G, Hart TB, Amerasinghe P, Babapulle M, Ellapola SB, Udupihille M, Basanayake V. (1993). An epidemiological study of the health of Sri Lankan tea plantation workers associated with long term exposure to paraquat. British Journal of Industrial Medicine; 50: 257-263.

Senthilselvan A, Dosman JA, Semchuk KM, McDuffie HH, Cessna AJ, Irvine DG, Crossley MF, Rosenberg A. (2000). Seasonal changes in lung function in a farming population. Canadian Respiratory Journal : Journal of the Canadian Thoracic Society; 7: 320-325.

Senthilselvan A, McDuffie HH, Dosman JA. (1992). Association of asthma with use of pesticides. Results of a cross-sectional survey of farmers. The American Review of Respiratory Disease; 146: 884-887.

Seth V, Ahmad RS, Suke SG, Pasha ST, Bhattacharya A, Banerjee BD. (2005). Lindane-induced immunological alterations in human poisoning cases. Clinical Biochemistry; 38: 678-680.

Sprince NL, Lewis MQ, Whitten PS, Reynolds SJ, Zwerling C. (2000). Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project. American Journal of Industrial Medicine; 38: 455-462.

Strong LL, Thompson B, Coronado GD, Griffith WC, Vigoren EM, Islas I. (2004). Health symptoms and exposure to organophosphate pesticides in farmworkers. American Journal of Industrial Medicine; 46: 599-606.

Sunyer J, Garcia-Esteban R, Alvarez M, Guxens M, Goni F, Basterrechea M, Vrijheid M, Guerra S, Anto JM. (2010). DDE in mothers' blood during pregnancy and lower respiratory tract infections in their infants. Epidemiology (Cambridge, Mass.); 21: 729-735.

Sunyer J, Torrent M, Garcia-Esteban R, Ribas-Fito N, Carrizo D, Romieu I, Anto JM, Grimalt JO. (2006). Early exposure to dichlorodiphenyldichloroethylene, breastfeeding and asthma at age six. Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology; 36: 1236-1241.

Sunyer J, Torrent M, Munoz-Ortiz L, Ribas-Fito N, Carrizo D, Grimalt J, Anto JM, Cullinan P. (2005). Prenatal dichlorodiphenyldichloroethylene (DDE) and asthma in children. Environmental Health Perspectives; 113: 1787-1790.

Weselak M, Arbuckle TE, Wigle DT, Krewski D. (2007). In utero pesticide exposure and childhood morbidity. Environmental Research; 103: 79-86.

Yabuhara A, Macaubas C, Prescott SL, Venaille TJ, Holt BJ, Habre W, Sly PD, Holt PG. (1997). TH2-polarized immunological memory to inhalant allergens in

atopics is established during infancy and early childhood. Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology; 27: 1261-1269.

Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J. (1997). Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. The Lancet; 350: 85-90.

Zhang LX, Enarson DA, He GX, Li B, Chan-Yeung M. (2002). Occupational and environmental risk factors for respiratory symptoms in rural Beijing, China. The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology; 20: 1525-1531.

Zuskin E, Mustajbegovic J, Schachter EN, Kern J, Pavicic D. (1997). Respiratory function in vineyard and orchard workers. American Journal of Industrial Medicine; 31: 250-255.

APPENDIX A SEARCH STRATEGY

SEARCH PROTOCOL FOR ASTHMA PREVALENCE AND EXACERBATION AND OTHER RESPIRATORY SYMPTOMS IN ASSOCIATION WITH PESTICIDE EXPOSURE

Research Question

Is there an association between respiratory ill health and pesticide exposure?

Search Strategy

Population:
Agricultural Workers
Agriculture
Farm/Farmers
Shepherd
Sheep Dippers
Sheep breeders
Forestry Workers
Pest Control
Pesticide applicators
Pesticide sprayers
Timber preservatives
Ground sprayers
Boom sprayers
Backpack sprayers
Knapsack sprayers
Aerial Sprayers
Fumigation
Soil fumigation
Chemigation
Space fumigation
Drenching
Showering
Crop dusting
Pet Grooming
Gardeners
Landscape gardeners
Market gardeners
Florists
Orchard workers
Veterinarians
Veterinary surgeons
Vets
Pesticide Sprayers
Home and garden
Non-occupational
Farm workers
Farmhands
Farm labourers

Herdsmen
Herders
Harvesters
Horticulturalists
Horticulture
Agricultural Inspectors

Operators
Workers
Bystanders
Residents
General Public
Children
Humans

Exposure
Occupational agricultural tasks
Occupational amenity tasks
Non-occupational exposure
    Bystander/resident
    Public

Acute exposure
Chronic exposure
Repeated exposure
Poisoning
Respirator
    Respiratory protection
    Face mask

Exposure Route
    Respiratory tract
    Dermal exposure
        Skin
    Ingestion
    Injection

Pesticides
    Agricultural pesticides
    Biocides
    Sheep dip
    Insecticides
    Herbicides
    Fungicides
    Avicides
    Rodenticide
    Nematicides
    Nematocides
    Acaricides
    Molluscicides
    Molluscacides
    Cholinesterase inhibitors
    Organophosphates

Organochlorines
Pyrethroids
Phosphoric acid esters
Arsenical pesticides
Non-arsenical pesticides

Pesticide Class OC
- Aldrin
- DDT
- Dieldrin
- Chlordane
- Endosulfan

Pesticide Class OP
- Chloropyrifos
- Dimethoate
- Malathion
- Parathion
- Diazinon
- Methyl parathion
- Methylparathion

Pesticide Class Carbamates
- Mancozeb
- Maneb
- Oxamyl
- Methomyl
- Carbaryl
- Carbofuran
- Methylcarbamate
- Propxur

Pesticide Class Other insecticides
- Permethrin
- Pyrethrins
- Pyrethroids
- Pyrethrum
- Lambda-cythalothrin
- Rotenone
- Nicotine

Pesticide Class CI
- Simazine
- Bromacil
- Atraxine
- Lenacil
- Terbacil

Pesticide Class D
- Diquat
- Paraquate

Pesticide Class O

- 2,4-D
- Dichlorprop
- MCPA
- Mecoprop
- Fluroxypyr
- Clopyralid

Other herbicides
- Glyphosate
- Linuron
- Diuron
- Dinoseb
- Diuron
- Diquat dibromide
- Bromacil
- Captan

Other Fungicides
- Copper Sulphate
- Benximidazole

Co-exposures
- Dust
- Grain Dust
- Hay/straw dust
- Endotoxin
- Mycotoxin
- Fungal spores
- Bacteria
- Mites
- Disinfectants
- Ammonia
- Farm animals
  - Dairy cows
  - Horses
  - Sheep
  - Pigs
  - Cattle
  - Cows
  - Poultry
  - Chicken
  - Hens
  - Dogs
- Smoking (confounder or risk factor)

Outcomes:

Respiratory Symptoms
Respiratory Ill Health
Respiratory Illness
Respiratory Effects
Respiratory Function
Respiratory Disease
Respiratory Tract Diseases

Respiratory Function Tests
Respiratory outcomes
Dyspnea
Shortness of breath
Breathlessness
Spirometry
Cough
Wheeze
Sputum
Phlegm
Chest pain
Asthma
Asthma Exacerbation
Allergic Asthma
Occupational Asthma
Bronchitis
Chronic bronchitis
COPD
Pulmonary disease, chronic obstructive
Rhinitis
Runny nose
Rhinorrhea
Nasal polyps
Long-term respiratory symptoms
RADS
Emphysema
Farmers Lung
Alveolitis, Extrinsic allergic
Respiratory sensitisation
Chronic respiratory symptoms
Respiratory hypersensitivity
Pulmonary function
Work related respiratory symptoms
Agricultural Workers Diseases
Irritant induced asthma
Chronic obstructive airways disease
Pulmonary fibrosis
Lung carcinoma
Atopy
Atopic disease
IgE
TH1/TH2 Lymphocytes
Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis
Cord blood
Cord blood mononuclear cell
CBMC
Interleukin 4
Interleukin 5
Interleukin 13
Interferon gamma

Study Designs
Systematic reviews
Reviews
Epidemiologic studies
Experimental case control studies
Experimental cohort studies
Case control studies
Cohort Analysis
Longitudinal studies
Cross-sectional studies
Retrospective studies
Observational Studies

Exclusion criteria
Published before 1990
Non-English language
Non peer-reviewed
Exposure through diet/food sources

Search Databases
Pubmed
MEDLINE
Embase
Scopus
CINAHL
Google Scholar
Cochrane Database of systematic reviews

b

APPENDIX B RESULTS OF SEARCHES

Search Term	Number Identified	Number of Screened Abstracts
Pesticides	843	225
2 4-D	23	5
Acaricides	1	0
Aldrin	3	0
Asthma Pesticides	232	53
Atraxine	11	0
Avicides	0	0
Benximidazole	3	0
Biocides	402	11
Captan	9	2
Carbaryl	9	2
Carbuforan	7	0
Chlordane	11	4
Chlorpyrifos	40	6
Cholinesterase Inhibitors	3	0
Clopyralid	25	0
Copper Sulphate	17	0
DDT	31	5
Diazinon	0	0
Dieldrin	6	0
Dimethoate	10	4
Dinoseb	1	0
Diquat	3	1
Diuron	4	0

Endosulfan	15	3
Fungicides	57	15
Glyphosate	7	4
Herbicides	192	48
Insecticides	261	65
Lamda cythalothrin	1	1
Lenacil	13	0
Linuron	1	0
Malathion	16	0
Maneb	5	1
MCPA	1	0
Methyl parathion	7	2
Methylcarbamate	1	0
Methylparathion	8	2
Molluscacides	7	2
Molluscicides	7	0
Molluscicide1	1	0
Nematicide	2	1
Nematicide 1	446	0
Nematocides	5	1
Nicotine	438	1
Non-arsenical pesticides	1	0
Organochlorines	323	14
Organophosphate	446	0
Organophosphates	97	18
Oxamyl	0	0

Paraquat	98	12
Parathion	14	2
Permethrin	7	2
Phosphoric acid esters	19	1
Propxur	4	1
Pyrethrins	29	5
Pyrethroids	31	3
Pyrethrum	2	0
Retenone	65	0
Rodenticide	16	1
Sheep dip	38	1
Simazine	3	0
Terbacil	12	0

APPENDIX C QUALITY ASSESSMENT

NOTES ON COMPLETION OF THE SPREADSHEET

The studies covered by this checklist are designed to answer questions of the type "What are the effects of this exposure?", It relates to studies that compare a group of people with a particular exposure with another group who either have not had the exposure, or have a different level of exposure. Cohort studies may be prospective (where the exposure is defined and subjects selected before outcomes occur), or retrospective (where exposure is assessed after the outcome is known, usually by the examination of medical records). Retrospective studies are generally regarded as a weaker design, and should not receive a "++" rating.

SECTION 1 identifies the study by author date and journal, the Ref Works identification number and the reviewer. After viewing the full paper a decision may need to be made whether to include or exclude the paper. If the paper is to be excluded please add the reasons for this exclusion to the relevant column.

SECTION 2 is the methodology checklist and this has been taken from the SIGN 50 guidance (SIGN 2008). The reviewer is asked to consider a series of aspects of cohort study design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown to be likely to influence the conclusions of a study.

Because of the potential complexity and subtleties of the design of this type of study, there are comparatively few criteria that automatically rule out use of a study as evidence. It is more a matter of increasing confidence in the strength of association between exposure and outcome by identifying how many aspects of good study design are present, and how well they have been tackled. A study that fails to address or report on more than one or two of the questions addressed below should almost certainly be rejected.

For each question in this section you should use one of the following to indicate how well it has been addressed in the study:

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- Not applicable.

2.1 THE STUDY ADDRESSES AN APPROPRIATE AND CLEARLY FOCUSED QUESTION?

Unless a clear and well defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.

2.2 THE TWO GROUPS BEING STUDIED ARE SELECTED FROM SOURCE POPULATIONS THAT ARE COMPARABLE IN ALL RESPECTS OTHER THAN THE FACTOR UNDER INVESTIGATION.

It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status, or the presence of specific prognostic factors or prognostic markers relevant to the study in question. **If the study does not include clear definitions of the source populations and eligibility criteria for participants it should be rejected.**

2.3 THE STUDY INDICATES HOW MANY OF THE PEOPLE ASKED TO TAKE PART DID SO, IN EACH OF THE GROUPS BEING STUDIED.

The participation rate is defined as the number of study participants divided by the number of eligible subjects, and should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of selection bias may be present, and the study results should be treated with considerable caution.

2.4 THE LIKELIHOOD THAT SOME ELIGIBLE SUBJECTS MIGHT HAVE THE OUTCOME AT THE TIME OF ENROLMENT IS ASSESSED AND TAKEN INTO ACCOUNT IN THE ANALYSIS?

If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial the final result will be biased. A well conducted study will attempt to estimate the likelihood of this occurring, and take it into account in the analysis through the use of sensitivity studies or other methods.

2.5 WHAT PERCENTAGE OF INDIVIDUALS OR CLUSTERS RECRUITED INTO EACH ARM OF THE STUDY DROPPED OUT BEFORE THE STUDY WAS COMPLETED?

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop out rate is a matter of judgement based on the reasons why people dropped out, and whether drop out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study.

2.6 COMPARISON IS MADE BETWEEN FULL PARTICIPANTS AND THOSE LOST TO FOLLOW-UP, BY EXPOSURE STATUS.

For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. Any indication that differences exist, should lead to the study results being treated with caution.

2.7 THE OUTCOMES ARE CLEARLY DEFINED.

Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart

disease in middle aged men, for example, participants might be followed up until death, or until reaching a predefined age. **If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.**

2.8 THE ASSESSMENT OF OUTCOME IS MADE BLIND TO EXPOSURE STATUS

If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done, or not done adequately.

2.9 WHERE BLINDING WAS NOT POSSIBLE, THERE IS SOME RECOGNITION THAT KNOWLEDGE OF EXPOSURE STATUS COULD HAVE INFLUENCED THE ASSESSMENT OF OUTCOME.

Blinding is not possible in many cohort studies. In order to asses the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups - e.g. frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.

2.10 THE MEASURE OF ASSESSMENT OF EXPOSURE IS RELIABLE.

A well conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study.

2.11 EVIDENCE FROM OTHER SOURCES IS USED TO DEMONSTRATE THAT THE METHOD OF OUTCOME ASSESSMENT IS VALID AND RELIABLE.

The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.

2.12 EXPOSURE LEVEL OR PROGNOSTIC FACTOR IS ASSESSED MORE THAN ONCE.

Confidence in data quality should be increased if exposure level is measured more than once in the course of the study. Independent assessment by more than one investigator is preferable.

2.13 THE MAIN POTENTIAL CONFOUNDERS ARE IDENTIFIED AND TAKEN INTO ACCOUNT ADEQUATELY IN THE DESIGN AND ANALYSIS.

Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate

which potential confounders have been considered, and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. **A study that does not address the possibility of confounding should be rejected.**

2.14 CONFIDENCE INTERVALS ARE PROVIDED.

Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.

2.15 OVERALL ASSESSMENT

relates to the assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 2 and using the following coding system:

++	**All or most** of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought *very unlikely* to alter.
+	**Some** of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought *unlikely* to alter the conclusions.
-	**Few or no** criteria fulfilled The conclusions of the study are thought *likely or very likely* to alter.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.

SECTION 3 asks for key points in relation to each study and this information will be used to develop evidence tables. Where relevant please include data or other information to allow easy population of the tables. It is not planned to put all this data into the table but it will give us a useful picture overall.

References

SIGN, 2008, SIGN 50: A guideline developers handbook. Scottish Intercollegiate Guidelines Network, Edinburgh. http://www.sign.ac.uk/pdf/sign50.pdf

APPENDIX D EXCLUSION LIST

Reference	Reasons for Exclusion
Abu Mourad T. (2005). Adverse impact of insecticides on the health of Palestinian farm workers in the Gaza Strip: a hematologic biomarker study. International Journal of Occupational and Environmental Health; 11: 144-149.	Biomarker study
Alexeeff GV, Shusterman DJ, Howd RA, Jackson RJ. (1994). Dose-response assessment of airborne methyl isothiocyanate (MITC) following a metam sodium spill. Risk Analysis : An Official Publication of the Society for Risk Analysis; 14: 191-198.	Paper explores dose-response data for MITC following a metam sodium spill and considers utility of Reference Exposure Levels (REL) in such emergencies
Al-Shatti AK, El-Desouky M, Zaki R, Abu Al-Azem M, Al-Lagani M. (1997). Health care for pesticide applicators in a locust eradication campaign in Kuwait (1988-1989). Environmental Research; 73: 219-226.	Acute exposures no long term follow up
American Thoracic Society. (1998). Respiratory health hazards in agriculture. American Journal of Respiratory and Critical Care Medicine; 158: S1-S76.	Non-systematic review.
Ames RG, Howd RA, Doherty L. (1993). Community exposure to a paraquat drift. Archives of Environmental Health; 48: 47-52.	Acute poisoning cases, no long-term follow-up
Arcury TA, Quandt SA. (2006). Health and social impacts of tobacco production. Journal of Agromedicine; 11: 71-81.	Systematic review of health effects of tobacco production but no useful data on pesticides and respiratory health outcomes.
Bailey KL, Meza JL, Smith LM, Von Essen SG, Romberger DJ. (2007). Agricultural exposures in patients with COPD in health systems serving rural areas. Journal of Agromedicine; 12: 71-76.	No pesticide data
Banerjee SR. (1993). Agricultural child labor in West Bengal. Indian Pediatrics; 30: 1425-1429.	No controls
Barry T, Oriel M, Verder-Carlos M, Mehler L, Edmiston S, O'Malley M. (2010). Community exposure following a drip-application of chloropicrin. Journal of Agromedicine; 15: 24-37.	Acute poisoning case series, no control group, no long-term follow-up

Beaumont JJ, Goldsmith DF, Morrin LA, Schenker MB. (1995). Mortality in agricultural workers after compensation claims for respiratory disease, pesticide illness, and injury. Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine; 37: 160-169.	No pesticide data
Beligaswatte AM, Kularatne SA, Seneviratne AB, Wijenayake MS, Kularatne WK, Pathirage LM. (2008). An outbreak of fatal pneumonitis caused by contamination of illicit alcohol with paraquat. Clinical Toxicology (Philadelphia, Pa.); 46: 768-770.	Exposure due to food adulteration
Blair A, Sandler D, Thomas K, Hoppin JA, Kamel F, Coble J, Lee WJ, Rusiecki J, Knott C, Dosemeci M, Lynch CF, Lubin J, Alavanja M. (2005). Disease and injury among participants in the Agricultural Health Study. Journal of Agricultural Safety and Health; 11: 141-150.	Non-systematic review
Bradberry SM, Proudfoot AT, Vale JA. (2004). Glyphosate poisoning. Toxicological Reviews; 23: 159-167.	Important toxicology review article - but does not appear to be a systematic review
Bradberry SM, Watt BE, Proudfoot AT, Vale JA. (2000). Mechanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. Journal of Toxicology.Clinical Toxicology; 38: 111-122.	Important toxicology review article as it reviews global reports of chlorphenoxy herbicide poisoning - but does not appear to be a systematic review
Burge S. (2000). Occupation and lung disease. Scandinavian Journal of Work, Environment & Health; 26: 369-371.	Editorial
Burgess JL, Morrissey B, Keifer MC, Robertson WO. (2000). Fumigant-related illnesses: Washington State's five-year experience. Journal of Toxicology.Clinical Toxicology; 38: 7-14.	Acute exposure - no long-term follow-up
Calvert GM, Sweeney MH, Morris JA, Fingerhut MA, Hornung RW, Halperin WE. (1991). Evaluation of chronic bronchitis, chronic obstructive pulmonary disease, and ventilatory function among workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. The American Review of Respiratory Disease; 144: 1302-1306.	Study of the health effects of TCDD a contaminant of trichlorophenol rather than of the health effects of the pesticide itself
Centers for Disease Control and Prevention (CDC). (2004). Illness associated with drift of chloropicrin soil fumigant into a residential area--Kern County, California, 2003. MMWR.Morbidity and Mortality Weekly Report; 53: 740-742.	Acute poisoning, no follow-up

Centers for Disease Control and Prevention (CDC). (2005). Update: hydrogen cyanamide-related illnesses--Italy, 2002-2004. MMWR.Morbidity and Mortality Weekly Report; 54: 405-408.	Acute toxicity of pesticide
Centers for Disease Control and Prevention (CDC). (2008). Illnesses and injuries related to total release foggers--eight states, 2001-2006. MMWR.Morbidity and Mortality Weekly Report; 57: 1125-1129.	Acute poisoning, no follow-up
Chen SY, Zhang ZW, He FS, Yao PP, Wu YQ, Sun JX, Liu LH, Li QG. (1991). An epidemiological study on occupational acute pyrethroid poisoning in cotton farmers. British Journal of Industrial Medicine; 48: 77-81.	No respiratory outcomes. Acute poisoning
Chomchai C, Tiawilai A. (2007). Fetal poisoning after maternal paraquat ingestion during third trimester of pregnancy: case report and literature review. Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology; 3: 182-186.	Case report of para-suicide
Chung K, Yang CC, Wu ML, Deng JF, Tsai WJ. (1999). Agricultural avermectins: an uncommon but potentially fatal cause of pesticide poisoning. Annals of Emergency Medicine; 34: 51-57.	Acute effects of Avermectin - suicidal exposure in most cases - data only on aspiration pneumonia. No respiratory outcomes other than 4 cases of aspiration pneumonia in cases of ingestion with suicidal intent
Collins JJ, Bodner K, Aylward LL, Wilken M, Bodnar CM. (2009). Mortality rates among trichlorophenol workers with exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. American Journal of Epidemiology; 170: 501-506.	Study of health effects of dioxins in trichlorophenol rather than PCP itself so exclude
Cone JE, Wugofski L, Balmes JR, Das R, Bowler R, Alexeeff G, Shusterman D. (1994). Persistent respiratory health effects after a metam sodium pesticide spill. Chest; 106: 500-508.	Acute poisoning, no control group
Cormier Y. (2007). Respiratory health and farming: an essay. Canadian Respiratory Journal : Journal of the Canadian Thoracic Society; 14: 419-422.	Non-systematic review of respiratory hazards of farming
Corsini E, Liesivuori J, Vergieva T, Van Loveren H, Colosio C. (2008). Effects of pesticide exposure on the human immune system. Human & Experimental Toxicology; 27: 671-680.	Expert review - non-systematic
Cypel Y, Kang H. (2010). Mortality patterns of Army Chemical Corps veterans who were occupationally exposed to herbicides in Vietnam. Annals of Epidemiology; 20: 339-346.	Study of mortality of military personnel involved in Operation Ranch-Hand, Vietnam war. Exposures not generaliseable to non-military populations.

Dahlgren J, Warshaw R, Horsak RD, Parker FM,3rd, Takhar H. (2003). Exposure assessment of residents living near a wood treatment plant. Environmental Research; 92: 99-109.	Exposure assessment paper - linked paper contains health data.
Dalphin JC, Maheu MF, Dussaucy A, Pernet D, Polio JC, Dubiez A, Laplante JJ, Depierre A. (1998). Six year longitudinal study of respiratory function in dairy farmers in the Doubs province. The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology; 11: 1287-1293.	No mention of pesticides
Dalvie MA, London L, Myers JE. (2005). Respiratory health effects due to long-term low-level paraquat exposure. American Journal of Respiratory and Critical Care Medicine; 172: 646-7; author reply 647.	No mention of pesticides as the studied group do not use them.
Danuser B, Weber C, Kunzli N, Schindler C, Nowak D. (2001). Respiratory symptoms in Swiss farmers: an epidemiological study of risk factors. American Journal of Industrial Medicine; 39: 410-418.	No pesticides data
Deschamps, D., Questel, F., Baud, F. J., Gervais, P. and Dally, S. Persistent asthma after acute inhalation of organophosphate insecticide 1994	Case report n=1
do Pico GA. (1992). Hazardous exposure and lung disease among farm workers. Clinics in Chest Medicine; 13: 311-328.	Non-systematic expert review
Draper A, Cullinan P, Campbell C, Jones M, Newman Taylor A. (2003). Occupational asthma from fungicides fluazinam and chlorothalonil. Occupational and Environmental Medicine; 60: 76-77.	Case report n=2, allergic sensitisation
Edwards FL, Tchounwou PB. (2005). Environmental toxicology and health effects associated with methyl parathion exposure--a scientific review. International Journal of Environmental Research and Public Health; 2: 430-441.	Non-systematic review of methyl parathion health effects
Ejigu D, Mekonnen Y. (2005). Pesticide use on agricultural fields and health problems in various activities. East African Medical Journal; 82: 427-432.	Cross-sectional survey of workers health. No pesticide data presented
El Asaal Ael S. (2008). Rural women's use of indoor air pollutants in Alexandria Governorate: relationship with sociodemographic characteristics and illness. Eastern Mediterranean Health Journal = La Revue De Sante De La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit; 14: 457-469.	Article in Arabic

Emerson GM, Gray NM, Jelinek GA, Mountain D, Mead HJ. (1999). Organophosphate poisoning in Perth, Western Australia, 1987-1996. The Journal of Emergency Medicine; 17: 273-277.	Acute OP poisoning
Ferreira AJ, Vieira DN, Marques EP, Pedro IS. (1997). Occupational exposure to pentachlorophenol: the Portuguese situation. Annals of the New York Academy of Sciences; 837: 291-299.	Biomonitoring data only - no health outcomes
Garcia SJ, Abu-Qare AW, Meeker-O'Connell WA, Borton AJ, Abou-Donia MB. (2003). Methyl parathion: a review of health effects. Journal of Toxicology and Environmental Health.Part B, Critical Reviews; 6: 185-210.	Expert review - non-systematic
Garnier R, Chataigner D, Efthymiou ML, Moraillon I, Bramary F. (1994). Paraquat poisoning by skin absorption: report of two cases. Veterinary and Human Toxicology; 36: 313-315.	Case report n=2
Goldstein DA, Acquavella JF, Mannion RM, Farmer DR. (2002). An analysis of glyphosate data from the California Environmental Protection Agency Pesticide Illness Surveillance Program. Journal of Toxicology.Clinical Toxicology; 40: 885-892.	Low quality data of uncertain validity. Vague description of 7 cases of respiratory effects alone (3 classed as probably due to glyphosphate, 4 as possibly, no definite cases)
Gomez MI, Hwang SA, Lin S, Stark AD, May JJ, Hallman EM. (2004). Prevalence and predictors of respiratory symptoms among New York farmers and farm residents. American Journal of Industrial Medicine; 46: 42-54.	No data on pesticides
Gorman D, Monigatti J, Glass B, Gronwall D, Beasley M. (2001). Assessment of pentachlorophenol-exposed timber workers using a test-of-poisoning model. International Journal of Occupational and Environmental Health; 7: 189-194.	Qualitative study, no controls
Gupta, R. C. (1994). Carbofuran toxicity. Journal of Toxicology and Environmental Health; 43:383-418.	Non-systematic review
Hashemi N, Mirsadraee M, Shakeri MT, Varasteh AR. (2006). Prevalence of work-related respiratory symptoms in Iranian farmers. Canadian Respiratory Journal : Journal of the Canadian Thoracic Society; 13: 198-202.	Exposures not defined and no control group
Hernandez AF, Casado I, Pena G, Gil F, Villanueva E, Pla A. (2008). Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects. Inhalation Toxicology; 20: 839-849.	Not a formal sample

Herzstein J, Cullen MR. (1990). Methyl bromide intoxication in four field-workers during removal of soil fumigation sheets. American Journal of Industrial Medicine; 17: 321-326.	Acute poisoning, no follow-up
Honda I, Kohrogi H, Ando M, Araki S, Ueno T, Futatsuka M, Ueda A. (1992). Occupational asthma induced by the fungicide tetrachloroisophthalonitrile. Thorax; 47: 760-761.	Case report
Innes DF, Fuller BH, Berger GM. (1990). Low serum cholinesterase levels in rural workers exposed to organophosphate pesticide sprays. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde; 78: 581-583.	Biomarker study
Iversen M. (1994). Is farming good for your lungs? Respiratory Medicine; 88: 559-560.	Editorial
Jeebhay MF, Quirce S. (2007). Occupational asthma in the developing and industrialised world: a review. The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union Against Tuberculosis and Lung Disease; 11: 122-133.	Non-systematic review
Jovic-Stosic J, Babic G, Todorovic V. (2009). Fatal diquat intoxication. Vojnosanitetski Pregled.Military-Medical and Pharmaceutical Review; 66: 477-481.	Acute poisoning 2 cases
Kossmann S, Konieczny B. (2001). Serum immunoglobulin E concentration in workers producing chlorfenvinphos. Przeglad Lekarski; 58 Suppl 7: 49-50.	Article in Polish
Lin CL, Yang CT, Pan KY, Huang CC. (2004). Most common intoxication in nephrology ward organophosphate poisoning. Renal Failure; 26: 349-354.	Acute OP poisoning - no long term follow-up
Lonsway JA, Byers ME, Dowla HA, Panemangalore M, Antonious GF. (1997). Dermal and respiratory exposure of mixers/sprayers to acephate, methamidophos, and endosulfan during tobacco production. Bulletin of Environmental Contamination and Toxicology; 59: 179-186.	pesticide dermal exposure patch sampling study: no health outcomes
Lu JL. (2005). Risk factors to pesticide exposure and associated health symptoms among cut-flower farmers. International Journal of Environmental Health Research; 15: 161-169.	No data on specific agents, respiratory symptoms grouped together, acute exposures only
Markowitz SB. (1992). Poisoning of an urban family due to misapplication of household organophosphate and carbamate pesticides. Journal of	Case report, n=3

Toxicology.Clinical Toxicology; 30: 295-303.	
Masley ML, Semchuk KM, Senthilselvan A, McDuffie HH, Hanke P, Dosman JA, Cessna AJ, Crossley MF, Irvine DG, Rosenberg AM, Hagel LM. (2000). Health and environment of rural families: results of a Community Canvass survey in the Prairie Ecosystem Study (PECOS). Journal of Agricultural Safety and Health; 6: 103-115.	Cross-sectional survey of farm and non-farm households. Limited pesticide data. Respiratory outcomes are reported by type of household and not by pesticide use
Mbaye I, Fall MC, Sow MB, Sow ML. (1999). Acute carbamate poisoning: apropos of 7 cases occurring in a Senegalese industrial unit. Dakar Medical; 44: 119-122.	Article in French
McDonald JC, Chen Y, Zekveld C, Cherry NM. (2005). Incidence by occupation and industry of acute work related respiratory diseases in the UK, 1992-2001. Occupational and Environmental Medicine; 62: 836-842.	No mention of pesticides
Mekonnen Y, Agonafir T. (2002). Effects of pesticide applications on respiratory health of Ethiopian farm workers. International Journal of Occupational and Environmental Health; 8: 35-40.	No data on which pesticides were used save for an oblique reference to OPs in the discussion (because no cholinesterase measurements were made…)
Melkas S, Svartengren K, Nordqvist E, Carlstedt-Duke B, Svartengren M. (2008). High exposure to respiratory tract irritants when identifying tsunami victims. 7 out of 10 forensic team members from Stockholm suffered of respiratory problems [in Swedish]. Lakartidningen; 105: 1296-1299.	Acute exposure, article in Swedish
Michalek JE, Ketchum NS, Akhtar FZ. (1998). Postservice mortality of US Air Force veterans occupationally exposed to herbicides in Vietnam: 15-year follow-up. American Journal of Epidemiology; 148: 786-792.	Study focussed on long term health effects of dioxins contaminating herbicides used in Operation Ranch Hand
Miller FD, Reed DM, Banta J. (1993). Sugarcane workers: morbidity and mortality. Hawaii Medical Journal; 52: 300-3, 306.	no data on respiratory disease or on pesticide use
Mortensen OS, Sorensen FW, Gregersen M, Jensen K. (2000). Poisonings with the herbicides glyphosate and glyphosate-trimesium [in Danish]. Ugeskrift for Laeger; 162: 4656-4659.	Article in Danish

Mpofu D, Lockinger L, Bidwell J, McDuffie HH. (2002). Evaluation of a respiratory health program for farmers and their families. Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine; 44: 1064-1074.	Only figure 1 presents any data on respiratory effects of pesticides (15%) reported respiratory effects. No QA on spirometry reported but states used ATS guidelines, No comparison group. No analysis adjusting for co-exposures or smoking
Muller-Mohnssen H. (1999). Chronic sequelae and irreversible injuries following acute pyrethroid intoxication. Toxicology Letters; 107: 161-176.	Case series
Noshad H, Ansarin K, Ardalan MR, Ghaffari AR, Safa J, Nezami N. (2007). Respiratory failure in organophosphate insecticide poisoning. Saudi Medical Journal; 28: 405-407.	Low quality case series on acute OP poisoning without biochemical confirmation
O'Malley M, Barry T, Ibarra M, Verder-Carlos M, Mehler L. (2005). Illnesses related to shank application of metam-sodium, Arvin, California, July 2002. Journal of Agromedicine; 10: 27-42.	Acute exposure, no controls, no long term follow-up
O'Malley M, Barry T, Verder-Carlos M, Rubin A. (2004). Modeling of methyl isothiocyanate air concentrations associated with community illnesses following a metam-sodium sprinkler application. American Journal of Industrial Medicine; 46: 1-15.	Acute exposure
Osimitz TG, Sommers N, Kingston R. (2009). Human exposure to insecticide products containing pyrethrins and piperonyl butoxide (2001-2003). Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association; 47: 1406-1415.	Acute exposure, no long term follow-up
O'Sullivan BC, Lafleur J, Fridal K, Hormozdi S, Schwartz S, Belt M, Finkel M. (2005). The effect of pesticide spraying on the rate and severity of ED asthma. The American Journal of Emergency Medicine; 23: 463-467.	Exacerbation of pre-existing respiratory disease
Pearce M, Habbick B, Williams J, Eastman M, Newman M. (2002). The effects of aerial spraying with Bacillus thuringiensis Kurstaki on children with asthma. Canadian Journal of Public Health.Revue Canadienne De Sante Publique; 93: 21-25. .	Study of exacerbations of asthma following environmental spraying with *Bacillus thuringiensis.* No effect found but given how different the mode of action of this agent is from other pesticides then the paper should be excluded
Petrie K, Thomas M, Broadbent E. (2003). Symptom complaints following aerial spraying with biological insecticide Foray 48B. The New Zealand Medical Journal; 116: U354.	Exclude as environmental spraying with Bacillus thuringiensis i.e. a biological agent

Radon K, Winter C. (2003). Prevalence of respiratory symptoms in sheep breeders. Occupational and Environmental Medicine; 60: 770-773.	No data on pesticides
Reynolds SJ, Parker D, Vesley D, Smith D, Woellner R. (1993). Cross-sectional epidemiological study of respiratory disease in turkey farmers. American Journal of Industrial Medicine; 24: 713-722.	No pesticides data
Reynolds SJ, Tadevosyan A, Fuortes L, Merchant JA, Stromquist AM, Burmeister LF, Taylor C, Kelly KM. (2007). Keokuk County rural health study: self-reported use of agricultural chemicals and protective equipment. Journal of Agromedicine; 12: 45-55.	Acute symptoms only. This paper identifies pesticides used and reports symptoms experienced but it does not present symptoms by agent analyses so should be excluded
Richter ED, Chuwers P, Levy Y, Gordon M, Grauer F, Marzouk J, Levy S, Barron S, Gruener N. (1992). Health effects from exposure to organophosphate pesticides in workers and residents in Israel. Israel Journal of Medical Sciences; 28: 584-598.	Acute exposures no long term follow up
Rivera JA, Rivera M. (1990). Organophosphate poisoning. Boletin De La Asociacion Medica De Puerto Rico; 82: 419-422.	Acute effects of OPs - no data on chronic respiratory disease
Royce S, Wald P, Sheppard D, Balmes J. (1993). Occupational asthma in a pesticides manufacturing worker. Chest; 103: 295-296.	Case report, n=1
Saadeh AM, al-Ali MK, Farsakh NA, Ghani MA. (1996). Clinical and sociodemographic features of acute carbamate and organophosphate poisoning: a study of 70 adult patients in north Jordan. Journal of Toxicology.Clinical Toxicology; 34: 45-51.	Study of acute effects of poisoning no long term follow up
Salameh P, Waked M, Baldi I, Brochard P, Saleh BA. (2006). Respiratory diseases and pesticide exposure: a case-control study in Lebanon. Journal of Epidemiology and Community Health; 60: 256-261.	Article in French
Salome CM, Marks GB, Savides P, Xuan W, Woolcock AJ. (2000). The effect of insecticide aerosols on lung function, airway responsiveness and symptoms in asthmatic subjects. The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology; 16: 38-43.	Study of insecticide aerosol acute effects in established asthma
Schreinemachers DM. (2003). Birth malformations and other adverse perinatal outcomes in four U.S. Wheat-producing states. Environmental Health Perspectives; 111: 1259-1264.	Study of birth structural anomalies

Scrivener, S., Yemaneberhan, H., Zebenigus, M., et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study 2001	Study of parasites in asthma: no pesticide exposure data
Shelton D, Urch B, Tarlo SM. (1992). Occupational asthma induced by a carpet fungicide--tributyl tin oxide. The Journal of Allergy and Clinical Immunology; 90: 274-275.	Case report
Sherman JD. (1995). Organophosphate pesticides--neurological and respiratory toxicity. Toxicology and Industrial Health; 11: 33-39.	Case series of acute OP poisoning
Singh VK, Jyoti, Reddy MM, Kesavachandran C, Rastogi SK, Siddiqui MK. (2007). Biomonitoring of organochlorines, glutathione, lipid peroxidation and cholinesterase activity among pesticide sprayers in mango orchards. Clinica Chimica Acta; International Journal of Clinical Chemistry; 377: 268-272.	Biomonitoring study
Smit LA, Zuurbier M, Doekes G, Wouters IM, Heederik D, Douwes J. (2007). Hay fever and asthma symptoms in conventional and organic farmers in The Netherlands. Occupational and Environmental Medicine; 64: 101-107.	No data on pesticides
Solecki L. (1999). Occupational and para-occupational diseases in agriculture. Annals of Agricultural and Environmental Medicine : AAEM; 6: 171-172.	Conference report
Solomon C, Poole J, Palmer KT, Peveler R, Coggon D. (2007). Acute symptoms following work with pesticides. Occupational Medicine (Oxford, England); 57: 505-511.	Study of acute symptoms
Soloukides A, Moutzouris DA, Kassimatis T, Metaxatos G, Hadjiconstantinou V. (2007). A fatal case of paraquat poisoning following minimal dermal exposure. Renal Failure; 29: 375-377.	Case report, n=1
Sosan MB, Akingbohungbe AE. (2009). Occupational insecticide exposure and perception of safety measures among cacao farmers in southwestern Nigeria. Archives of Environmental & Occupational Health; 64: 185-193.	Survey, no control group
Spencer J, O'Malley M. (2006). Pyrethroid illnesses in California, 1996-2002. Reviews of Environmental Contamination and Toxicology; 186: 57-72.	Acute poisonings, no follow-up data
Tagiyeva N, Devereux G, Semple S, Sherriff A, Henderson J, Elias P, Ayres JG. (2010). Parental occupation is a risk factor for childhood wheeze and	No clear differentiation between exposure to pesticides/biocides and latex

asthma. The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology; 35: 987-993.	
Talbot AR, Shiaw MH, Huang JS, Yang SF, Goo TS, Wang SH, Chen CL, Sanford TR. (1991). Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. Human & Experimental Toxicology; 10: 1-8.	Case series of acute glyphosphate poisoning
Talini D, Monteverdi A, Carrara M, Paggiaro PL. (2003). Risk factors for chronic respiratory disorders in a sample of farmers in middle Italy. Monaldi Archives for Chest Disease = Archivio Monaldi Per Le Malattie Del Torace / Fondazione Clinica Del Lavoro, IRCCS [and] Istituto Di Clinica Tisiologica e Malattie Apparato Respiratorio, Universita Di Napoli, Secondo Ateneo; 59: 52-55.	No pesticide data
Tsai JR, Sheu CC, Cheng MH, Hung JY, Wang CS, Chong IW, Huang MS, Hwang JJ. (2007). Organophosphate poisoning: 10 years of experience in southern Taiwan. The Kaohsiung Journal of Medical Sciences; 23: 112-119.	Acute OP poisoning
Vandenplas O, Delwiche JP, Auverdin J, Caroyer UM, Cangh FB. (2000). Asthma to tetramethrin. Allergy; 55: 417-418.	Case report
Verhulst L, Waggie Z, Hatherill M, Reynolds L, Argent A. (2002). Presentation and outcome of severe anticholinesterase insecticide poisoning. Archives of Disease in Childhood; 86: 352-355.	Acute OP poisoning
von Essen SG, Banks DE. (2009). Life-long exposures on the farm, respiratory symptoms, and lung function decline. Chest; 136: 662-663.	Editorial
Wagner SL. (1990). Pesticide illness surveillance: review of the National Pesticide Hazard Assessment Program. American Journal of Industrial Medicine; 18: 307-312.	Acute exposure - no follow-up
Walters JK, Boswell LE, Green MK, Heumann MA, Karam LE, Morrissey BF, Waltz JE. (2009). Pyrethrin and pyrethroid illnesses in the Pacific northwest: a five-year review. Public Health Reports (Washington, D.C.: 1974); 124: 149-159.	Acute poisoning no long term follow-up
Wang TN, Lin MC, Wu CC, Leung SY, Huang MS, Chuang HY, Lee CH, Wu DC, Ho PS, Ko AM, Chang PY, Ko YC. (2010). Risks of Exposure to Occupational Asthmogens in Atopic and Nonatopic Asthma: A Case-control Study in Taiwan. American Journal of Respiratory and Critical Care Medicine.	No pesticide data

Weinbaum Z, Samuels SJ, Schenker MB. (1995). Risk factors for occupational illnesses associated with the use of paraquat (1,1'-dimethyl-4,4'-bipyridylium dichloride) in California. Archives of Environmental Health; 50: 341-348.	Acute pesticide illness
Wesseling C, Hogstedt C, Picado A, Johansson L. (1997). Unintentional fatal paraquat poisonings among agricultural workers in Costa Rica: report of 15 cases. American Journal of Industrial Medicine; 32: 433-441.	Case series of acute poisoning
Zock JP, Sunyer J, Kogevinas M, Kromhout H, Burney P, Anto JM. (2001). Occupation, chronic bronchitis, and lung function in young adults. An international study. American Journal of Respiratory and Critical Care Medicine; 163: 1572-1577.	no pesticide data

APPENDIX E STUDIES INCLUDED IN THE REVIEW

Author and Date	Study design and quality assessment	Study Population	Pesticide	Health outcomes measured	Exposure metric to pesticides	Medical tests used	Summary of findings	Comments/confounders or sources of bias	Applicability to the UK
Beard, J., Sladden, T., Morgan, G., Berry, G., Brooks, L. and McMichael, A. Health impacts of pesticide exposure in a cohort of outdoor workers 2003	Historical cohort study, case control primarily a mortality study, in addition to a morbidity questionnaire +	1,999 outdoor staff working as part of an insecticide application program during 1935–1996 with that of 1,984 outdoor workers not occupationally exposed to insecticides, and with the Australian population. 270 exposed workers were lost to follow-up. For the sub-study (questionnaire), 1,533 were contacted and the response rate was 54.9%.	Arsenic trioxide, DDT, Benzene hexachloride, Coumaphos, Carbophenothion, Carbaryl, Chlorpyrifos, Bromophos, ethyl Dioxothion, Ethion, Chlordimeform Cymyazole, Chlormethiuron, Amitraz, Promacyl, Cypermethrin, Chlorfenvinphos, Flumethrin	Asthma (both deaths from, and self-reported morbidity), bronchitis (self reported), hayfever (self-reported)	Exposure by questionnaire	Death certificates. Exposure measurements and some DDT serum levels from a previous monitoring program	Compared with the general Australian population, mortality over the total study period was significantly increased for asthma [standardized mortality ratio (SMR) = 3.45; 95% confidence interval (CI), 1.39–7.10]. Self-reported asthma symptoms was significantly increased OR=1.59, 1.05-2.43 compared to controls.	Main study adjusted for age and duration of follow-up. Questionnaire study adjusted for smoking and age. Note that respondents to the questionnaire were significantly more likely to have ever smoked than their controls: whether this is also true of the main cohort is unknown.	
Boers, D., van Amelsvoort, L., Colosio, C., et al. Asthmatic symptoms after exposure to ethylenebisdithiocarbamates and other pesticides in	Cross-sectional survey +	248 pesticide exposed workers and 231 unexposed workers from 5 field studies in the Netherlands, Italy, Bulgaria (2 studies) and Finland. Total RR not given	ethylenebisdithiocarbamate	Asthma, wheezing, chest tightness	Questionnaire and urinary metabolites. Respiratory questions were modified from the IUATLD (International Union Against Tuberculosis and Lung	None	Inverse associations, all not statistically significant, between occupational exposure to pesticides and asthma diagnosis, chest tightness,	Adjustment for age, education, residence, smoking, gender and field study.	registered in the UK

the Europit field studies 2008		Disease) questionnaire. This was translated into the local language and later back-translated in English to check on the correct translation.	wheeze, asthma attack were found. Adjusted OR 0.90 (0.79–1.03) for chest tightness by ETU level on biomonitoring. Associations between urinary (ETU), as a marker of (EBDCs) exposure, and asthma outcome measurements for exposed versus controls (adjusted) OR 0.99 (0.87–1.13). Asthma diagnosis by physician by exposure OR 0.41, 95%CI 0.15-1.11 adjusted for all confounders. However, univariate associations between urinary (ETU), as a marker of (EBDCs) exposure, and asthma outcome measurements for exposed versus controls

						shows an adjusted OR 1.19 (0.93–1.52) for doctor diagnosed asthma

Chakraborty, S., Mukherjee, S., Roychoudhury, S., Siddique, S., Lahiri, T. and Ray, M. R. Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India 2009	Cross-sectional survey +	376 agricultural workers from Eastern India who sprayed organophosphate and carbamate pesticides in the field. 348 age and sex-matched controls with non-agricultural occupations from the same locality.	Methyl parathion, Phosphamidon, Carbofuran, Dichlorvos, Monocrotophos, Carbaryl, Chlorpyrifos, Dimethoate	Asthma (doctor diagnosed), COPD (GOLD), bronchitis, wheezing, breathlessness on exertion, cough, phlegm, runny nose, nasal blockage, sore throat, sinusitis, chest discomfort/pain, dyspnoea (MRC cat 1-3)	Questionnaire based on the respiratory questionnaire of the British MRC and the ATS-DLD-78-C, COPD assessed using the GOLD criteria. AChE tested using RBC. MRC, ATS DLD.	Spirometry followed ATS protocol, best of three blows, electronic spirometer calibrated prior to each day's testing with a 2 litre syringe and after every 50 patients.	Doctor diagnosed asthma more common in agricultural workers than controls (3.7% vs. 2%). OR 1.34 (95%CI 1.09-1.79)for >50% AChE inhibition vs. reference. COPD - GOLD criteria used. COPD diagnosed in 18.1% of agricultural workers and 6.9% of controls. AChE inhibition associated with COPD OR 1.59 (95%CI 1.32-2.28). More frequent spraying was associated with increased risk of COPD 21.6% in regular sprayers vs. 14.8% in occasional sprayers. For bronchitis - 6% in controls vs. 19.1% in all agricultural workers. OR 4.1 (95%CI 2.2-6.3) for >50% AChE inhibition vs. reference	Comparison group were adequately matched on age, family size, BMI, marital status, working hours and biomass fuel use but were significantly better educated and better paid than agricultural day labourers. Confounding factors -years of schooling and income as these differed significantly between groups. Smokers and those with cardiovascular disease or extremes of BMI were excluded. Height and weight not taken into account. Respiratory symptoms more common in agricultural workers after adjusting for income, education residual confounding a problem, agricultural workers have reduced lung function no although no adjustment for

					category of inhibition <50%.Dyspnoea classified using MRC 6 point dyspnoea grading scale. 21.8% in comparison group vs 55.0% in agricultural workers. When considering AChE inhibition OR for dyspnoea was 3.7 (95%CI 2.7-4.8) among those workers with >50% inhibition. Cough subdivided into dry cough and wet cough: the prevalence of both was significantly higher in exposed agricultural workers. Dry cough prevalence 14.9% in comparison group vs. 45.2% in agricultural workers; wet cough 16.7% vs. 34%. Chest discomfort and pain 16.1% vs. 40.4% in agricultural workers. Association	height. Dose response associations with inhibition of AChE and symptoms asthma, COPD and lung function after limited adjustment, still could be a consequence of residual confounding by SES and occupational exposure.

							between AChE inhibition and chest discomfort and pain OR 3.1 (95%CI 2.1-5.4) for >50% inhibition. Runny or stuffy nose 20.1% vs. 77.4% in agricultural workers. Association between AChE inhibition and runny or stuffy nose OR 4.8 (95%CI 2.3-6.9) for >50% AChE inhibition. Period prevalence (12mo.) of sore throat was 12.9% in comparison group vs. 24.5% in agricultural workers. Association between AChE inhibition and sore throat OR 2.6 (95%CI 1.5-4.7) for >50% inhibition

Faria, N. M., Facchini, L. A., Fassa, A. G. and Tomasi, E. Pesticides and respiratory symptoms among farmers 2005	Cross-sectional survey +	1379 interviewed, equalling a 95% participation rate, representing 20% of total workforce	fenthion, dimethoate, trichlorfon, methyl parathion, methamidophos, deltamethrin, cypermethrin, atrazine, copper sulphate, simazine, mancozeb, maneb, captan, dodine, benzimidazole, glyphosate, paraquat	Asthma (defined as two or more episodes of wheezing with shortness of breath in a lifetime), chronic bronchitis (defined as self-reported symptoms of cough and phlegm during most days of the week, for 3 or more months per year, and lasting at least 2 years), Chronic respiratory disease (defined as the presence of at least one of the following symptoms: cough or phlegm during most days of the week for 3 or more months per year, recurrent wheezing most days and nights, or 2 or	Modified ATS respiratory questionnaire. Self-reported exposure to pesticides evaluated by investigating different forms of contact e.g. Mixing, exposures classified according to days per month of chemical contact. No data on validation presented	None	Symptoms of asthma were associated with pesticide application for more than 3 days/month (OR 2.11, 95%CI 1.14-3.92 adjusted). Self-reported pesticide poisoning was associated with 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).	Analyses adjusted for sex, age, schooling, marital status, smoking (never, former, current), socioeconomic indicators, agricultural production, dust exposure, industrial rations (animal feed), years of exposure.

	more episodes of wheezing with shortness of breath.	

Hoppin, J. A., Umbach, D. M., Kullman, G. J., et al. Pesticides and other agricultural factors associated with self-reported farmer's lung among farm residents in the Agricultural Health Study 2007	Cross-sectional survey +	~50000 famers and farm spouses in Iowa and North Carolina. Response rate 40% in farmers (take-home questionnaire)	Lindane, DDT, Aldicarb, Benomyl	Asthma, bronchitis, wheezing, breathlessness, rhinitis, sore runny eyes. Symptoms asked about not in relation to pesticides, but in relation to doctor-diagnosed farmer's lung	self-reported lifetime use of pesticides including a lifetime days variable for each agent, self reported doctor-diagnosed farmers lung; current farming exposures	None	Among farmers handling silage, high pesticide exposure events HPEE (OR 1.75, 95%CI 1.39-2.21), ever use of organochlorine pesticides (OR 1.34, 95%CI 1.04-1.74) and carbamates (OR 1.32, 95%CI 1.03-1.68) were associated with farmers lung. Pesticides may be worthy of further study as risk factors for farmers lung but may be confounded by past agricultural activities (only current agricultural activities recorded but lifetime pesticide use). No one pesticide linked to HPEE so this may reflect safety behaviours rather than a pesticide effect. The validity of this study is dependent on self-report of	Yes -age, state, smoking status (current, ex, never), cigarettes/day (applicators only).	Lindane & DDT are not licensed in the UK. Aldicarb is licensed on onions. Benomyl is licensed but no longer manufactured and high resistance so probably irrelevant to modern UK practice.

							doctor diagnosed farmers lung: any imprecision in diagnosis is unlikely to vary with pesticide exposure and so should not bias results.

Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C. and Sandler, D. P. Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study 2002	Cross-sectional survey +	A total of 20,468 applicators - response rate not reported	Herbicides: 2,4-D, Alachlor, Atrazine, Butylate, Chlorimuron ethyl, Cyanazine, Dicamba, EPTC, Glyphosate, Imazethapyr, Metolachlor, Metribuzin, Paraquat, Pendimethalin, Petroleum oil, Trifluralin; Insecticides: Organophosphates: Chlorpyrifos, Coumaphos, Diazinon, Dichlorvos, Fonofos, Malathion, Parathion, Phorate, Terbufos, Trichlorfon; Carbamates: Aldicarb, Carbaryl, Carbofuran; Other insecticides: Lindane, Permethrin	Wheeze (How many episodes of wheezing or whistling in chest in the past 12 months)	Self-reported, questionnaire	None	Among pesticides suspected to contribute to wheeze, paraquat, three organophosphates (parathion, malathion, and chlorpyrifos), and one thiocarbamate (S-ethyl-diprop-ylthiocarbamate [EPTC]) had elevated odds ratios (OR). Parathion had the highest OR (1.5, 95% confidence interval [CI] 1.0, 2.2). Chlorpyrifos, EPTC, paraquat, and parathion demonstrated significant dose–response trends. The herbicides, atrazine and alachlor, but not 2,4-D, were associated with wheeze. Atrazine had a significant dose–response trend with participants applying atrazine more than 20 days/year having	adjusted for age, state, past smoking, current smoking, and asthma/atopy.

	(crops), Permethrin (poultry); Fungicides: Benomyl, (also carbamate), Captan, Chlorothalonil, Maneb, Metalaxyl, Ziram; Fumigants: Aluminum phosphide, Brom_O_Gas	an OR of 1.5 (95% CI 1.2,1.9).

Hoppin, J. A., Umbach, D. M., London, S. J., et al. Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study 2008	Cross-sectional survey +	25814 farm women in Agricultural Health Study, 702 of whom had adult onset asthma. No data on response rate provided.	Herbicides: 2,4-D, Alachlor, Atrazine, Butylate, Chlorimuron-ethyl, Cyanazine, Dicamba, Glyphosate, Imazethapyr, Metolachlor, Metribuzin, Paraquat, Pendimethalin, Petroleum oil, Trifluralin; Insecticides: Carbamates: Carbaryl Carbofuran; Organophosphates: Chlorpyrifos, Coumaphos, Dichlorvos, Diazinon, Fonofos, Malathion, Parathion, Phorate, Terbufos; Organochlorines: Aldrin, Chlordane, DDT, Heptachlor, Lindane; Pyrethroids:	Asthma (doctor diagnosed)	exposure history - validated method, questionnaire	None	7 of 16 insecticides including 3 OPs (carbaryl, phorate, parathion, malathion, coumaphos, permethrin, DDT), 2 of 11 herbicides (2,4-D, glyphosphate) 1 of 4 fungicides (metalaxyl) significantly associated with atopic asthma.	yes. Adjustment for age, smoking status, state (Ohio or North Carolina), growing up on a farm, big

	Permethrin (animals), Permethrin (crops); Fungicides: Captan, Chlorothalonil, Maneb, Metalaxyl; Fumigants: 80/20 mix, Methyl bromide	

Hoppin, J. A., Umbach, D. M., London, S. J., Lynch, C. F., Alavanja, M. C. and Sandler, D. P. Pesticides and adult respiratory outcomes in the agricultural health study 2006	Cross-sectional survey +	The AHS study enrolled over 52,000 licensed private pesticide applicators, mostly farmers, from 1993 to 1997. After completing the enrolment questionnaire, 22,916 (44%) applicators returned a second mailed questionnaire; applicators who did or did not return this second questionnaire were similar regarding demographics, farming practices, and medical history. US farmers 17920, commercial applicators 2255	Herbicides (2,4-D, alachlor, atrazine, butylate, chlorimuron-ethyl, cyanazine, dicamba, EPTC, glyphosate, imazethapyr, metolachlor, metribuzin, paraquat, pendimethalin, petroleum oil, trifluralin), Insecticides (aldicarb, carbaryl, carbofuran, chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, trichlorfon, lindane, permethrin - animals, permethrin-crops), Fungicides (benomyl,	Wheezing (one or more episodes of wheezing or whistling in chest in the past 12 months)	Questionnaire of work practices and exposures	None	40 pesticides only one really associated. Although chlorpyrifos, malathion, parathion reported to be associated in farmers, only malathion borderline significant, for commercial sprayers chlorpyrifos, dichlorvos, phorate reported as associated, only dichlorvos and phorate significant, dose response associations for both groups noted for chlorpyrifos but not associated on primary analysis. Note the differences in the commercial vs farmers, tend to be less well associated in the commercial.	Yes, but no adjustment for Socioeconomic Status. Odds ratios adjusted for age, BMI, smoking, asthma/atopy and previous use of pesticide. Commercial applicators models include adjustment for chlorimuron-ethyl; farmer models include state.

	captan, chlorothalonil, maneb, metalaxyl, ziram), Fumigants (aluminium phosphide, methyl bromide)	

Hoppin, J. A., Umbach, D. M., London, S. J., Lynch, C. F., Alavanja, M. C. and Sandler, D. P. Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study 2006	Cross-sectional survey +	4916 commercial pesticide applicators in Iowa (47% of registered applicators) The response rate to the second, more detailed, questionnaire was 2375 of 4916 applicators (48% response)	Herbicides: 2,4-D, Alachlor, Atrazine, Butylate, Chlorimuron-ethyl, Cyanazine, Dicamba, EPTC, Glyphosate, Imazethapyr, Metolachlor, Metribuzin, Paraquat, Pendimethalin, Petroleum oil, Trifluralin; Insecticides: Organophosphates: Chlorpyrifos, Coumaphos, Diazinon, Dichlorvos, Fonofos, Malathion, Phorate, Terbufos, Trichlorfon; Carbamates: Carbaryl, Carbofuran; Other insecticides: Lindane, Permethrin (crops), Permethrin	Asthma (doctor diagnosed), wheeze ('How many episodes of wheezing or whistling in your chest have you had in the past 12 months?' Any positive response was defined as wheeze)	Self-reported, questionnaire	None	36 agents studied. 21% of applicators reported wheeze in last 12 months. Evidence of association between 5 OPs and wheeze - strongest association for applying chlorpyrifos for more than 40 days/year (OR 2.40, 95%CI 1.24-4.65). Main effect (wheeze) associated with the herbicide chlorimuron-ethyl (OR 1.62, 95%CI 1.25-2.10) and 5 OPs terbufos (OR 1.36, 0.87-2.12) , fonofos (OR 1.46, 95%CI 0.86-2.46), chlorpyrifos (OR 1.27, 95%CI 0.92-1.74), phorate (OR 2.35, 95% CI 1.36-4.06) and dichlorovos (OR 2.48, 95%CI 1.08-5.66). Dose-response trends observed for chlorimuron-ethyl, chlorpyrifos, phorate.	Factors taken into account: current smoking habits, pack years of smoking, asthma/atopy, age, BMI and pesticides confounding associations between other pesticides and wheeze. Study weakened by low (NB response rate different by pesticide usage) response rate to second questionnaire but strength of study is limited agricultural exposure beyond pesticides. Other studies in animal models suggest mechanism involves autoinhibitory muscarinic receptors on parasympathetic nerves in lung.

	(poultry); Fumigants: Aluminum phosphide; Fungicides: Benomyl, Captan, Chlorothalonil, Maneb, Metalaxyl.	Chlorimuoron- ethyl is only available as a dry formulation which may increase inhalation potential.

Hoppin, J. A., Valcin, M., Henneberger, P. K., et al. Pesticide use and chronic bronchitis among farmers in the Agricultural Health Study 2007	Cross-sectional survey +	20908 private pesticide applicators (44% response within study)	Carbaryl, carbofuran, DDT, Heptachlor, Diazinon, Malathion, Permethrin (crops), 2,4,5-T, 2,4,5-TP, Chlorimuron, petroleum oil	Asthma (doctor diagnosed), bronchitis (doctor diagnosed after age of 19), wheezing,	self-reported use of agents including a lifetime days variable for each agent	None	11 pesticides associated with increased risk of chronic bronchitis (the organochlorine heptachlor had the highest OR at 1.50, 95%CI 1.19-1.89) and also increased risk for those who reported a high pesticide exposure event (HPEE) OR 1.85, 95%CI1.51-2.25. Co-existent asthma did not explain this finding nor did current farm activities. Important paper because of dose response relationships for DDT (p=0.019), heptachlor (p==0.013), malathion (p=0.008), with one or 2 others near to significance.	Yes- state, age, gender, pack years of smoking.

Hoppin, J. A., Umbach, D. M., London, S. J., et al. Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study 2009	Cross-sectional survey ++	17,920 farmers and 2,255 commercial pesticide applicators. Part of the Agricultural Cohort Study, that has a population of around 89,000.	10 of 48 associated herbicides (2,4,5-TP, EPTC, and paraquat), organochlorines: chlordane, heptachlor, DDT, and lindane; organophosphates: diazinon, parathion, phorate, malathion and coumaphos, fungicide (captan), and fumigants (ethylene dibromide and 80/20 mix – carbon tetrachloride and carbon disulfide) (table 3)	Asthma (doctor diagnosed after age of 20yrs), wheezing, hayfever, runny nose, itchy watery eyes	Two metrics of lifetime pesticide use were employed lifetime days of use and intensity-adjusted lifetime days of use. The intensity-adjusted metric accounted for application methods, mixing habits, repairs, and use of PPE	None	High pesticide exposure events were associated with a doubling of both allergic and non-allergic asthma. For ever use, 12 individual pesticides were associated with allergic asthma and four with non-allergic asthma. For allergic asthma, coumaphos (odds ratio (OR) =2.34, 95% Confidence Interval (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), 80/20 mix (carbon tetrachloride/carbon disulfide) (OR=2.15, 95%CI=1.23,3.76) and ethylene dibromide (OR=2.07, 95%CI=1.02,4.20), all had odds ratios greater than 2.0 and significant exposure-response trends. For non-allergic asthma, DDT had the strongest	Adjusted for age, state, smoking, HPEE and BMI. Failed to adjust for SES? Note that 2.2% had asthma, ?population attributable fraction. No attempt made to see if asthma developed after start of pesticide application. Associations between acute exposures and asthma and between use of listed chemicals and allergic and non-allergic asthma, also dose response associations noted for most of the exposures

		association (OR=1.41, 95%CI=1.09,1.84) but with little evidence of increasing asthma with increasing use. Current animal handling and farm activities did not confound these results.

Huang, J., Aoyama, K., Ueda, A. and Matsushita, T. Respiratory effects and skin allergy in workers exposed to tetrachloroisophthalonitrile 1995	Cross-sectional survey +	Twenty eight workers (nineteen men and nine women) in the chlorothalonil manufacturing workshop of a pesticide plant were investigated. The participation of the work force in this study was 93.3% (28/30), and two workers were absent at the time of the study owing to vacation.	Tetrachloroisophthalonitrile	Asthma, bronchitis (cough and phlegm for a minimum of 3 months a year and for not less than 2 successive years), wheezing, breathlessness, cough (cough on most days for at least 3 months in a year), phlegm (phlegm production on most days for at least 3 months in a year), chest tightness, nose irritation, throat irritation, eye irritation	exposure measured based on job title and air monitoring	Forced expiratory flow-volume test was performed using an electronic spirometer (Minato Medical Device Co., AS-4, 500). The best of three acceptable curves was used in deriving the forced expiratory vital capacity (FVC), the forced exph'ed volume in 1 sec (FEV0, the FEVI/FVC multiplied by 100 (%FEV,), the maximum mid-expiratory flow (MMF) and the peak exph-atory flow (PEF). Smokers were asked to refrain from smoking for at least one hour before measurement. The flow-volume study was conducted by an examiner who was blind to whether or not	Chlorothalonil workers had more respiratory symptoms, including irritation symptoms, chronic cough and phlegm, chest tightness, and asthma-like symptoms such as shortness of breath and wheezing at work as compared to the reference workers. Also, the lung function tests revealed a significant decrement of FEV1 and %FEVI in them, particularly in the six chlorothalonil workers with asthma-like symptoms at work, suggesting a typical obstructive ventilatory disturbance.	Confounding factors, but not adjusted for.

						the examinees were chlorothalonil workers.			
Jones, D. R., Sutton, A. J., Abrams, K. R., Fenty, J., Warren, F. and Rushton, L. Systematic review and meta-analysis of mortality in crop protection product manufacturing workers 2009	Systematic review ++	Meta-analysis of 21 papers reporting on 37 separate cohorts for mortality	phenoxy herbicides and pesticdes more generally	Bronchitis, emphysema, asthma	employment in relevant industry - authors highlight lack of more detailed exposure data.	Death certificates	SMR for bronchitis, emphysema and asthma 1.08, 95%CI 0.859-1.351 based on 23 studies and 1.06, 95%CI 0.814-1.381 for phenoxy herbicides based on 16 studies . No clear evidence of an increased risk of death due to asthma, bronchitis or emphysema in this meta-analysis of chemical industry workers manufacturing pesticides or specifically phenoxy herbicides.	Standardised Mortality Ratios	Unsure

Nriagu, J., Robins, T., Gary, L., et al. Prevalence of asthma and respiratory symptoms in south-central Durban, South Africa 1999	Cross-sectional survey +	Health study in South Africa. 213 households, 367 children, 693 adults.	No agent identified	Asthma (doctor diagnosed), bronchitis (doctor diagnosed), wheezing, breathlessnes s, cough, phlegm, chest tightness, sinusitis (doctor diagnosed), runny nose, nasal blockage	Modified questionnaire recommended by the WHO for asthma studies, parental/self reported	None	Essentially a health survey that included some assessment of home insecticide use, association in adults between wheeze and insect coilds (but not asthma) and between asthma and insecticide pump (not wheeze though), no associations in children, plenty of scope for bias, reverse causation.	Confounding factors taken into account	Unsure, no agents identified
Salam, M. T., Li, Y. F., Langholz, B., Gilliland, F. D. and Children's Health Study. Early-life environmental risk factors for asthma: findings from the Children's Health Study 2004	Nested case control study using counter-matching for disease status, with retrospective assessment of exposures in first year and later years of childhood +	Children's Health Study population of 6259. Average classroom participation of 82%, Study base of 4244, from this base, 338 with asthma and 570 controls were identified, with 279 cases (83%) and 412 controls (72%) participating.	No specified agent	Asthma (parental report of doctor diagnosed)	Parent/guardia n report of ever/never exposed and whether this occurred in first year of life.	None	Pesticide, herbicide exposure in first year of life onwards associated with increase in asthma, however mothers of asthmatic children more likely to take part and recall of herbicide and pesticide exposure 7-17 years before is susceptible to recall bias	Subjects matched on age, sex, and community of residence, countermatched on in utero maternal smoking and adjusted for race/ethnicity. Low quality exposure metrics, possibility of confounding by other exposures remains although analysis results were not modified by farming exposure. Study employed counter matched design.	Unsure, no agents identified

Salameh, P. R., Baldi, I., Brochard, P., Raherison, C., Abi Saleh, B. and Salamon, R. Respiratory symptoms in children and exposure to pesticides 2003	Cross-sectional survey +	4644 questionnaires sent to 18 schools with a response rate of 71% (total = 3291)	No specified agent	Asthma, wheezing, cough, phlegm, chronic respiratory disease (recurrent cough or expectoration more than three times a week and more than three months a year, or recurrent wheezing or more than one episode of dyspnoea and wheezing).	Exposure to pesticides was divided into residential, para-occupational and domestic. Residential exposure was characterised by residing in the proximity of a treated field, in addition to the regions of dwelling. Domestic exposure included domestic use by a household member or treatment of the house and garden by a professional. Para-occupational exposure was due to the occupational use of pesticides by one of the household members.	None	Cross sectional survey parental report of ever parental occupational use, ever use in the home, living in area or fields heavily contaminated. Any exposure to pesticides, including residential, para-occupational and domestic, was associated with respiratory disease and chronic respiratory symptoms (chronic phlegm, chronic wheezing, ever wheezing) except for chronic cough. A chronic respiratory disease was reported in 407 (12.4%) out of 3,291 children. The baseline difference in mean age was small but statistically significant.	Adjustments were made for passive smoking, sex, age, weight and body mass index, father's and mother's respiratory disease, father's and mother's educational levels, animal raising, and playing with dust. Residential: regional exposure or near a treated field; domestic: domestic use by a household member or treatment of the house and garden by a professional; para-occupational: occupational use by a household member; any exposure: residential, domestic or para-occupational exposure. Plenty of scope for recall bias, differential response between schools.	Unsure, no agents identified

Schenker, M. B., Stoecklin, M., Lee, K., et al. Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure 2004	Cross-sectional survey ++	219 paraquat handlers and 110 non-handlers working on Costa Rican banana, palm oil and coffee farms. Of 560 subjects identified 338 participated (77.5%)	Paraquat	Asthma (self reported symptoms), bronchitis (self-reported), wheeze (persistent, self-reported), compound outcome 'shortness of breath with wheeze', chronic cough,	Structured self report - cumulative paraquat exposure index created based on job history, handling of paraquat in each job, years of employment in each job, weighting for type of crop and use of PPE . No validation data presented, validated elsewhere.	Spirometry and single breath CO diffusing capacity measured to ATS criteria using Collins CPL PFT system. Only spirometry meeting ATS quality standards were included in analysis. Maximal cardiopulmonary tests used Monark cycle ergometer	Self-reported asthma - OR 1.6, 95%CI 0.9-3.0. Self-reported bronchitis - OR 1.3, 95%CI 0.9-2.0. Self-reported persistent wheeze OR1.1, 95%CI 0.7-1.6. 'Shortness of breath with wheeze' OR 2.3, 95%CI 1.2-5.1. Chronic cough OR 1.8 95%CI 1.0-3.1. Sub-clinical deficits identified but no clinically significant increase in restrictive defects. Ventilatory equivalent of CO2 although within normal range was significantly higher with cumulative paraquat exposure. Oxygen desaturation greater than 5% from rest to peak exercise was significantly greater with cumulative paraquat index OR 1.7, 95%CI 0.9-3.0 adjusted for age, weight and smoking status.	PFTs adjusted for age, height and smoking. Cardiopulmonary function adjusted for age, weight and smoking.

Senanayake, N., Gurunathan, G., Hart, T. B., et al. An epidemiological study of the health of Sri Lankan tea plantation workers associated with long term exposure to paraquat 1993	Case-control study ++	All tea workers - 85 paraquat spraymen, with 76 factory workers and 79 general workers as controls in Sri lanka. Response rate not given.	Paraquat	Lung function	Occupational history questionnaire.	Pulmonary function tests (FVC, FEV1, FEV1/FVC%, TLCO, single breath CO diffusion), chest x ray film, renal function (serum creatinine and blood urea nitrogen), liver function (serum alanine aminotransferase, aspartate transferase, and alkaline phosphatase, bilirubin, total protein, and albumin), a haematological screen (haemoglobin and packed cell volume), and a general clinical examination	There were no clinically important differences in any of the measurements made between the study group and the two control groups. In particular the results of the lung function tests, appropriate for paraquat toxicity of the study group, were similar to those of the control groups. The same was true of blood tests for liver and kidney function.	Confounding factors taken into account. No response rates and blinding was an issue.

Sprince, N. L., Lewis, M. Q., Whitten, P. S., Reynolds, S. J. and Zwerling, C. Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project 2000	stratified two-stage cluster sample, cross-sectional +	989 invited, 385 participated (response rate 39%)	No agent identified	Respiratory symptoms (including flu), bronchitis, wheezing, breathlessness, cough, phlegm, chest tightness,	questionnaire, no objective measures	None	The most frequently reported respiratory symptoms were flu-like symptoms in connection with dusty work (22%), dyspnea (21%), and phlegm (15%). Current smoking was uncommon (13%). Among farmers, applying pesticides to livestock was associated with significantly increased odds of phlegm (OR=1.91, 95% CI 1.02–3.57), chest ever wheezy (OR=3.92, 95% CI 1.76–8.72), and flu-like symptoms (OR=2.93, 95% CI 1.69–5.12) in models adjusting for age and smoking. Conventional vertical silos were significantly associated with increased odds of chest ever wheezy (OR=2.75, 95% CI 1.23–6.12) and flu-like symptoms (OR=2.40, 95% CI 1.31–4.37).	Minimal: age and smoking	Unsure, no agents identified

Sunyer, J., Garcia-Esteban, R., Alvarez, M., et al. DDE in mothers' blood during pregnancy and lower respiratory tract infections in their infants 2010	Birth cohort ++	657 women recruited, approx 50% of those eligible, 584 had blood and completed 6 month questionnaire, 538 completed 14 month questionnaire. In the end - 520 non-immigrant mothers and children were analysed	DDE, DDT, PCBs, hexachloroben zene, B-hexachlorocycl ohexane	Lower Respiratory Tract infections in children (incl. acute bronchitis - parental report of doctor diagnosis)	Questionnaire, blood DDE, DDT, PCB, HCB	None	Maternal DDE at first trimester associated with more LRTI in 0-14 months. DDE was the only organochlorine that showed an association with recurrent lower respiratory tract infection (at levels >83 ng/g, the first tertile, relative risk = 2.40 [95% confidence interval = 1.19-4.83]), lower respiratory tract infection at 6 months (1.68 [1.06-2.66]), and lower respiratory tract infection at 14 months (1.52 [1.05-2.21]). Adjusting for PCBs, hexachlorobenzene or beta-hexachlorocyclohex ane did not confound the association.	Confounding factors taken into account

Sunyer, J., Torrent, M., Garcia-Esteban, R., et al. Early exposure to dichlorodiphenyldichloroethylene, breastfeeding and asthma at age six 2006	Birth cohort, longitudinal ++	Birth cohort n=482. 462 followed up at 6.5 years. DDE and DDT measured in 402 infants and 285 4 year olds	DDE, DDT	Asthma (doctor diagnosed), wheeze (parental report)	Questionnaire, DDE and DDT measured in cord and at 4 years measured.	None	Birth cohort study associations between cord blood DDE and asthma, wheeze at 6.5 years. No association with DDE at 4 years, breast fed babes had more DDE, formula fed had reduced levels.	Confounding factors taken into account
Sunyer, J., Torrent, M., Munoz-Ortiz, L., et al. Prenatal dichlorodiphenyldichloroethylene (DDE) and asthma in children 2005	Birth cohort, longitudinal ++	482 recruited, 468 participated at 4 years with 306 blood tests at 4 years	DDE, hexachlorobenzene, polychlorobiphenyls	Asthma (doctor diagnosed), wheeze (parental report, in the last year)	Validated questionnaire, measurement of cord blood	None	Birth cohort looking at cord blood DDE and wheeze and asthma at 4 years. Associations with DDE and wheeze but not asthma or IgE, no associations with HCB, PCB.	Confounding factors taken into account: maternal asthma, breatfeeding, education, social class, other organochlorines

Weselak, M., Arbuckle, T. E., Wigle, D. T. and Krewski, D. In utero pesticide exposure and childhood morbidity 2007	cross sectional retrospective children born to mothers in study, exposure to pesticides on farm during pregnancy ++	2964 parents of which 64% returned all 3 questionnaires. Responding couples identified 5853 pregnancies, after exclusion resulted in 3405 children.	Broad groups of Insecticides, Fungicides, Herbicides and Other pesticides. Includes Phenoxy, Triazine, Thiocarbamate, Organophosphates, Dicamba, Glyphosate, 2,4-DB, 2,4-D, MCPA, Atrazine, Cyanazine, Carbaryl, Captan	Asthma (doctor diagnosed), persistent bronchitis or cough, allergies or hayfever (doctor diagnosed),	Exposure questionnaire, parental report of doctor diagnosis	None	No associations with chronic cough (2.6% prevalence), asthma (5%), hayfever/allergies (10%). Associations between exposure during pregnancy hayfever/allergies and any pesticide, insecticide, herbicide, Phenoxy, Organophosphate, 2,4 D.	Confounding factors taken into account
Yemaneberhan, H., Bekele, Z., Venn, A., Lewis, S., Parry, E. and Britton, J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia 1997	Cross-sectional survey +	9844 urban, 3032 rural Ethiopian people. Estimated over 95% response rate (as unreliable census data, rate based on fieldworkers).	Not completely listed, includes Malathion, DDT	Asthma, wheezing, cough	Exposure questionnaire, self reported - not validated. Atopy testing by allergen skin-test.	None	Study of asthma and atopy prevalence in rural and urban Ethiopia, insecticide included as a potential explanation for rural/urban difference. Complex association with atopy. Any home insecticide, malathion use in the home but not DDT associated with HDM sensitisation but not wheeze	Confounding factors taken into account - atopy and smoking. Pesticides simply added in as a potential causal group

Zhang, L. X., Enarson, D. A., He, G. X., Li, B. and Chan-Yeung, M. Occupational and environmental risk factors for respiratory symptoms in rural Beijing, China 2002	Cross-sectional, longitudinal +	22528 people from two villages in China, 98% response rate.	Not listed, mostly organophosphates, pyrethrin	Asthma, wheezing (wheezing or whistling in your chest in the last 12 months), breathlessness, cough, phlegm, chest tightness (woken up with a feeling of tightness in your chest in the last 12 months).	Self-reported questionnaire of symptoms and insecticide exposure	None	Only 3.1% exposed to insecticides, associated with increases in symptoms even after adjustment, no objective exposures or outcomes.	Confounding factors taken into account: age, sex smoking, county of residence

APPENDIX F REVIEWED PAPERS WITH NEGATIVE SCORES

Author and Date	Study Design and Quality Assessment	Study Population	Pesticide	Health Outcomes Measured	Exposure Metric (to pesticides)	Medical tests used (to measure respiratory effect of pesticides)	Summary of findings	Comments/confounders or sources of bias	Applicability to the UK
Abu Sham'a F, Skogstad M, Nijem K. Lung function and respiratory symptoms in male Palestinian farmers 2010	Cross-sectional survey -	250 subjects approached, 10 refused so an additional 10 were recruited. Of 250 subjects participating 197 did spirometry and of those 195 had technically adequate records. 3000 eligible	No specified agent, some banned internationally	Asthma, COPD (FEV1/FVC<70%), bronchitis, wheezing, breathlessness, cough, phlegm	Modified ATS-DLD-78-A based on the ATS respiratory questionnaire - hours of spraying/year, organophosphate use yes/no, currently spraying. Not validated.	Spirometry - best of 3 blows	No associations found between pesticide exposure and respiratory outcomes.	adjustment was made for potential confounders such as age, education level, BMI, PPE, and smoking. Study of farmers, most with limited education, nearly all 92% currently spraying pesticides, dose response not really possible because hours per year pesticide spraying looks like a random response, also the expected association between smoking and FEV1 not present, no adjustment for height. One third of farmers reported over 1800 hours of pesticide spraying /year which seems implausible.	Unsure, no agents identified

Bener, A., Lestringant, G. G., Beshwari, M. M. and Pasha, M. A. Respiratory symptoms, skin disorders and serum IgE levels in farm workers 1999	Cross-sectional survey -	98 farmers, 98 non-farmers as controls. From UAE.	No specified agent	Asthma, bronchitis, wheezing, breathlessness, shortness of breath, cough, phlegm, chest tightness, rhinitis, runny nose, sinusitis, sore throat (pharyngitis), eye irritation, nose irritation	Questionnaire - exposed yes/no	Clinical exam - IgE, spirometry	Farmers had a very high prevalence of chronic dermo-respiratory symptoms. These differences are statistically significant when compared with the reference group, particularly for the following symptoms: cough ($p < 0.003$), pharyngitis ($p < 0.0003$), bronchitis ($p < 0.02$), asthma ($p < 0.008$), respiratory insufficiency ($p < 0.006$), pneumonia ($p < 0.003$), dyspnoea ($p < 0.006$), nasal catarrh ($p < 0.001$), sinusitis ($p < 0.05$), pharyngeal irritation ($p < 0.01$), nasal irritation (dryness, sneezing and secretions) ($p <$	No confounding factors taken into account. Clear differences in socio economic status of farmers vs non farmers, differences in height, weight, smoking, presumably biomass exposure, no adjustment for differences in height for lung function, no adjustment of symptoms for smoking, SES etc	Unsure, no agents identified

		0.005), ocular irritation ($p < 0.05$), cutaneous pruritus ($p < 0.002$), and contact dermatitis ($p < 0.02$). The spirometer tests (all parameters together) measured in the farmers were significantly reduced by comparison with the reference group.

Beseler, C. L., Stallones, L., Pesticide poisoning and respiratory disorders in Colorado farm residents 2009	Cross-sectional survey -	761 farm operators and their spouses, representing 479 farms in northeastern Colorado, were recruited from 1993 to 1997. Overall response rate was 55%	No specified agent	Doctor diagnosed chronic bronchitis (possibly MRC), wheezing (any time in the last 12 months), breathlessness (defined as shortness of breath when hurrying on level ground or walking up a slight hill), cough (for 3 months or more), phlegm (for 3 months or more)	Questionnaire: Have you ever been ill following pesticide exposure? Self reported symptoms, report of physician confirmed allergies, chronic bronchitis, emphysema.	FEV1/FVC ratio measured in a sub-sample of 196 subjects excluding those with known respiratory disease. Calibrated using a 3 litre syringe by a NIOSH trained technician.	In unadjusted models, pesticide poisoning was associated with all four respiratory conditions (cough, allergy, wheeze, and organic dust toxic syndrome), and stayed significant in adjusted models of allergies and cough in non-smokers. In age- and gender-adjusted models, pesticide poisoning was significantly associated with lower FVC and FEV1 in current smokers and in those who were not heavy drinkers.	Superficially, not clear if lung function adjusted for age, height, gender, methods suggest adjustment for gender and age only. Smoking (current vs. never or past) and heavy drinking (vs. all other categories of alcohol consumption). Not adjusted for SES.	Unsure, no agents identified

Burns, C. J., Cartmill, J. B., Powers, B. S. and Lee, M. K. Update of the morbidity experience of employees potentially exposed to chlorpyrifos 1998	retrospective cohort study -	study cohort to 1994 comprised 496 potentially exposed subjects and 911 control subjects. Response rate not relevant as study used existing records.	Chlorpyrifos	COPD and allied conditions (this includes asthma and bronchiectasis)	plasma AChE, airborne monitoring data and potential for dermal exposure	None	COPD and allied conditions (includes asthma and bronchiectasis) - OR 1.41, 95%CI 0.95-2.09	two unexposed employees (controls) were sought for each exposed subject (cases) matching for age (within 7.5 years), race, sex, year of hire (within 7.5 years), and pay (hourly, salary exempt, or salary non-exempt). Matching appears to have been successful but no statistical tests presented.	registered in the UK

Castro-Gutierrez, N., McConnell, R., Andersson, K., Pacheco-Anton, F. and Hogstedt, C. Respiratory symptoms, spirometry and chronic occupational paraquat exposure 1997	Cross-sectional survey -	134 exposed, 152 un exposed, clear differences in gender, no other details given. Population well matched by age, gender, smoking	Paraquat	Lung function (FVC of <80% of the predicted value classified as having a restrictive defect; FEV1:FVC ratio of <0.70 classified as having an obstructive defect), bronchitis (productive cough for more than 3 months yearly for 2 or more years), wheezing, breathlessness (3 grades of dyspnoea), cough and phlegm (as part of bronchitis)	Modified MRC questionnaire, self-reported use of rucksack sprayers. Intensity of exposure characterised by history of paraquat exposure (>24 months) and history of paraquat induced skin burns or rash - unvalidated metric.	Spirometry to ATS standards.	Bronchitis - low exposure group and 23% in heavily exposed groups no significant difference between groups OR 2.0 (95%CI 0.94-4.4) in high exposed group. Wheezing reported as episodic wheezing with dyspnoea 115, 13% and 28% across the three groups. OR 2.9 (95%CI 1.406.3) for high exposed group. Prevalence of dyspnoea was 37% in unexposed, 52% in low exposure and 63% in high exposure workers. Significant excess of grade 3 dyspnoea among exposed workers. OR 2.8 (95%CI 1.4-5.6) for low exposure workers and 4.6 for high	Exposure metric styled by authors as a measure of chronic exposure but a history of skin rash/burns more likely reflects a single acute dermal exposure. Adjusted for age, gender, smoking history (lifetime smoking of more than 20 packs of cigarettes), no comparison of cases/controls, no obvious adjustment of spirometry. It is not clear whether a pack years metric or a dichotomous variable was employed for smoking in adjusted analyses. No adjustment for SES, BMI, plenty of room for confounding, subgroup

							exposure workers (95%CI 2.4-9.0)	analysis.	
Dahlgren, J., Warshaw, R., Thornton, J., Anderson-Mahoney, C. P. and Takhar, H. Health effects on nearby residents of a wood treatment plant 2003	Cross-sectional survey -	1269 exposed residents who were plaintiffs or potential plaintiffs in a lawsuit against a wood treatment plant were evaluated by questionnaire for a health history and symptoms. A representative sample of 214 exposed subjects was included in the analysis. One hundred thirty-nine controls were selected from 479 unexposed volunteers and matched to the exposed subjects as closely as possible by gender and age. All of the subjects analyzed from the selected population were African American.	Timber treatments – pentachlorophenol, creosote	Asthma, chronic bronchitis, breathlessness, cough, sore throat, sore runny eyes	self report save for doctor diagnosed asthma and chronic bronchitis. Ever vs never	Evaluated by a medical physician for medical history and physical examination, blood and urine testing (chem25, complete blood count and urinalysis), respiratory testing (pulmonary function tests of spirometry, diffusing capacity, or lung volumes).	Asthma – doctor diagnosed (13.1% vs. 12% in controls NS) and asthma by history of wheezing (40.5% vs. 11.0%, p<0.0001). Chronic bronchitis diagnosed by MD 17.8% vs. 5.8% in controls, p<0.0001. Breathlessness 5.6 vs 3.1 adjusted for age and sex (sig) On an 11 point scale (1=never to 11=always present). Cough 5.4 vs 3.1 (significant). Sore throat – 6.0 vs. 2.9 significant. Sore runny eyes – 6.9 vs. 3.1 significant.	Age and gender but not other factors (height). Inadequate adjustment for smoking (years of smoking is used rather than pack years). All cases were plaintiffs in class action against wood firm, funded by law firm, 214 of 1269 studied, not known if representative, potential for collusion questionnaires completed in church halls 40-50 at a time.	Registered in the UK

Fieten, K. B., Kromhout, H., Heederik, D. and van Wendel de Joode, B. Pesticide exposure and respiratory health of indigenous women in Costa Rica 2009	Cross-sectional survey -	134 women in Bribri territory, Costa Rica invited to participate: 95% response rate (not broken down by exposed/unexposed groups). 69 exposed women who worked at plantain plantations, 58 unexposed women who worked at organic banana plantations or other locations without pesticide exposure.	Terbufos, Chlorpyrifos, Paraquat	Asthma (doctor diagnosed, or occurance of asthma attack in last year), wheezing (whistling sounds in the chest in the last 12 months), breathlessness (waking up at night because of shortness of breath in the past 12 months), cough (chronic – defined as having reported waking up at night because of a cough attack as well as coughing for at least 3 consecutive months in the last 12 months), rhinitis (defined as the occurrence of 2 or more nasal symptoms, such as sneezing, runny nose, or nasal itching, during the last 12 months, without having a cold or the flu)	Exposure questionnaire	Spirometry – MIR Spirotel spirometer, 8 blows, with 3 curves selected	Wheeze more common in exposed 20 vs 9% p=0.07, although dyspnoea reported more common in exposed, there is no p value reported. Asthma, atopic symptoms, chronic cough, lung function no different.	Yes: height, age, smoking, atopy were included in the models. BMI not adjusted for. Small sample size, OP co-exposures were common meaning the effects of Terbufos and Chlorpyrifos could not be separated.

Garry, V. F., Kelly, J. T., Sprafka, J. M., Edwards, S. and Griffith, J. Survey of health and use characterization of pesticide appliers in Minnesota 1994	Cross-sectional survey -	719 of 1000 pesticide applicators selected by random number from 25,854 licensed applicators in southern Minnesota . More detailed follow-up of 60 applicators and 18 non-exposed agricultural controls	Not completely listed in article. Mentioned are: 111ermissib, tertrafume, actellic, Lasso (111ermissi), Counter, Captan, aluminium phosphide, 2,4-D, Carbaryl, phosphine	Asthma	Questionnaire – all exposed, occupational history. AchE tested and site visit in subset of 60 people	None	Use of fumigants in enclosed spaces appears to be associated with increased risk of asthma 4.9% vs 3% in pesticide applicators overall.	Analyses adjusted for smoking and age	
Jones, S. M., Burks, A. W., Spencer, H. J., et al. Occupational asthma symptoms and respiratory function among aerial pesticide applicators 2003	Prospective case control study -	Arkansas Agricultural Aviators Association members (n=135) and members of local Lions clubs (comparison group) n=118	No agent identified	Asthma, cough, phlegm, wheeze, shortness of breath, bronchitis, hay fever, sinus trouble	Modified ATS questionnaire, daily study diary to record daily symptoms and pesticide exposure. In addition, inhaled and dermal exposure levels at one aviation firm	Spirometry to ATS standards using PortaScreen System; serial peak flow using Air Watch system (5 recordings daily for 14 consecutive days).	No evidence of differences in self-reported asthma or change in PEF between aviators and comparison group.	Groups similar on race, age and gender and smoking. Comparison group had higher education. No statistical adjustments made. Study findings limited by high drop-out rate and inclusion of limited PEF data in analysis (at least 2 recordings/day over 7 of 14 days)	Unsure, no agents identified

Konieczny, B., Kossmann, S. and Makuch, M. Impaired respiratory muscle function in chemical plant workers producing chlorfenvinphos 1999	Case control study -	Workers in a chlorfenvinphos plant. All 35 male workers took part, with 22 healthy age-matched controls	chlorfenvinphos	Bronchitis (chronic), Respiratory muscle function	BMRC questionnaire, airborne contamination, plasma and RBC AchE.	Pulmonary function, SGAW, TLC, MIP, MEP	Mean air chlorfenvinphos concentrations in the work environment estimated with gas-liquid chromatography were from 0.0008-0.0018 mg/m3. The activity of erythrocyte acetylcholinesterase was similar to that observed in people who were not exposed to chemicals, however, a slightly lowered activity of plasma cholinesterase in the studied population was evidently the result of mild liver impairment. Spirometric investigations performed in the studied workers revealed slight alterations manifested by increased intrathoracic gas volume (ITGV)	No confounding factors taken into account. All workers in factory with very low exposures. Controls – no explanation where they came from. Workers older, more likely to smoke, more chronic bronchitis, less pack year smoking, ?lower SES, no adjustment for any of these. Also no difference in AchE levels in cases and controls, how can they postulate a difference

					(the value of the index was 138.6% of the mean value, 24 workers with an abnormally high index), as well as by decreased specific airway conductance (sGaw); its mean value in the studied group was 58.5% of the mean standard (11 people showed an abnormal index). Substantial functional changes were found in the respiratory muscles. Maximal inspiratory pressures (MIP = 97. 2 +/- 28.3 cm H2O) as well as maximal expiratory pressures (MEP = 113.9 +/- 44.2 cm H2O) in the studied group were significantly lower ($p < 0.01$) as compared to

				those observed in the control group (MIP = 120.7 +/- 31.7; MEP = 154.4 +/- 40.2 cm H2O) of 22 males having similar cigarette smoking habit, without occupational exposure to chemicals. It was also found that the people who had worked for more than 10 years under conditions of exposure to chlorfenvinphos showed significantly lower ($p < 0.05$) values of maximal inspiratory pressure (87.2 +/- 28.06 cm H2O, n = 17) compared to the workers whose period of employment was shorter than 10 years (106.6 +/- 26.8 cm H2O, n = 18).

Kossmann, S., Konieczny, B. and Hoffmann, A. The role of respiratory muscles in the impairment of the respiratory system function in the workers of a chemical plant division producing pesticides 1997	Case control study -	Pesticide manufacturers, cases 54, controls 37	Ops (fenitrothion, 115ermissibl, glyphosate), pyrethroids (alphametrin and prometryne), triazines, carbamates, dithiocarbamates, 2,4-D, captan, carboxine, carbendazim, dodine, 115ermissib, thiophanate 115ermis and cupric oxychloride	Obstructive impairment of pulmonary function, bronchitis (BMRC)	Environmental Protection Burueau measurements used to confirm levels of chemicals did not exceed 115ermissible levels	Spirometric investigations, including evaluation of vital capacity (VC), 1 second forced expiratory volume (FEV1) and its percentage index (FEV1%VC), peak expiratory flow and maximal end-expiratory flow (MEF25),	Chronic bronchitis was diagnosed in every second worker. In 11 males and females obstructive impairment of pulmonary function was established; 41% of females and 27% of males were found to have diminished peak expiratory flow. Maximal inspiratory pressures were significantly lower both in the studies males ($p < 0.001$) and females ($p < 0.02$) than those in the control groups and amounted to 74.4 +/- 21.5 and 58.1 +/- 24.3 cm H2O, respectively. Maximal expiratory pressures were also significantly lower in the studied males (p	Although the case control study reports more chronic bronchitis, airflow obstruction and respiratory muscle function in workers manufacturing pesticides, we are given no information about the control group, its sources, smoking, no adjustment for potential differences in height, age, smoking between cases and controls.

		< 0.001) and females ($p < 0.05$) and amounted to 116.6 +/- 28.4 and 74.5 +/- 17.9 cm H_2O, respectively. Significant correlation between decreased PEF and the force of expiratory muscles-MEP (In males $r = 0.3279$, $p < 0.05$; In females $r = 0.7049$, $p < 0.01$) was founded.

Ohayo-Mitoko, G. J., Kromhout, H., Simwa, J. M., Boleij, J. S. and Heederik, D. Self reported symptoms and inhibition of acetylcholinesterase activity among Kenyan agricultural workers 2000	Repeated cross-sectional surveys, longitudinal -	623 exposed workers, 390 followed up (62.6%), with 256 subjects having complete data. 515 unexposed agricultural workers, 276 followed up (53.6%), with 152 subjects having complete data	OPs - dimethoate and malathion; carbamates - benomyl, mancozeb, methomyl, aldicarb, propineb	Respiratory symptoms cluster - includes wheezing, breathlessness, cough, chest tightness, chest pain, sore throat. Eye symptoms - includes lacrimation and irritation	Questionnaire survey for symptom clusters based on self-reported symptoms and AChE inhibition measured using field spectrophotometric kit from EQM research. Biological effect monitoring using WHO approved kit rather than exposure measurement.	None	Respiratory symptoms cluster shows higher prevalence in high exposure period than low exposure period for exposed workers 19.3% vs. 14.7% but among unexposed workers the opposite held with lower prevalence of respiratory symptoms during high exposure period (5.4% in high exposure vs. 14.8% in low exposure period). Authors attribute difference to hot dry weather conditions during low exposure period. When considering the prevalence ratio for respiratory symptom cluster on day on interview by	Age and sex were adjusted for. Note that researchers translated questions into local languages orally - potential for inconsistent approach. Note also high drop-out rate, no smoking data. Symptom methodology imperfect, however shows a clear relationship between AC inhibition and resp Symptoms in the acute component

		exposure group based on AChE inhibition compared with no inhibition then the PR for medium inhibition (>5.5%-<30% was 2.04, 95%CI 0.78-5.38 and for high inhibition (>30%) the PR was 2.92, 95%CI 1.12-7.61.

Peiris-John, R. J., Ruberu, D. K., Wickremasinghe, A. R. and van-der-Hoek, W. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction 2005	Cross-sectional study of lung function and AChE with repeated measures, group comparison. -	25 farmers, 22 freshwater fishermen and a comparison group of 40 marine fishermen living away from agricultural areas from Sri Lanka	Organophosphates but type not stated. Used 52% methoxy compounds and 36% used ethoxy compounds.	Change in pulmonary function and AChE inhibition	Questionnaire. Haemoglobin corrected erythrocyte acetylcholinesterase (AChE) levels were measured during and between (baseline estimation) spray seasons using a portable WHO-approved Test-mate system (EQM Research, Ohio).	Spirometry (FEV1, FVC, FEF25-75%) measured using Microspiro HI-601 spirometer,	FVC ratio was lower in the farmers as compared to the controls (P<0.001) between exposure seasons. In the farmers, FVC ratio decreased further during the exposure season (P=0.023). FEV(1) was lower in the farmers as compared to the controls in both periods (P<0.05). In the fishermen, the decrease in ratios of FVC and FEV(1) following exposure to pesticides was not significant. FEV(1)/FVC ratios were similar in the three groups between (P=0.988) and during (P=0.159) exposure	Smoking adjusted for	Unsure, no agents identified

			periods. Following exposure to OPs, AChE levels dropped 12.75% in the farmers (P<0.001) and 5.62% in the freshwater fishermen (P=0.001).

Radon, K., Winter, C. Prevalence of respiratory symptoms in sheep breeders 2003	cross-sectional survey -	325 eligible sheep breeders participated. Overall response rate was 81.9%.	No agent identified	Asthma (self reported asthma symptoms), wheezing, shortness of breath, cough without phlegm, cough with phlegm, phlegm, nasal allergy	Questionnaire based on use of foot baths, sheep showers, shearing, time spent in barns and sheep numbers. European Farmers Study questionnaire previously validated.		Self-reported asthma related symptoms (ARS) OR 2.5, 95%CI 1.4-4.4 for full time sheep farming. Wheezing combined with shortness of breath, cough, cough with phlegm during work as work-related respiratory symptoms (WRS) OR 1.9, 95%CI 1.2-3.1 for main job as sheep breeder. Phlegm - OR 2.7, 95%CI 1.4-5.0 for main job is sheep breeder. No convincing evidence of an association between pesticides used in sheep dip and respiratory symptoms independent of sheep numbers. However the use of chemical footbaths was	Adjusted for age, gender, smoking habits.	Unsure, no agents identified

			associated with work related respiratory symptoms OR 2.1, 95%CI 1.2-3.7. Chemical footbaths contain formaldehyde (20%) or copper sulphate (18%). The authors suggested that use of footbaths is a surrogate for exposure to endotoxin.

Salameh, P., Waked, M., Baldi, I., Brochard, P. and Saleh, B. A. Respiratory diseases and pesticide exposure: a case-control study in Lebanon 2006	Case-control study -	245 cases of incident asthma and 262 controls from 10 medical centres were analysed from 1500 questionnaires distributed but proportion of cases and controls invited to take part is unspecified	No specified agent	Asthma (doctor diagnosed)	self report - unvalidated method vulnerable to reporting bias except environmental metric	None	Any exposure to pesticides was associated to asthma OR=2.11 (1.47 to 3.02). Occupational use presented the highest association OR=4.98 (1.07 to 23.28), followed by regional exposure OR 3.51 (2.11 to 5.85).	Confounding factors taken into account - age, education, nationality, paternal lung problem, work in dust or fumes	Unsure, no agents identified
Senthilselvan, A., Dosman, J. A., Semchuk, K. M., et al. Seasonal changes in lung function in a farming population 2000	Longitudinal study -	n=200 (106 men, 94 women). In winter season, 358 patients participated. Of theses, 234 returned in summer. After exclusion of 34 children, 200 used for analysis.‘	No specified agent	Lung function	Questionnaire.	Spirometry to ATS standards	mid flow rates increased in summer in urban residents, declined in farmers, same for FEV1/FVC ratio, ?effect of pesticide or occupation	Confounding factors taken into account	Unsure, no agents identified

Senthilselvan, A., McDuffie, H. H. and Dosman, J. A. Association of asthma with use of pesticides. Results of a cross-sectional survey of farmers 1992	Cross-sectional survey -	81.6% of 2375 farmers, n=1939	phenoxyacetic acid, carbamates, trifluralin, benzoics, cyanogens, propanil, trichloroacteic acid, phosphorodithioates, chlorinated hydrocarbons	Asthma (doctor diagnosed), wheezing, breathlessness, cough, phlegm, nasal allergy	Questionnaire - use in the last 5 years.	Spirometry	Carbamates associated with asthma, however asthma prevalence was low at 4.3%, plenty of scope for recall/response bias. No association between spirometry and pesticide use reported.	No adjustment for socioeconomic status nor smoking.
Strong, L. L., Thompson, B., Coronado, G. D., Griffith, W. C., Vigoren, E. M. and Islas, I. Health symptoms and exposure to organophosphate pesticides in farmworkers 2004	Cross-sectional survey -	211 agricultural workers in Eastern Washington US	Organophosphates including azinphos-methyl, phosmet, methyl parathion, chlorpyrifos, malathion, among others	Breathlessness, burning eyes	employment questionnaire and urinary OP metabolites and dust collection	None	Shortness of breath less common in exposed, no association with urinary metabolites or dust levels, burning eyes more common if pesticide in dust residues. No significant associations were found between reporting health symptoms and the proportion of detectable urinary pesticide metabolites.	No cofounding factors taken into account

Zuskin, E., Mustajbegovic, J., Schachter, E. N., Kern, J. and Pavicic, D. Respiratory function in vineyard and orchard workers 1997	Case-control study -	174 vineyard and orchard workers in Croatia. Clear differences in SES (vineyard workers migrants). No description of response rates or how they were recruited.	No agent identified	Occupational asthma (physician confirmed), bronchitis (MRC), breathlessness, cough, phlegm, chest tightness, runny nose, irritation or dryness of throat, eye irritation	MRC questionnaire on respiratory symptoms	Lung function tests, FVC, FEV1, FEF50, and FEF25	There was a significantly higher prevalence of dyspnea and chest tightness in exposed compared to control workers. In particular, exposed nonsmokers had significantly higher prevalences of dyspnea and chest tightness than controls; this was found for exposed nonsmokers with both short (≤10 years) and long (>10 years) exposure. Smokers exposed for more than 10 years had significantly higher prevalences of chronic cough, chronic phlegm, chronic bronchitis, and chest tightness than smokers with shorter exposures (p <	Smoking only. Essentially a study of vineyard and orchard workers, some not exposed to pesticides at all, clear differences in socioeconomic status between cases and controls, cases and controls 'similar' no adjustment for confounding, lung function analysed as difference between observed and predicted.	Unsure, no agents identified

					0.01 or p < 0.05). Workers employed for more than 10 years had higher prevalences of most of the acute (shift-related) symptoms than those workers with shorter employment; however, the differences were significant only for cough in smokers (p < 0.05). Significantly lower than predicted FVC values were measured in smokers and nonsmokers after both short and long duration of employment. Differences between measured and predicted FEV_1, FEF_{50}, and FEF_{25} were significant for workers employed for more than 10

		years. A separate analysis of individual data as a percent of predicted values demonstrated that many workers had FVC (5.2%), FEV_1 (6.3%), FEF_{50} (27.6%), and FEF_{25} (40.2%) lower than 70% of predicted values.