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Research into Malignant and Non-malignant Respiratory Disease Prescriptions: Report for Agriculture and COPD

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1 Introduction

The link between exposure to agricultural pollutants, including vehicle emissions, organic dusts and chemicals, including pesticides, and the development of chronic obstructive pulmonary disease (COPD) is the fourth of 6 high-priority occupational exposure-disease combinations that were identified with IIAC as being of highest priority for more detailed investigation (see Report of Phase 1 of this project).

This document contains a commentary on the extracted data for relevant occupational epidemiological studies and is meant to be read in conjunction with the associated spreadsheets containing the data extraction from these studies (Appendix 1).

2 Methods

Searches of Web of Science and NLM PubMed databases were undertaken in February 2023 using the following search string:

Exposure AND (farm* OR agriculture OR pesticides OR fertiliz* OR fertilis* OR crops) AND (COPD OR "chronic obstructive pulmonary disease" OR "chronic bronchitis" OR emphysema)

It should be noted that chronic bronchitis is a separate diagnosis from COPD that does not have airways obstruction within its definition, however the term was included in the search strategy as a conservative measure to ensure that potentially relevant papers were included. Bibliographies of the studies included in the agriculture and COPD reviews found in our earlier literature searches (see below) were searched to identify any additional individual studies that should be screened for inclusion in the tables of evidence.

We did not run searches more broadly on organic dust exposures and COPD.

3 Results

Overall, 375 relevant papers were identified from the literature searches and screened using title and abstract. Following title and abstract screening, 32 papers were identified for full text screening. One additional paper, not already identified in the searches, was identified from bibliographies of recent systematic reviews (Guillien et al., 2019; Pourhassan et al., 2019; Tarmure et al., 2020; Sigsgaard et al., 2020). One additional paper known to the study team was also included (Plombon et al., 2022).

Of the 34 papers identified for full text screening (32 from the literature searches, 1 from bibliography of reviews and Plombon et al), 9 studies were included for data extraction, of which 5 were cohort and 4 were case-control studies. One of the case-control studies was of paddy farmers in Indonesia and was thought not to be relevant to the UK experience, and so was excluded from further consideration. The 25 papers excluded at this stage were for the following reasons:

- 5 cross-sectional studies
- 10 studies not specifically of farmers
- 4 reviews
- 2 prevalence studies
- 2 papers not in English
- 1 full text unavailable
- 1 not COPD

To interpret the weight of the evidence, the following two subsections will summarise the results of both the (longitudinal) cohort and case-control studies in order of year of publication.

3.1 (Longitudinal) Cohort studies

Five relevant cohort studies were identified and had their data extracted (Heederik et al., 1990; Thaon et al., 2011; Rinsky et al., 2019; Silver et al., 2021, Plombon et al., 2022). Three of the five studies were from the US, with the others from France (Thaon et al., 2011) and the Netherlands (Heederik et al., 1990). One of the US studies (Rinsky et al., 2019) and the French study assessed populations of farmers specifically, and the other US studies (Silver et al., 2021, Plombon et al., 2022) and the Netherlands study were wider population based studies. (See accompanying spreadsheet).

A cohort of 878 men aged 40-59 years was recruited from Zutphen, an old industrial town in the Netherlands (Heederick et al., 1990) and followed up with annual medical examinations until 1973, then 1977-78 and finally 1985. A health questionnaire was also administered in 1980 and 1982. Physician diagnosed long-term chronic non-specific lung disease (CNSLD) was recorded, comprising either (a) regular cough and phlegm for more than 3 months or episodes of wheezing or shortness of breath reported by the survey physician or (b) diagnosis of CNSLD (including chronic bronchitis or emphysema) by a clinical specialist. After exclusion of 58 men with CNSLD prior to 1960 and 16 men with limited occupational data, a complete dataset was available for 804 participants. The incidence density (calculated by taking the total number of new cases and dividing that by the sum of the person-time of the at-risk population) was compared between occupational groups, with white-collar workers used as the baseline for the calculation of incidence density ratios (IDRs). There were 30 farmers in the study group among whom 10 incident cases of CNSLD were diagnosed, resulting in an IDR of 1.58 [95% CI: 0.82- 3.13], after adjustment for current age during follow-up, calendar period and smoking (5 categories based on current smoking habit – non-smokers, ex-

smokers, and low, medium, high intensity current smokers). There was no evidence of an increased IDR among the 26 participants with regular contact with animals (0.91 [95% CI: 0.43-1.92]).

A cohort of 219 dairy farmers, 130 non-dairy agricultural workers and 99 administrative employees from agricultural companies completed medical and occupational questionnaires, and underwent spirometric tests at recruitment in 1993-94 and at follow-up in 2006 (Thaon et al., 2011). Chronic bronchitis was defined as cough and expectoration for ≥3 months of the year for at least two consecutive years. At follow-up, 8 dairy farmers, 3 non-dairy farmers and 1 administrative worker were diagnosed with chronic bronchitis. Using the administrative workers as controls this resulted in an OR for dairy farmers of 4.66 [95% CI: 0.53-40.78], and for non-dairy farmers of 2.00 [95% CI: 0.20-20.06], after adjustment for age and smoking. Similar analyses for farmers handling animal food resulted in an OR for chronic bronchitis for those currently handling vs never handling of 2.63 [95% CI: 0.23-30.44] and for those previously handling vs never handling of 7.39 [95% CI: 0.85-64.16].

A study based on 22,491 participants from the US Agricultural Health Survey, who were recruited between 1993 and 1997 and attended follow-up in 2005-2010, investigated associations between animal production activities and prevalence of self-reported COPD (Rinsky et al., 2019). Exposure experience of farmers with a diagnosis of COPD and/or chronic bronchitis was compared to that of farmers with no COPD. Exposure assessment was based on self-reported information about raising animals and personal use of insecticides registered for use on or around animals as proxies for occupational exposure to the animal production environment. All analyses were adjusted for age, state, gender, education and smoking status. No association was found for any type of animal raised with farmers with a COPD diagnosis only. For those with COPD and chronic bronchitis an increased OR was found for raising hogs (1.41 [95% CI: 1.05-1.89]). For those with chronic bronchitis only, increased ORs were found for raising hogs (1.25 [95% CI: 1.06-1.47]) and beef cattle (1.29 [95% CI: 1.13-1.47]). Applying insecticides to animals or animal shelters in the year prior to enrolment was associated with an increased risk of chronic bronchitis with COPD (1.39 [95% CI: 1.08-1.78]) and chronic bronchitis without COPD (1.21 [95% CI: 1.05-1.38]).

Silver et al, (2021) studied the association between longest held industry or occupation and incident diagnosis of COPD in 7,907 individuals employed by 1972 and still working in 1992 who did not have COPD at the baseline survey. The individuals were part of the US Health and Retirement Study. Follow-up took place between 1994 and 2016 and individuals were included if they completed at least one follow-up survey. COPD was based on self-reports of a doctor diagnosis of a chronic lung disease such as chronic bronchitis or emphysema. For each industry group, the subhazard ratio (SHR) and 95% CIs were calculated which compared incident COPD among workers in the selected industry with incident COPD among workers from all other industries combined. Similar analyses were carried out for occupational exposures, regardless of industry. Analyses were adjusted for sex, race, ethnicity, education, family income, and smoking (including daily amount smoked). Farm workers, including farming, forestry and fishing, had an elevated SHR (1.88 [95% CI: 1.09-3.25]). In analysis of occupational exposures, farmworkers exposed to pesticides had a significantly elevated SHR (3.40 [95% CI: 1.40-8.23]) compared to individuals who were neither farmers nor exposed to pesticides. For all workers exposed to pesticides the SHR was 1.31 [95% CI: 0.97-1.76] compared to those not exposed.

A cohort study of residents of Keokuk county, Iowa collected data on environment, occupational history and medical examinations including spirometry between June 1994 and February 1998 (1st wave) with follow-up rounds in 1999-2004 and 2006-2011. Plombon et al., (2022) investigated the association of chronic bronchitis and airflow obstruction with farm activities using baseline data collected for 1699 adult participants, after exclusions for missing data. Among the 1,234 farmers in this cohort, 104 (8.4%) had chronic bronchitis, 75 (6.1%) fulfilled the criteria for airflow obstruction (both FEV_1 and FEV_1/FVC ratio below the lower limit of normal values based on sex, height and race/ethnicity), and the two outcomes overlapped by 18 participants. Chronic bronchitis without airflow obstruction (n = 86) had a statistically significant association with crop storage insecticides (OR 3.1, 95% CI 1.6, 6.1) and a low number of years (≤ 3) worked with turkeys (OR 3.3, 95% CI 1.2, 9.4). The latter result should be interpreted with caution because it is based on a small number of cases (n = 5). Airflow obstruction with or without chronic bronchitis (n = 75) was significantly associated with ever working in a hog or chicken confinement setting (OR 2.2, 95% CI 1.0, 4.5).] and the lifetime exposure of a high number of years (> 3) worked with turkey vs never worked with turkey (OR 3.1, 95% CI 0.8, 11.4) was borderline statistically significant ($0.05 < p < 0.10$).

3.2 Case-control studies

One case-control study in France compared 197 cases of male dairy farmers with chronic bronchitis (cough and daily expectoration 3 months per year for 2 consecutive years) with 163 male dairy farmers without chronic bronchitis (Dalphin et al., 1993). The focus of the study was on exposure to plant mould through barn threshing and foddering and also on a comparison of respiratory syndromes experienced by the case and control groups. No significant difference was seen between the groups for either of the tasks related to plant exposure during cattle foddering or barn threshing, with 79% of farmers with chronic bronchitis currently doing cattle foddering tasks compared to 83% of controls and 79% of farmers with chronic bronchitis doing barn threshing tasks compared to 74% of controls.

Mastrangelo et al. (2003) investigated the risk of COPD in different occupations compared to a reference group of office workers. The study group comprised patients attending an occupational medical clinic in Italy. Individuals were classified according to ever/never working in an occupation and years spent working in an occupation. COPD cases were defined as individuals with a clinical history of ≥ 2 years shortness of breath and/or winter phlegm and FEV_1 < 80% of predicted value, minimally reversible with bronchodilators. Controls were those attending the clinic for other diseases (typically dermatitis, but also e.g. cardiovascular disease, hand-arm vibration). In the study overall, there were 131 cases with COPD and 298 controls. Occurrence of COPD in specific occupations was compared to 72 office workers, of whom 12 (17%) had COPD. The OR for farmers compared to office workers, for univariable analysis was 8.13 [95% CI: 2.77-23.9] and, after adjustment for age, smoking and calendar year of hire, was 15.1 [95% CI: 3.18-71.6] based on 13 cases among 21 farmers included in the study. Analysis in relation to years spent, showed an age-adjusted OR for farmers of 1.09 [95% CI: 1.03-1.16] for each extra year of exposure. The authors noted that the referral route to their clinic (most often via the National Institute for Workers' Compensation for COPD or another occupational disease whenever the diagnosis was controversial and, for the remaining patients, who required therapy, via their family doctors) may have resulted in an overestimation of the risk for COPD because of a preferential referral of patients with respiratory illness and past occupational exposure.

Working conditions were compared in a nested case-control study of dairy farmers in the French Doubs region (Marescaux et al., 2015). COPD was defined in two different ways – the Global Initiative for Chronic Obstructive Lung Disease (GOLD) fixed cut-off criterion (FEV_1/FVC <0.70) resulting in 69 cases of dairy farmers with COPD and 506 controls of dairy farmers without COPD; and the fifth percentile of the FEV_1/FVC ratio distribution (FEV_1/FVC<lower limit of normal (LLN)) resulting in 32 cases and 543 controls. Univariable and multivariable analyses were carried out and comparisons made between:

- Traditional farm (house and cowshed in a common building) vs Modern farm (separation between house and cowshed) – Model 1
- Traditional farm (having a tie stall housing system) vs Modern farm (loose housing system) – Model 2

Both models and both definitions of COPD showed an increased OR for COPD prevalence in traditional farms compared to modern farms and a higher OR for smokers than for non-smokers (see Table below extracted from Marescaux et al., 2015).

Table 4 Combined effect of smoking and type of farm on COPD prevalence (multivariate analysis)

	OR (95% CI)	
	GOLD	**LLN**
Model 1		
Non-smokers/modern farm	1	1
Non-smokers/traditional farm	1.11 (0.51 to 2.41)	1.93 (0.57 to 6.51)
Smokers/modern farm	1.49 (0.69 to 3.23)	1.52 (0.47 to 4.91)
Smokers/traditional farm	4.02 (1.96 to 8.25)	3.42 (1.11 to 10.54)
Model 2		
Non-smokers/modern farm	1	1
Non-smokers/traditional farm	2.20 (0.83 to 5.82)	5.39 (1.16 to 25.11)
Smokers/modern farm	1.65 (0.54 to 5.11)	1.33 (0.18 to 9.61)
Smokers/traditional farm	5.65 (2.23 to 14.27)	8.29 (1.86 to 37.1)

Model 1: A modern farm is defined as having a separation between the house and the cowshed, and a traditional farm as having a house and a cowshed in a common building.
Model 2: A modern farm is defined as having a loose housing system, and a traditional farm as having a tie stall housing system.
OR: OR with 95% CI, after adjustment on age.
COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal.

4 Synthesis and Discussion

Exposure within agricultural and COPD has not previously been assessed by IIAC. At present, the only occupation prescribed for COPD relates to work as a coalminer (as detailed in Appendix 2).

Four recent (past 5 years) reviews on occupational exposure to pesticides or agricultural work and COPD were included in our phase 1 report, (Guillien et al., 2019; Pourhassan et al., 2019; Tarmure et al., 2020; Sigsgaard, 2020). Two of the reviews included meta-analyses with Pourhasson at al. (2019) reporting pooled ORs for occupational exposure to pesticides and obstructive lung disease of 1.33 [95% CI: 1.21-1.47], chronic bronchitis of 1.27 [95% CI: 1.23-1.31], and COPD of 1.44 [95% CI: 1.14-1.81]. The authors noted that heterogeneity among the studies was high, but that there was no evidence of publication bias. Guillien et al. (2019) carried out a pooled analysis, with a resulting increased OR for COPD (defined either by airflow limitation or by chronic bronchitis) among farmers of 1.77 [95%CI: 1.50-2.08].

Our search of the literature for relevant epidemiological evidence for agricultural exposures and COPD yielded five cohort studies and three relevant case-control studies. The searches were focused on studies specifically of agriculture and farming, and not on exposure to organic dusts more widely. As such, we cannot in this review comment on the associations COPD and organic dust exposure in general.

Three of the cohort studies were population-based studies and two were studies of groups of farmers; all of the studies adjusted for smoking in their analyses. Two of the population studies (Heederik et al., 1990; Silver et al., 2021) were based on low numbers of farmers (30 farmers, and 20 farmers exposed to pesticides respectively), and both studies used non-standard definitions of COPD. Heederik et al. reported findings for 'chronic non-specific lung disease' which, based on the symptoms analysed, could encompass chronic bronchitis, asthma, COPD or a combination of these, while Silver et al. used self-reports of COPD rather than medical diagnosis. After adjustment for smoking, a significantly raised OR for self-reported COPD was seen among the 20 farmers exposed to pesticides, but due to the small number of subjects, and the self-reported health outcomes, inferences from this study are limited. The third population study included over 1,000 farmers and diagnosed airflow obstruction from spirometric readings of FEV_1 and FEV_1/FVC ratio. This study showed a significant association between airflow obstruction and working in hog and/or chicken confinement with an OR of 2.2.

In the two studies of farmers, one study (Rinsky et al., 2019) compared agricultural exposures among farmers with COPD to those without COPD. The study used self-reported rather than medically diagnosed occurrence of COPD. The study showed higher levels of exposure to raising hogs among farmers with COPD and chronic bronchitis, but the study does not provide ORs for farmers in relation to other occupational groups. Thaon et al. (2011) compared risk of chronic bronchitis among dairy and non-dairy farmers with risks in administrative workers. The study was based on small numbers of cases (8 among dairy farmers, 3 among non-dairy farmers and 1 in the controls) resulting in wide 95% CIs and non-significantly raised ORs.

Similarly to Rinski et al. (2019), two of the three case-control studies investigated the impact of different agricultural practices on occurrence of lung disease within groups of farmers, rather than comparing farmers to other occupational groups or to the general population. Dalphin et al. (1993) investigated exposure to plant mould among farmers with and without chronic bronchitis, and found no differences between the two groups. Marescaux et al. (2015) compared occurrence of COPD in farmers using traditional and modern housing systems on their farms, and found significantly increased prevalence of COPD among those using traditional methods, particularly among smokers. The third case-control study (Mastrangelo et al., 2003) compared risk of COPD in farmers compared to office workers. The authors reported significantly increased ORs of 8.13 (univariable analysis) and 15.1 (after adjustment for smoking

and other factors), and evidence of an increasing risk with increasing years of exposure. These findings were based on 13 cases of COPD among 21 farmers in the study.

5 Conclusions

Overall, the occupational epidemiological evidence for agricultural exposures and COPD is limited, but there is some evidence of increased risks, with two recent reviews reporting pooled ORs for COPD of 1.4 for occupational exposure to pesticides and 1.8 for farmers. Of the eight papers which are included in this current report, four investigated differences in agricultural exposure within groups of farmers, and four compared farmers to other occupational groups. Three of the four studies in this latter group were based on small numbers of farmers (20-30 individuals) so conclusions from these are limited; nonetheless two of these studies reported significantly increased risks of COPD with ORs > 2.0. The fourth study, which had a relatively larger study group but small numbers of cases of COPD did not find a significantly increased risk. A cohort study of over 1,000 farmers in Iowa, US found a significantly elevated OR=2.2 for airflow obstruction among farmers working with hogs or chickens in confined environments.

Based on this review alone, there is currently insufficient evidence of a doubling of the relative risk to recommend prescription for additional occupational circumstances for COPD, however more data are developing in this area, and an updated review in the relatively short-term would be beneficial. As noted above, this review did not focus on the impacts of exposure to organic dusts or other potential agricultural exposures including bacteria, spores or gases. Thus, it would also be beneficial to carry out review of the association between COPD and these more specific exposures. In addition, exposures to allergens on farms, such as grain dust, have been associated with respiratory disease other than COPD (e.g. asthma, reduced lung function, 'farmers lung'). Further investigation of these other health outcomes would complement the findings of this report.

6 References

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Appendix 1 – Data Extraction Spreadsheet and List of All the References Considered.

Data_Extraction_Farmers_COPD_Final_fc

Farming_and_COPD_All_Papers.xlsx

Appendix 2 – Current prescription for COPD

Disease Number	Name of Disease or Injury	Type of job
	Miscellaneous conditions not included elsewhere in the list	**Any job involving**
D12	Chronic obstructive pulmonary disease – COPD where, with maximum effort, where there is evidence of a forced expiratory volume in one second which is: (i) at least one litre below the appropriate mean value predicted, obtained from the following prediction formulae which give the mean values predicted in litres: 1. For a man, where the measurement is made without back-extrapolation, (3.62 x Height in metres) minus (0.031 x Age in years) minus 1.41; or, where the measurement is made with back-extrapolation, (3.71 x Height in metres) minus (0.032 x Age in years) minus 1.44 2. For a woman, where the measurement is made without backextrapolation, (3.29 x Height in metres) minus (0.029 x Age in years) minus 1.42; or, where the measurement is made with back- extrapolation, (3.37 x Height in metres) minus (0.030 x Age in years) minus 1.46 or (ii) less than one litre.	Exposure to coal dust (whether before or after 5th July 1948) by reason of working– (a) underground in a coal mine for a period or periods amounting in aggregate to at least 20 years; (b) on the surface of a coal mine as a screen worker for a period or periods amounting in aggregate to at least 40 years before 1st January 1983; or (c) both underground in a coal mine, and on the surface as a screen worker before 1st January 1983, where 2 years working as a surface screen worker is equivalent to 1 year working underground, amounting in aggregate to at least the equivalent of 20 years underground. Any such period or periods shall include a period or periods of incapacity while engaged in such an occupation.

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