SHORT REPORT

Association of allergic rhinitis with pesticide use among grape farmers in Crete, Greece

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Objective: To explore the association of allergic rhinitis with the use of pesticides among grape farmers in Crete.

Methods: A cross-sectional study of 120 grape farmers and 100 controls at the Malevisi region in Northern Crete was conducted. The protocol consisted of a questionnaire, skin prick tests for 16 common allergens, measurement of specific IgE antibodies against 8 allergens, and spirometry before and after bronchodilatation.

Results: Grape farmers who used pesticides had higher prevalence rates of allergic rhinitis symptoms (OR, 3.0; 95% CI, 1.4 to 6.2) compared with grape farmers who reported no current use of pesticides, and control subjects. Logistic regression models controlling for age, sex and smoking status showed that 6 of the 12 predefined groups of major pesticides were significantly related to allergic rhinitis symptoms. The highest risks were observed for paraquat and other bipyridyl herbicides (OR, 2.2; 95% CI, 1.0 to 4.8), dithiocarbamate fungicides (OR, 2.5; 95% CI, 1.1 to 5.3) and carbamate insecticides (OR, 3.0; 95% CI, 1.4 to 6.5). A factor analysis of pesticides used identified 3 distinct factors. The most common factor was that of multiple pesticide use that included 9 pesticides and was significantly associated with allergic rhinitis (OR, 1.5; 95% CI, 1.0 to 2.3). ORs were higher when allergic rhinitis was defined using both questionnaire data on symptoms and atopy.

Conclusions: Occupational exposure to multiple agricultural chemicals could be related to allergic rhinitis in grape farmers.

Agricultural workers have been shown to have a high risk of occupational respiratory disease, due to exposure to different irritants and allergens.[1] While there have been several studies on occupational asthma among agricultural workers, few studies have examined the presence of allergic rhinitis among farmers. A recent cross-sectional study on the prevalence of respiratory symptoms in European and Californian animal and crop farmers has shown that cultivation of fruits and berries was a significant risk factor for rhinitis symptoms (OR, 1.3; 95% CI, 1.1 to 1.5).[2] Another study among New York farmers showed that the prevalence of stuffy nose/watery eyes was 57%, and it was significantly associated with being a worker on the farm, rather than being an owner/operator or resident, and having done spraying in the past year.[3] Senthilselvan and Dosman[4] found a significant association between rhinitis and raising horses, raising other animals (cattle, cows, sheep, poultry or swine) and the use of the herbicide cyanogens among Saskatchewan farmers.

Although agricultural workers are occupationally exposed to different types of pesticides, there is insufficient evidence of the impact of pesticides in allergic respiratory disorders. It is known that organophosphate and carbamate insecticides inhibit acetylcholinesterase activity and can induce bronchoconstriction by increasing the cholinergic activity, whereas the herbicide paraquat is a cause of pulmonary fibrosis in humans after exposure to a high dose.[5–9] The Agricultural Health Study has shown that paraquat, organophosphates and thiocarbamate pesticides were associated with increased wheezing among pesticide applicators.[10 11] Additionally, Senthilselvan *et al*[7] reported that the use of carbamate insecticides was associated with self-reported asthma among Saskatchewan farmers.

We recently observed that grape farmers in Crete had a high prevalence of allergic rhinitis (AR) and work-related respiratory symptoms compared with controls, and an increased allergic sensitisation to specific pollens.[12] The present study was conducted in order to investigate the association between AR and the use of pesticides among the above grape farmers group.

METHODS

Study population

This study was conducted from April to November 2002 and the study methods have been described in detail previously.[12] The exposed group consisted of 150 grape farmers with no other occupation besides grape farming. They were randomly selected from 459 grape farmers in the age group of 25–70 years who were listed in the agricultural co-operative in the Malevisi region of Northern Crete. The non-exposed group consisted of a random sample of 150 employees in the tourist industry, aged 25–70 years, from the total population of employees in the tourist industry who live in the Malevisi region (n = 408). This occupational group was chosen as the control group because tourism is the second major occupation in this region after agriculture.

The response rate was 80% (120 of 150) for the grape farmers and 67% (100 of 150) for the control group. Non-responders from both groups were contacted and interviewed by telephone, and were found to be comparable to the responders in terms of mean age, sex and smoking status.

All participants gave their written informed consent. The study protocol had been approved by the ethical committee of the University Hospital of Crete, Crete, Greece.

Questionnaire

All of the participants completed a questionnaire during a face-to-face interview performed by the same trained physician. The questionnaire included questions on medical and occupational history. AR based on the questionnaire was defined as the occurrence of two or more nasal symptoms (eg, rhinorrhoea, sneezing, nasal obstruction and nasal itching) during the last 12 months, apart from a cold. AR with atopy was the combination of AR according to the questionnaire, with a positive skin prick test (SPT) and/or a positive enzyme

Abbreviations: AR, allergic rhinitis; SPT, skin prick test immunoassay test.[13 14] The definition of current asthma according to the questionnaire was based on asthma symptoms or medication (attack of asthma during the last 12 months, having been woken up by an attack of shortness of breath during the last 12 months or current use of asthma medication). A second definition for asthma included the previous definition, followed by a positive bronchodilatation test.[12 15] The bronchodilatation test was performed using 400 μg salbutamol. An increase of >12% predicted in forced expiratory volume in one second. was considered a positive bronchodilator response.[16]

In the second part of the questionnaire (occupational history), there were questions regarding occupational characteristics such as the number of working hours per day, the number of years working in grape cultivations, the preventive measures used during working time (eg, gloves, mask, glasses), the use of pesticides and work-related symptoms. At the end of the questionnaire, there was a list of 50 commonly used pesticides (brand names), and grape farmers were asked to identify the pesticides they currently used. Grape farmers were also given the opportunity to add other pesticides that they had used and that were not included in the list. For those who could not remember the brand names of the pesticides they had used, there were photographs of each pesticide that was included in the list.

Allergy tests

SPTs were performed by a trained physician on the volar side of the forearm, with a standardised skin test needle for 16 different allergens/4 groups of allergens: pollens, mites, moulds and cat epithelium (SARM Allergens, Rome, Italy). A positive SPT was defined as the presence of a mean wheal diameter of 3 mm or more than the negative control. The enzyme immunoassay method was used to quantify IgE antibodies against eight different allergens/four groups of allergens: pollens, mites, moulds, and cat epithelium (Cypress Diagnostics, Langdorp, Belgium). A positive result was defined as ⩾0.35 EU/ml. All subjects from both groups performed the allergy tests.

In the present study, a subject was considered to be atopic if he or she demonstrated a positive reaction to one or more of the tested allergens in the SPT test and/or when at least one specific IgE measurement was ⩾0.35 EU/ml.

Statistical analysis

The statistical software SPSS V.13.0 was used for the analysis. Univariable analysis of categorical variables was made using the Pearson χ^2 test. Continuous variables were presented as means and standard deviations (SDs), and their univariable analysis was done using the analysis of variance test.

Pesticides exposure in single-agent model was evaluated using logistic regression modelling controlling for age (continuous variable), sex (female, male) and smoking status (non-smokers, ex-smokers, current smokers). Since subjects with atopy and subjects with AR symptoms could differ, we created a four-category AR-atopy status variable (AR according to both the questionnaire and atopy, AR according to the questionnaire alone, atopy alone, and neither).

Dose–response was evaluated using a semiquantitative proxy based on the number of pesticides used (1–7, 8–11, 11+ pesticides). The reference category included those who reported no use of pesticides. We tested for linear trends in ORs with increasing exposure.

We did two types of analysis to examine multiple pesticide use. First, we did pairwise correlations between the pesticides that were associated with AR in the single-agent model. For pairs of currently used pesticides with a Pearson correlation coefficient >0.1, we designed models including both chemicals.

We followed a factor analysis to define patterns of pesticide use (principal component method). Factors were extracted in descending order of importance with respect to the proportion of variance in the observed data accounted for each factor. We considered only the pesticides for which the loading coefficient was >0.2 or <–0.2, as this value roughly corresponds to a statistical significance of p = 0.05. To investigate the association between each pattern (factor) of pesticide use and AR, we performed logistic regression models adjusting for age, sex, smoking status and other factors. For all statistical tests, a probability <0.05 was taken as significant.

RESULTS

In all, 78 (65%) grape farmers reported that they used between 1 and 21 pesticides in their grape cultivations, with a median of 7 pesticides. The most often used herbicides were the broad-spectrum, non-selective systemic herbicide glyphosate (n = 67, 86%), and the bipyridyl herbicide paraquat (n = 38, 49%). The most often used inorganic fungicide was the sulphur dioxide (n = 74, 95%). Organic fungicides most often used were, triadimefon, a family of triazole fungicides (n = 65, 83%) and fenarimol, a family of pyrimidine fungicides (n = 57, 73%). The most often used insecticides were the carbamate insecticide carbaryl (n = 66, 85%) and the organophosphate insecticide parathion methyl (n = 32, 41%).

Table 1 shows the main characteristics of the grape farmers who reported current use of pesticides, those who reported no use of pesticides and control subjects. Grape farmers who used pesticides were older and included a higher proportion of men than the other two groups (p<0.01), while the controls had a higher prevalence of current smokers.

The prevalence of AR based on symptoms reported in the questionnaire was 51% for grape farmers who used pesticides (OR, 3.0; 95% CI, 1.4 to 6.2), 36% for grape farmers who did not use pesticides (OR, 1.4; 95% CI, 0.6 to 3.3) and 27% for the controls (p<0.01). AR based on the questionnaire combined with atopy was also elevated in grape farmers who used pesticides (OR, 3.5; 95% CI, 1.5 to 8.5) compared with the other two groups after adjusting for age, sex and smoking status (table 1).

According to the questionnaire, the prevalence of asthma for grape farmers who used pesticides was 9%, for those who did not use pesticides 17% and for the controls 12% (p = 0.357). When asthma according to the questionnaire was combined with the bronchodilatation test, the prevalence rates were 5%, 9% and 12%, respectively (p = 0.152). Analysis by type of pesticides or by type of chemical substances did not show statistically significant relationships between asthma and pesticide use.

Table 2 presents the ORs for the use of each group of pesticides relating to AR after adjusting for age, sex and smoking status. Among herbicides, bipyridyls, including paraquat and diquat, had the highest OR for AR on the basis of symptoms reported in the questionnaire (OR, 2.2; 95% CI, 1.0 to 4.8), and for the combination of AR with atopy (OR, 4.0; 95% CI, 1.4 to 11.2). Among fungicides, the highest ORs were observed for dithiocarbamates (AR: OR, 2.5; 95% CI, 1.1 to 5.3; AR with atopy: OR, 3.5; 95% CI, 1.2 to 10.2), whereas for insecticides the highest ORs were observed for carbamates (AR: OR, 3.0; 95% CI, 1.4 to 6.5; AR with atopy: OR, 2.4; 95% CI, 1.0 to 6.0).

Adjustment of the OR of specific pesticides for potential confounding by exposure to other correlated pesticides resulted, in most cases, in lower OR and wider CIs than those obtained from models that included only one pesticide (data not shown).

Table 1 Description of the study population and prevalence of allergic rhinitis among grape farmers and controls

	Controls non-farmers, n = 100	Grape farmers no use of pesticides, n = 42	Grape farmers current use of pesticides, n = 78	p Value*
Age in years, mean (SD)	34.9 (7.4)	43.3 (11.7)	46.9 (12.2)	<0.01
Sex				
Male, n (%)	29 (29)	7 (17)	36 (46)	<0.01
Female, n (%)	71 (71)	35 (83)	42 (54)	
Smoking				<0.001
Non-smokers, n (%)	32 (32)	31 (74)	40 (51)	
Ex-smokers, n (%)	9 (9)	3 (7)	12 (15)	
Current smokers, n (%)	59 (59)	8 (19)	26 (34)	
AR questionnaire†, n (%)	27 (27)	15 (36)	40 (51)	
OR (95% CI)‡	1	1.4 (0.6 to 3.3)	3.0 (1.4 to 6.2)	<0.01
AR with atopy§, n (%)	26 (26)	15 (36)	34 (44)	<0.01
OR (95% CI)‡	1	1.3 (0.5 to 3.2)	3.5 (1.5 to 8.5)	

AR, allergic rhinitis.
*χ^2 test was used for categorical variables; analysis of variance was used for continuous variables.
†The reference category included subjects who had no AR according to the questionnaire (less than 2 nasal symptoms apart from a cold during the last 12 months).
‡OR with 95% CI derived from logistic regression models by comparison with the control subjects after adjusting for age, sex and smoking status.
§Atopy: positive for at least one skin prick test or enzyme immunoassay test. The reference category included subjects who had no AR according to the questionnaire, or did not have a positive allergy test.

The highest ORs adjusted for other pesticides were found for bipyridyl herbicides (AR combined with atopy adjusted for glyphosate herbicide: OR, 3.5; 95% CI, 1.0 to 11.9; adjusted for dithiocarbamate fungicides: OR, 2.7; 95% CI, 0.8 to 9.8; adjusted for carbamate insecticides: OR, 3.7; 95% CI, 1.1 to 12.9).

Three major patterns of pesticide use were determined through factor analysis. The first factor (labelled ''multiple pesticide use'') included 9 pesticides (bipyridyl and glyphosate herbicides, dithiocarbamate, thiophthalimide, pyrimidine, triazole and inorganic fungicides, and the use of carbamate and organophosphate insecticides). The second factor (limited pesticide use) included triazine herbicides and organochlorine insecticides, whereas the third factor (biological pesticide use) included four pesticides and was positively correlated with the use of bio-insecticides (*bacillus thuringiensis*). The first factor explained 54% of the total variance, the second 9.5% and the third 8%.

The pattern of multiple pesticide use was significantly associated with a higher prevalence of allergic rhinitis according to the questionnaire (OR = 1.5, 95% CI, 1.0 to 2.3) and allergic rhinitis according to the questionnaire combined with atopy (OR = 1.8, 95% CI, 1.1 to 3.2), after adjusting for age, sex, smoking status and the other two factors. The other two patterns were not significantly associated with allergic rhinitis.

A semiquantitative proxy based on the number of pesticides used (1–7, 8–11, 11+ pesticides) showed that the ORs were higher in the higher exposure category compared with the reference group (no use of pesticides), although the associations were not statistically significant (AR: OR, 2.1; 95% CI, 0.7 to 5.9, p for trend 0.134; AR with atopy: OR, 1.8; 95% CI, 0.6 to 5.4, p for trend 0.062).

DISCUSSION

The main finding of the study is that grape farmers who used pesticides had higher prevalence rates of AR symptoms, and AR symptoms combined with atopy compared with grape farmers who did not use pesticides and control subjects. High risks were found for exposure to specific pesticides, and also for exposure to multiple pesticide use. To the best of our knowledge, the association of AR with pesticide use in agricultural workers has not been reported previously.

In the single-agent models, the highest odds of AR regarding the three categories of pesticides were observed for bipyridyl herbicides, dithiocarbamate fungicides and carbamate insecticides. Carbamate compounds may contribute to respiratory symptoms through cholinesterase inhibition.[7 8 10] The use of carbofuran (carbamate insecticide) was significantly associated with self-reported asthma among Saskatchewan farmers.[7] Among Kenyan agricultural workers with recent organophosphate and carbamate exposure, reports of three or more respiratory symptoms were four times more common than in subjects not using pesticides.[8]

In the present study, bipyridyl herbicides were the group of pesticides most strongly associated with AR, both in single and multiple-agent models. This group contained the herbicides paraquat and diquat. Paraquat has been shown to cause fatal lung (mainly pulmonary fibrosis) and kidney damage in large oral doses, in animals and humans.[9 17–19] The main biochemical mechanism of its toxicity is thought to occur through its reaction with oxygen to form toxic oxygen radicals.[17] Several studies reported positive relationships between occupational exposure to paraquat and respiratory symptoms. In the Agricultural Health Study, the bipyridyl herbicide paraquat was found to be significantly associated with wheezing,[10] whereas in the study on South African fruit farmers, long term exposure to paraquat was significantly associated with arterial oxygen desaturation during exercise, independent of short term exposure.[20] Castro-Gutierrez *et al*[21] had previously found a positive association between exposure to paraquat and reported dyspnoea on walking, as well as episodic wheezing with shortness of breath among workers at Nicaraguan banana plantations. A more recent study on farm workers in Costa Rica observed a significant independent association of shortness of breath with wheezing with cumulative paraquat exposure and a small increase in chronic cough with paraquat exposure.[22] Moreover, this study has shown that paraquat exposure was associated with oxygen desaturation and possibly with a subclinical abnormality of pulmonary gas exchange in this population.[22]

Most grape farmers used more than one pesticide in their cultivations. This finding is in accordance with the nature of grapevine cultivation that requires use of different herbicides, fungicides and insecticides. Our analysis showed evidence of confounding of OR estimated for several pesticides by current use of other pesticide groups. Similarly, the Agricultural Health Study has shown confounding for wheezing by exposure to multiple chemicals, and especially by exposure to the organophosphate insecticide chlorimuron-ethyl.[11]

To examine exposure to multiple pesticides, we evaluated patterns of pesticide use defined from factor analysis. Factor analysis is a simple statistical method used to explain the

Table 2 Association of allergic rhinitis with pesticide use*

Pesticides	Allergic rhinitis based on questionnaire† OR (95% CI)	Allergic rhinitis based on questionnaire with atopy‡ OR (95% CI)
Herbicides n = 72	2.7 (1.2 to 6.2)	3.2 (1.2 to 8.6)
Bipyridyl n = 50	2.2 (1.0 to 4.8)	4.0 (1.4 to 11.2)
Glyphosate n = 67	2.3 (1.0 to 5.0)	2.5 (1.0 to 6.5)
Triazine n = 7	3.8 (0.7 to 21.6)	–
Fungicides n = 72	2.8 (1.2 to 6.5)	3.1 (1.2 to 8.1)
Dithiocarbamate n = 63	2.5 (1.1 to 5.3)	3.5 (1.2 to 10.2)
Thiophthalimide n = 46	2.2 (1.0 to 4.8)	3.3 (1.2 to 8.7)
Pyrimidine n = 57	1.2 (0.6 to 2.6)	1.3 (0.5 to 3.4)
Triazole n = 70	2.2 (1.1 to 4.6)	2.7 (1.0 to 7.0)
Inorganic n = 74	1.5 (0.7 to 3.4)	2.2 (0.9 to 5.9)
Insecticides n = 78	1.8 (0.8 to 4.2)	2.6 (1.0 to 7.0)
Carbamate n = 75	3.0 (1.4 to 6.5)	2.4 (1.0 to 6.0)
Organophosphate n = 37	1.4 (0.6 to 3.2)	2.6 (0.9 to 7.9)
Organochlorine n = 5	1.2 (0.2 to 7.8)	–
Bioinsecticides (*Bacillus thuringiensis*) n = 12	1.9 (0.5 to 7.0)	1.5 (0.3 to 7.6)

*Odds ratios adjusted for age, sex and smoking status. Never use among grape farmers was the reference category.
†The reference category included subjects who had no AR according to the questionnaire (less than 2 nasal symptoms apart from a cold during the last 12 months).
‡Atopy: positive for at least one skin prick test or enzyme immunoassay test. The reference category included subjects who had no AR according to the questionnaire, or had a positive allergy test.

relationships between several correlated variables, and has already been used to explain patterns of pesticide use among pesticide applicators in the Agricultural Health Study.[23] Three distinct factors of pesticide use were identified, and one of these factors was significantly related to AR. This factor, labelled as the pattern of multiple pesticide use, included the current use of 9 of the 12 major pesticides examined. The associations remained statistically significant after adjustment for the other two patterns of pesticide use. This is the first report to our knowledge on patterns of pesticide use in association with respiratory symptoms, and it clearly describes the increased risk of AR in relation to agricultural practices that involve exposure to multiple chemicals.

In the present study, AR and asthma were not self-reported but were defined rigorously according to validated epidemiological criteria.[12 13 15] Grape farmers were found to have a high prevalence of atopy (64%); 89% of those diagnosed as having allergic rhinitis according to the questionnaire were found to be atopic.[12] For this reason, we used two definitions of allergic rhinitis: the first was based on symptoms present in the last 12 months according to the questionnaire, and the second was a combination of symptoms with positive allergy tests. Grape farmers seemed to report accurately on pesticide application questions; in most cases, they were not grape workers but the owners of the farm. They used to buy the pesticides themselves and cultivated grapes for a long period of time (mean (SD) time of grape farming: 25.0 (11.7) years). As has been reported elsewhere, the health worker effect does not seem to have played an important role in the results presented.[12]

The present study, being a cross-sectional study, cannot establish causal relationships but can suggest associations between allergic rhinitis and pesticide use. It also refers to a small area of research in northern Crete, and a relatively small sample size of grape farmers. The absence of quantitative exposure information on pesticide use did not allow us to construct dose–response models. When we performed a semiquantitative proxy based on the number of pesticides used, we observed higher OR in the higher exposure level, although the trend was not statistically significant.

Main messages

- Grape farmers who use pesticides in Crete have a high prevalence of allergic rhinitis and are occupationally exposed to a variety of pesticides.
- The highest risk was observed for use of bipyrifyl herbicides (paraquat and diquat).
- A pattern of multiple pesticide use was found to be significantly associated with allergic rhinitis.

Policy implications

- Although pesticides may contribute to respiratory symptoms and disease, there is insufficient evidence of their association with allergic respiratory disorders. Further studies are needed in order to provide more information on the impact of pesticide exposure in the development of upper airway allergic disorders, and to investigate the biological mechanisms underlying the associations.

Another limitation of the present study is that it is focused on current pesticide use and we had no information on pesticide exposure in the past. Although information on past exposure would be extremely useful, pesticide applications are highly variable and are subject to change over time as a result of a variety of factors, including temperature, wind, rainfall, insect and herbicide burden, and application methods.[24] Thus, there are several difficulties resulting in misclassification in the retrospective analysis of pesticide exposure. Finally, the lack of prior hypothesis could be considered a limitation and a challenge for the present study.

In conclusion, this study showed that grape farmers in Crete were occupationally exposed to a variety of pesticides, and that exposure to multiple pesticides was significantly associated with a higher prevalence of AR. Further studies are needed in order to confirm the presented results, to provide more information on the impact of occupational exposure to specific chemicals and the development of upper airway allergic disorders.

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