ORIGINAL ARTICLES AAEM

Ann Agric Environ Med 1998, 5, 147–153

EFFECTS OF EXPOSURE TO GRAIN DUST IN POLISH FARMERS: WORK-RELATED SYMPTOMS AND IMMUNOLOGIC RESPONSE TO MICROBIAL ANTIGENS ASSOCIATED WITH DUST

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Skórska C, Mackiewicz B, Dutkiewicz J, Krysińska-Traczyk E, Milanowski J, Feltovich H, Lange J, Thorne PS: Effects of exposure to grain dust in Polish farmers: work-related symptoms and immunologic response to microbial antigens associated with dust. *Ann Agric Environ Med* 1998, **5**, 147–153.

Abstract: Medical examinations were performed in a group of 76 Polish farmers heavily exposed to grain dust during harvesting and threshing, and in a group of 63 healthy urban dwellers not exposed to organic dusts (controls). The examinations included: interview concerning the occurrence of respiratory disorders and work-related symptoms, physical examination, lung function tests, and allergological tests comprising skin prick test with 4 microbial antigens associated with grain dust and agar-gel precipitation test with 12 microbial antigens. As many as 34 farmers (44.7%) reported the occurrence of work-related symptoms during harvesting and threshing. The most common was dry cough reported by 20 individuals (26.3%). Dyspnoea was reported by 15 farmers (19.7%), tiredness by 12 (15.7%), chest tightness by 8 (10.5%), plugging of nose and hoarseness by 5 each (6.5%). No control subjects reported these work-related symptoms. The mean spirometric values in the examined group of farmers were within the normal range, but a significant post-shift decrease of these values was observed after work with grain. The farmers showed a frequency of the positive early skin reactions to environmental allergens in the range of 10.8 - 45.5%, and a frequency of positive precipitin reactions in range of 3.9 - 40.8%. The control group responded to the majority of allergens with a significantly lower frequency of positive results compared to the farmers. The obtained results showed a high response of grain farmers to inhalant microbial allergens and indicate a potential risk of occupational respiratory diseases (such as allergic alveolitis, asthma, Organic Dust Toxic Syndrome) among this population.

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Key words: farmers, grain dust, harvesting, threshing, occupational exposure, health effects, work-related symptoms, allergy, microbial antigens.

INTRODUCTION

The long-term inhalation of organic dusts may cause inflammation of the respiratory tract in exposed agricultural workers as a result of specific allergic reactions [15, 19, 25, 28, 33, 38, 44, 57] or non-specific immunotoxic reactions with the participation of activated alveolar macrophages, cytokines and complement [1, 3, 5, 30, 34, 43, 51]. These reactions are induced mostly by micro-organisms associated with organic dusts, in particular by:

Received: 28 September 1998
Accepted: 9 November 1998

Gram-negative bacteria producing allergens and endotoxins [10, 12, 26, 35, 36, 41, 45, 48, 49, 50] allergenic actinomycetes [17, 24, 25, 38], and filamentous fungi producing allergens, (1→3)-β-D-glucans and mycotoxins [25, 36, 51, 53]. These microorganisms have been identified as common causative agents of respiratory disorders due to inhalation of organic dusts, such as: allergic alveolitis (hypersensitivity pneumonitis, granulomatous pneumonitis), asthma, and Organic Dust Toxic Syndrome (toxic pneumonitis) [19, 26, 27, 40, 41, 42, 44, 51, 58].

Among various tasks associated with exposure to organic dusts, handling grain (harvesting, threshing, loading, unloading, shuffling) may be associated with heavy exposure to grain dust and is regarded as a hazardous occupation [3, 4, 5, 15, 18, 22, 26, 27, 29, 36, 52, 54, 58, 59, 60]. Work-related symptoms have been reported in 20-44% of farmers handling grain in England, Poland and Canada [4, 12, 58] and in 44.8-89.4% of grain silo workers in Poland, USA, Canada and Hungary [8, 9, 12, 18, 46, 55, 59]. These effects of grain dust are largely due to the action of microorganisms associated with grain and their products (mostly bacterial endotoxins) which occur in great concentrations in air polluted with grain dust [4, 6, 11, 14, 21, 24, 35, 54].

Of particular importance is Gram-negative bacterium *Pantoea agglomerans* (synonyms: *Erwinia herbicola, Enterobacter agglomerans*) which may constitute 75-90% of total culturable microflora present on freshly harvested grain [11]. This organism produces strong endotoxin [10, 31, 32, 50] and has been identified as a main cause of allergic alveolitis in Eastern Poland [13, 22, 33]. Actinomycetes and fungi developing in incorrectly preserved and overheated grain were reported as a cause of allergic alveolitis and other diseases in many countries [25, 26, 27, 29, 36, 44].

The aim of the present work was to assess the effects of the exposure to grain dust in the populations of the Polish farmers engaged at harvesting and threshing of grain. This has been carried out on the basis of the study of the occurrence of work-related symptoms, and of the immunologic response of the farmers to microbial antigens associated with grain dust.

MATERIALS AND METHODS

Examined population. Demographics of the study population are shown in Table 1. A group of 76 farmers (farm owners and their relatives) living in the Lublin region (eastern Poland) was examined. The farmers were examined when harvesting and threshing grain. Of the 76 examined persons, 11 were engaged in combine harvesting and 65 in machine threshing of wheat and rye. As a control group, 63 office workers not exposed to organic dusts were examined. Human subjects protocols were reviewed and approved by the University of Iowa Institutional Review Board and all subjects gave informed consent.

Table 1. Demographics of the study population.

	Farmers	Controls
N	76 65 machine threshers 11 combine harvesters	63
Male	45 (59%)	34 (54%)
Female	31 (41%)	29 (46%)
Age (years)	41.4 ± 14.7	37.4 ± 11.4
Current Smokers	49 (64%)	16 (26%)
Ex-smokers	0	4 (6%)
Never Smoked	27 (36%)	43 (68%)

Medical examinations. Farmers were interviewed with the American Thoracic Society (ATS) standard questionnaire, and with the questionnaire developed in the Institute of Agricultural Medicine in Lublin for the study of work-related symptoms. They were subjected to routine physical examinations and to lung function examinations with the spirometer produced by MES (Kraków, Poland). The spirometric values of the forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC (%), and peak expiratory flow (PEF) were determined.

Allergological tests. Skin tests and agar-gel precipitation tests with the antigens of microorganisms occurring in the working environment were applied in the groups of grain farmers and controls. In both tests lyophilised saline extracts of bacterial or fungal mass, produced in the Institute of Agricultural Medicine in Lublin, were used as antigens. In the case of mesophilic, non-branching bacteria, the mass was harvested from nutrient agar cultures, while in the case of actinomycetes and fungi the mass was harvested from sugar broth cultures. The mass was then homogenised and extracted in saline (0.85% NaCl) in the proportion 1:2 for 48 hrs at 4°C, with intermittent disruption of cells by 10-fold freezing and thawing. Afterwards, the supernatant was separated by centrifugation, dialysed against distilled water for 24 hrs, concentrated by evaporation to 0.1-0.15 of previous volume and lyophilised [33].

Skin tests were carried out by prick method with the antigens of *Pantoea agglomerans* (syn.: *Erwinia herbicola, Enterobacter agglomerans*), *Streptomyces albus*, *Saccharopolyspora rectivirgula (*syn.: *Micropolyspora faeni, Faenia rectivirgula*) and *Aspergillus fumigatus.* The antigens were dissolved in saline (P.B.S., Biomed, Kraków, Poland) at the concentration of 5 mg/ml, sterilised by filtering and checked for sterility and lack of toxicity. The test was performed on the forearm with the antigenic extracts and P.B.S. as a control. The test sites were observed at 20 minutes. The wheal and/or erythema reactions of 3 mm or more in diameter were regarded as positive.

The agar-gel precipitation test was performed by Ouchterlony double diffusion method in purified 1.5% *Difco* agar with the antigens of *Acinetobacter calcoaceticus, Alcaligenes faecalis, Arthrobacter globiformis, Bacillus subtilis, Pantoea agglomerans, Streptomyces albus, Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris, Alternaria alternata, Aspergillus candidus, Aspergillus fumigatus,* and *Penicillium citrinum.* The undiluted serum separated from the circulatory blood sample of the examined subject was placed in the central well, and antigens, at the concentration of 30 mg/ml, in the peripheral wells. The plates were incubated for 6 days at room temperature, then washed in saline and in 5% sodium citrate solution (for preventing false positive reactions), and stained with azocarmine B [37].

Statistical analysis. The obtained results were analysed by the Student's t-test and by Pearson's test for correlation. These tests were chosen after stating by Kolmogorov-Smirnov test that the analysed variables show a normal distribution. All tests were done with the use of the CSS Statistica^{TM} ver. 4.5 package.

Table 2. Prevalence of work-related symptoms in farmers engaged in combine harvesting and threshing of grain (n=76).

Work-related symptoms	Workers reported symptoms (number, percent)
Dry cough	20 (26.3%)
Productive cough	2 (2.6%)
Dyspnoea	15 (19.7%)
Chest tightness	8 (10.5%)
Blocking of the nose	5 (6.5%)
Chest rattling	0
Hoarseness	5 (6.5%)
Fever	0
Shivering	0
Nausea	3 (3.9%)
Vomiting	0
Headache	4 (5.2%)
General weakness	2 (2.6%)
Sweating	3 (3.9%)
Joint and muscle aching	2 (2.6%)
Body aching	1 (1.3%)
Fatigue	12 (15.7%)
Body itching	3 (3.9%)
Rash	1 (1.3%)

Control subjects (n=63) reported none of these symptoms associated with work.

Table 3. Mean spirometric values in farmers engaged in combine harvesting and threshing of grain and in control subjects.

	Grain farmers (n=76)		Controls (n=63)	
Spirometric values	Mean ± SD	$\%_{pv}$	Mean ± SD	$\%_{pv}$
FVC I (ml)	3485 ± 1.032	84.1	3950 ± 0.231	89.3
FVC II (ml)	3291 ± 1.018**	81.6	3900 ± 1.013	88.0
FEV_1 I (ml)	2928 ± 0.217	80.6	3120 ± 0.947	86.1
FEV_1 II (ml)	2861 ± 1.024***	80.1	3095 ± 0.625	85.3
FEV_1/FVC I (%)	75.2 ± 0.217	92.1	81.1 ± 0.890	94.6
FEV_1/FVC II (%)	72.7 ± 0.271**	91.5	79.8 ± 0.120*	93.9
PEF I (ml/sec)	8430 ± 0.170	82.3	8921 ± 0.216	85.1
PEF II (ml/sec)	7961 ± 0.261	78.1	8863 ± 0.248	84.0

$\%_{pv}$ – percent of predicted value, I - before work, II - after work; * - *** a significant cross-workshift decline: *p<0.05, **p<0.01, ***p<0.001. The predicted value for each individual has been corrected for age, height, sex and smoking status [39].

RESULTS

Occurrence of work-related symptoms in grain handling farmers. Thirty-four out of 76 interviewed farmers (44.7%) reported occurrence of work-related general and respiratory symptoms during handling of grain (Tab. 2). The most common complaint was a dry cough reported by 20 farmers (26.3%), followed by dyspnoea reported by 15 (19.7%), fatigue - by 12 (15.7%), chest tightness - by 8 (10.5%), blocking of the nose and/or hoarseness - by 5 (6.5%). Among 34 farmers having work-related symptoms, eight persons reported only one symptom, ten - two symptoms, seven - three symptoms, four - four symptoms, nine - as many as nine symptoms, and one person each - ten and twelve symptoms. Ten out of 76 examined farmers (13.2%) reported symptoms characteristic for chronic bronchitis according to the ATS questionnaire.

None of the members of the control group reported the occurrence of work-related symptoms.

Lung function changes. The mean baseline spirometric values in the groups of farmers and controls did not show significant differences compared to the normal values [39]. Significant differences between the spirometric values measured before and after work with grain were found in the group of farmers; however, the post-shift values remained within the normal range (Tab. 3). These differences occurred not only in the farmers who reported work-related symptoms, but also, and even to higher extent, in the farmers not reporting such symptoms (data not shown). The significant differences between the spirometric values before and after work were not found in control subjects (Tab. 3), except for FEV_1/FVC. A limitation of the comparisons made between the groups of grain farmers and controls was a greater frequency of smokers in the group of farmers.

Table 4. Frequency of positive skin reactions in grain farmers and controls (%).

Allergens	*Pantoea agglomerans*	*Streptomyces albus*	*Saccharopolyspora rectivirgula*	*Aspergillus fumigatus*	Solvent (PBS)
Control group (n = 63)	1.6	1.6	0	1.6	0
Combine harvesters (n = 11)	45.5	36.4	27.3	18.2	0
Machine threshers (n = 65)	18.5	10.8	23.1	32.3	0
Mean value for both groups of grain farmers (n = 76)	22.4***	14.5**	23.7***	30.3***	0

- *: value significantly higher compared to the control group. **p<0.01, ***p<0.001

Allergic reactions. The frequency of positive skin response of the farmers to microbial allergens associated with grain dust was within the range of 14.5–30.3%. Seventeen farmers (22.4%) showed immediate positive skin reactions to *Pantoea agglomerans,* eleven (14.5%) to *Streptomyces albus,* eighteen (23.7%) to *Saccharopolyspora rectivirgula* and twenty-three (30.3%) to *Aspergillus fumigatus* (Tab. 4). The frequency of positive skin response to the same allergens in the control group was within the range 0–3.1% and was significantly lower compared to farmers ($p < 0.01$).

The frequency of positive precipitin reactions to microbial allergens associated with grain dust was within the range of 0–40.8% in the group of farmers, and within the range of 0–20.6% in the control group (Tab. 5). In the case of allergens from *Alcaligenes faecalis, Thermoactinomyces vulgaris, Aspergillus candidus* and *Penicillium citrinum*, the positive precipitin reactions occurred significantly more requently in the group of farmers than in the control group ($p < 0.05$). Farmers showed the highest frequency of positive precipitin reactions to the antigens of Gram-negative bacteria: *Alcaligenes faecalis* (40.8%) and *Pantoea agglomerans* (32.9%). A high response rate was also found to the antigen of the fungus *Aspergillus fumigatus* (21.1%). The frequency of positive reactions to six other bacterial and fungal allergens (*Acinetobacter calcoaceticus, Streptomyces albus, Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris, Aspergillus candidus, Penicillium citrinum*) was much lower being in the range of 3.9–9.2%, while with three antigens (*Arthrobacter globiformis, Bacillus subtilis, Alternaria alternata*) no positive reactions were found.

A significant correlation ($p < 0.05$) was found between occurrence of work-related symptoms and positive precipitin reaction to *Pantoea agglomerans*, as well as between occurrence of chronic bronchitis and positive precipitin reactions to *Pantoea agglomerans* and *Alcaligenes faecalis.* No other significant relationships were found between the response to particular antigens and occurrence of work-related symptoms and/or chronic bronchitis.

DISCUSSION

The obtained results indicate that farmers exposed to large concentrations of grain dust and associated microorganisms during harvesting and threshing are under

Table 5. Frequency of positive precipitin reactions in grain farmers and controls (%).

Antigens	Combine harvesters (n=11)	Machine threshers (n=65)	Mean value for both groups of grain farmers (n=76)	Control group (n=63)
Acinetobacter calcoaceticus	0	9.2	7.9	3.2
Alcaligenes faecalis	36.4	41.5	40.8***	11.1
Pantoea agglomerans	36.4	32.3	32.9	20.6
Arthrobacter globiformis	0	0	0	0
Bacillus subtilis	0	0	0	0
Streptomyces albus	0	4.6	3.9	1.6
Saccharopolyspora rectivirgula	9.1	4.6	5.3	0
Thermoactinomyces vulgaris	18.2	4.6	6.6*	0
Alternaria alternata	0	0	0	0
Aspergillus candidus	0	7.7	6.6*	0
Aspergillus fumigatus	9.1	23.1	21.1	9.5
Penicillium citrinum	0	10.8	9.2*	0

*- ***: value significantly higher compared to the control group. *p<0.05, **p<0.01, ***p<0.001.

increased risk of work-related pulmonary disorders, such as allergic alveolitis, asthma, chronic bronchitis and Organic Dust Toxic Syndrome. This presumption is supported by:

- The high frequency of work-related respiratory and general symptoms among grain handling farmers;
- Significant decrease of spirometric values (FVC, FEV_1) after work with grain, while the mean values before work do not show any abnormalities. These results correspond to those reported by El Karim *et al.* [16];
- The high frequency of early (prick) and/or delayed (precipitin-mediated) allergic reactions with particular microbial antigens (*Alcaligenes faecalis, Pantoea agglomerans, Saccharopolyspora rectivirgula, Aspergillus fumigatus*) which are common in grain dust and have been reported as a cause of allergic alveolitis and other diseases due to inhalation of organic dusts [13, 15, 19, 22, 23, 25, 26, 33].

The frequency of work-related symptoms found in the present work (44.7%) conforms exactly to the upper limit of the range reported by earlier authors for grain handling farmers [4, 12, 58], and to the lower limit of the range reported for grain silo workers [8, 9, 12, 18, 46, 55, 59]. Although in most cases we were not able to find a significant relationship between the positive response to tested allergens and work-related symptoms, it must be stressed that according to some authors [15, 23, 38] the persons showing positive immunologic reactions to dust-borne allergens are "potential patients", and with further exposure may develop symptoms. On the other hand, some symptoms may be evoked before the production of specific antibodies by the non-specific stimulation of immunologic system by highly active microbial substances, such as endotoxins [1, 31, 32, 45] or fungal products [43, 51, 53]. It is assumed, that prolonged exposure to organic dusts may lead to chronic bronchitis [2] which possibly could be a chronic stage of Organic Dust Toxic Syndrome (ODTS) [41]. The observed correlation between positive serologic response to *Pantoea agglomerans* and *Alcaligenes faecalis* and occurrence of chronic bronchitis and work-related symptoms in farmers suggests a possibility of participation of an antibody-mediated reaction in an unknown process of a purported transition from ODTS to chronic bronchitis.

All the microbial species selected for preparation of antigens used in the present work have been reported as potential agents of allergic and/or immunotoxic diseases associated with the exposure to organic dusts [10, 12, 15, 17, 20, 22, 23, 25, 27, 29, 33, 36, 38, 41, 47, 48, 49, 50]. Their presence in the working environment of examined farmers was confirmed by microbiological air sampling, the results of which have been reported elsewhere [21]. It is noteworthy that the Gram-negative bacterium *Pantoea agglomerans* (syn.: *Erwinia herbicola, Enterobacter agglomerans*), which was identified as a common cause of allergic reactions in exposed farmers, had been also found in large quantities in the working environment of farmers, in the air of the respiratory zone polluted with grain dust. This organism, reported as a frequent cause of allergic alveolitis in eastern Poland [13, 22, 33], and proved as an extremely strong source of endotoxin on grain and cotton [10, 31, 32, 41, 50], should be classified among the most hazardous agents causing diseases due to inhalation of organic dusts.

The response rates of farmers to microbial antigens associated with grain dust are comparable to those found by us earlier in the groups of rural inhabitants, grain silo workers and juvenile workers of urban origin having ODTS symptoms after grain shuffling [12, 52], except for response to *Aspergillus fumigatus* which was distinctly higher in the present study, and precipitin response to *Thermoactinomyces vulgaris*, which was lower compared to the adolescent group with ODTS.

The frequency of positive precipitin reactions to *Aspergillus fumigatus* found in the present study was also higher compared to the values reported by other authors for grain silo workers [9, 56]. By contrast, the frequency of positive skin reactions to this antigen was distinctly lower compared to the results obtained by Skoulas *et al.* [47] and Tse *et al.* [56] among grain silo workers in skin tests with the antigens of *Aspergillus* and other storage fungi. The frequency of positive skin reactions to *Aspergillus fumigatus* in the present work is comparable to that recorded by Darke *et al.* [4] in British grain farmers with the allergens of field fungi commonly found by them at harvest (*Aphanocladium album, Paecilomyces farinosus, Verticillium lecanii*). By contrast, the frequency of positive precipitin reactions to fungal allergens in this work is distinctly lower compared to the results obtained by the cited authors [4]. In the present study, the precipitin response rate to *Saccharopolyspora rectivirgula* was lower compared to those obtained by DeWeck and Bütikofer [7] among Swiss farmers, and by Warren *et al.* [57] among symptomatic Canadian farmers and grain elevator workers, but higher compared to that obtained by DoPico *et al.* [9] among American grain silo workers. The high precipitin response rate to *Alcaligenes faecalis* (40.8%) is comparable to that obtained by Kuś *et al.* [23] in the group of the Polish herb processing workers exposed to the inhalation of large quantities of these bacteria.

CONCLUSION

Farmers engaged in harvesting and threshing of grain show a high incidence of work-related symptoms and cross-workshift declines in pulmonary function during work with grain. They reveal also a high frequency of allergic reactions to bacteria and fungi associated with grain dust.

Acknowledgements

This study was supported in part by the Polish State Committee for Scientific Research (KBN) (grant No. 4P05D02214).

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