Bronchial hyperresponsiveness and exposure in pig farmers

Objective: To study the effect of exposure on bronchial responsiveness in pig farmers. Method: A group of 196 pig farmers were tested for lung function and bronchial responsiveness to histamine in the summer of 1992. To achieve sufficient contrast in respiratory morbidity and exposure, 96 of the farmers were selected because they had chronic respiratory symptoms and the remaining 100 because they were free from any respiratory symptoms. Personal exposure to dust, endotoxins and ammonia was measured during 1 working day in the summer of 1991 and 1 day in the winter of 1992. Data on farm characteristics were gathered in the same period. Results: After adjusting for age and smoking behaviour, mild bronchial responsiveness, defined as PC_{10} ≤ 16 mg/ml, was associated with the use of quaternary ammonium compounds as disinfectant [prevalence odds ratio (POR) 6.7, 95% confidence interval (CI) 1.4–32.8], use of wood-shavings as bedding (POR 13.3, CI 1.3–136.7), use of automated dry feeding (POR 2.8, CI 1.0–7.8), use of pellets as feeding material (POR 4.8, CI 1.1–21.1) and location of air exhaust via pit or roof in the confinement units (POR 2.7, CI 1.2–6.3). The association with the use of disinfectants other than quaternary ammonium compounds was not significant (POR 2.4, CI 0.7–8.4). No associations between bronchial responsiveness and measured exposure to dust, endotoxins or ammonia were discernible. Conclusion: Protective measures, designed to prevent airway disease in confinement farming, should be based on information about the operational and other characteristics of farms that are related to high exposure and health effects. Specifically, the use of quaternary ammonium compounds as disinfectant, the use of wood-shavings as bedding and the use of automated dry feeding should be discouraged.

Keywords: Occupational exposure • Confinement farming • Quaternary ammonium compounds • Lung function

Introduction

Work in swine confinement buildings is associated with the occurrence of respiratory symptoms. Most of the evidence to date points to the development of airway disease, especially chronic bronchitis, as an important health risk in this kind of work [16, 44]. In swine confinement units a large number of environmental factors with possible harmful effects on the airways have been identified. Among these are dust, endotoxins, Gram-negative and other bacteria, moulds, ammonia and hydrogen sulfide (H_{2}S) [17, 21, 23, 29, 42, 52].

A large number of studies among pig farmers have focused on work-related or chronic respiratory symptoms, while fewer studies have concentrated on lung function as such. A limited number of studies has been published on the role of bronchial responsiveness. With a few exceptions [15, 26, 27] most of these were based on small numbers [7, 13, 29, 35, 36, 48, 54] and/or one-dose provocation protocols, in which no degree of response can be assessed [4, 45, 47]. None of the studies on bronchial responsiveness have so far dealt with associ-
ations between exposure of the pig farmer and the prevalence of hyperresponsiveness. If such associations can be demonstrated, this provides clues for prevention.

In the pathogenesis of airway disease, hyperresponsiveness of the bronchial mucosa to non-specific irritants plays an important role. A number of the environmental factors mentioned above can increase the responsiveness of the bronchial mucosa by underlying inflammatory processes. The resulting hyperresponsiveness will contribute to the early development of signs and symptoms of obstructive airway disease. Therefore, the aims of the present study are to evaluate the relationship between characteristics of the pig farmer and his confinement units, measured exposure to environmental factors and the prevalence of bronchial hyperresponsiveness.

**Population and methods**

**Study population**

In 1990 a questionnaire was mailed to 2433 male owners of pig farms in the southern part of the Netherlands. This questionnaire contained questions on chronic respiratory symptoms, the appearance of respiratory symptoms during or shortly after work and 4–8 h after work, symptoms of atopy and hyperresponsiveness, personal characteristics and characteristics of the farm. The response rate was 62%. A full description is given elsewhere [49].

To be able to study exposure-response relations, a study group was formed with sufficient contrast in respiratory morbidity, and therefore presumably in exposure. In 1991 200 randomly selected subjects from among the respondents with one or more chronic respiratory symptoms (chronic cough, chronic phlegm, shortness of breath, ever wheezing, frequent wheezing, chest tightness(asthma)), and 199 randomly selected subjects without symptoms were invited for a medical examination including a more extensive interview and lung function testing. From the 200 farmers with one or more chronic symptoms in the postal questionnaire, 115 answered to stricter criteria for chronic obstructive pulmonary disease (COPD) and/or asthma on the basis of the interview at the medical examination. They were considered to be consistently symptomatic. From the 199 farmers without chronic symptoms in the postal questionnaire, 145 had no chronic symptoms in the more extensive interview. They were considered to be consistently asymptomatic. Ninety-eight of the consistently symptomatic and 100 of the consistently asymptomatic were randomly selected for a follow-up programme that included measurements of environmental and personal exposure in their own confinement units [37]. All worked at least 5 h per day in pig farming. In 1992 196 of them participated in a second medical examination, with a measurement of lung function and a histamine challenge test.

**Histamine challenge**

Before testing, participants were interviewed about current use of medication, upper respiratory tract infections in the week preceding the test, consumption of caffeine-containing beverages on the day of the test and current smoking behaviour. Lung function was performed with a Vicultest dry-swall spirometer, according to European Respiratory Society guidelines [41]. Highest forced expiratory volume (FEV1) obtained was taken as the baseline value for the histamine provocation. Participants with FEV1 < 0.80 L (predicted value) or FEV1/VC < 0.70 were excluded from further testing. The test for hyperresponsiveness was done in a shortened procedure as described by Hargreave and coworkers [22].

Participants inhaled aerosolized histamine for 2 min, starting with saline control and then with doubling concentrations from 0.03 to 16 mg/ml histamine. PC10 and PC20 were assessed by linear interpolation in a log dose-response curve. If more than a 20% decrease was seen after inhalation of saline control (one farmer) then PC20 was arbitrarily set at 0.01 mg/ml histamine. If 20% decrease was not reached after the maximum concentration, PC20 was set at 32 mg/ml. A cut-off point of PC20 ≤ 8 mg/ml was used to define "clinical hyperresponsiveness", and one of PC10 ≤ 16 mg/ml to define "mild bronchial responsiveness". The latter has been shown to be a valid index of responsiveness in population-based studies [43].

**Farm characteristics**

In the winter of 1992 an inventory of farm characteristics was made by walk-through surveys. Data were collected separately for each compartment on: the number of animals, feeding methods, heating and ventilation system, type of floor and bedding material, use of disinfectants and degree of contamination, by visual inspection. In summer 1991 and again in winter 1992 the farmers completed a diary on time spent on activities in pig farming, covering a 7-day period. Based on the information from the surveys and the diaries, the average time a farmer was exposed to a particular characteristic was estimated. For the purpose of the present study, dummy variables were used: a characteristic was present or not present, depending on the amount of time a farmer worked in compartments with particular characteristics. The methods used to estimate exposure to farm characteristics for the same study population are fully described by Preller and coworkers [38].

**Personal exposure**

Personal samples of inhalable dust and ammonia were taken during one work shift of on average 8.3 h in summer 1991 and winter 1992, as described by Preller and coworkers [39]. Dust samples were collected using a dust sampler with a 6-mm diameter inlet opening and an airflow of 2 l/min. Analyses on endotoxin content were performed with a modified kinetic Limulus Amoebocyte Lysate test. Long-term average exposure to dust and endotoxins was estimated by using a mathematical modelling technique described previously [38]. Number of animals was not analysed in the present study as a risk factor, but was important in the modelling to calculate long-term average exposure. Personal ammonia exposure was determined in duplicate using a passive monitoring method. A modified indophenol detection method was used and concentration was assessed by spectrophotometry. The exposure concentration was expressed as time-weighted average exposure.

**Analysis**

Differences in percentages and in group means were tested with chi-square and t-tests. Smoking behaviour has a strong effect on bronchial responsiveness and could confound any associations. This was adjusted for by inclusion of smoking status (dichotomized as current smoker vs non-smoker) in multivariate analysis. Associations between farm characteristics and mild bronchial responsiveness to histamine were tested with logistic regression, adjusting for age and smoking behaviour, as well as for all other factors in the model. Other potential confounders of the associations between responsiveness and farm characteristics did not alter risk estimates and were therefore left out of final models [24]. Results are presented as prevalent odds ratios (POR), with 95% confidence intervals.

Previously we demonstrated associations between several farm characteristics and chronic symptoms [49]. To avoid the confounding of the associations between farm characteristics and bronchial responsiveness, separate analyses were performed for the pig farmers with and without symptoms.

Differences in (log-transformed) exposure to dust, endotoxin and ammonia between farmers with and without mild bronchial responsiveness were first analysed with t-tests. For further analysis,
bronchial responsiveness was expressed as the log-transformed slope of the concentration-response curve to histamine, similar to [1]. In this way a continuous variable was created to avoid censored data and to maximize statistical power. Pearson correlations were calculated between the log of the concentration-response slope to histamine and the log of the exposure to dust, endotoxins and ammonia. In the analyses on associations between exposure and bronchial responsiveness, modelled long-term average exposure to dust and endotoxin and time-weighted average exposure to ammonia were used. Computations were completed with Statistix for personal computers.

Results

Histamine challenge

Of the 196 participants 194 could be tested with histamine provocation. One of them did not meet the admission criteria of minimum lung function and another refused further participation before completion of the test. Of those tested 94 were pig farmers with chronic symptoms and 100 were without. There were small differences in age [arithmetical mean (AM) 41.2 years, standard deviation (SD) 10.1 vs 37.3 years, SD 8.6] and mean number of years worked in swine confinement (AM 17.7 years, SD 7.8 vs 15.1 years, SD 8.1) between the two groups. More relevant was the difference in smoking behaviour (42% vs 15% current smokers). The number of farmers reporting an upper respiratory tract infection during the past week was only slightly different (11% vs 7%).

The associations between different chronic symptoms and bronchial responsiveness are shown in Table 1. The associations with mild bronchial responsiveness were stronger for asthma-like symptoms than for COPD-like symptoms, but were present for all chronic symptoms. If corrected for baseline FEV1 as well as for age and smoking, the prevalence of one or more chronic symptoms showed a separate association with mild bronchial responsiveness (POR 2.1, CI 1.0–4.7).

The prevalence of mild bronchial responsiveness sharply increased with the number of years which all respondents had worked in pig farming (Fig. 1). Mild bronchial responsiveness was seen more often in those with chronic symptoms, higher age, lower FEV1, in smokers and slightly so after recent upper respiratory tract infection.

Exposure

Among the pig farmers the geometric mean of the long-term average exposure to inhalable dust was 2.7 mg/m3 [geometric standard deviation (GSD) 1.3] and to endotoxins 111 ng/m3 (GSD 1.5). Time-weighted average exposure to ammonia was 1.7 mg/m3 (GSD 1.6).

Associations between farm characteristics, measured exposure and bronchial responsiveness

Statistically significant associations were found between the prevalence of mild bronchial responsiveness and use of quaternary ammonium compounds (QACs) as disinfectant (POR 6.7, CI 1.4–32.8), use of wood-shavings as bedding material (POR 13.3, CI 1.3–136.7), use of an automated dry feeding system (POR 2.8, CI 1.0–7.8), feeding with pellets (POR 4.8, CI 1.1–21.1) and location of air exhaust other than through the side of the building (POR 2.7, CI 1.2–6.7; Table 2). The association with the use of disinfectants other than QACs was not significant (POR 2.4, CI 0.7–8.4). No associations were found be-

Table 1  Associations between the prevalence of chronic respiratory symptoms, mild bronchial responsiveness (PC10 ≤ 16 mg/ml) and clinical hyperresponsiveness (PC20 ≤ 8 mg/ml). POR prevalent odds ratio (adjusted for age and smoking)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Farmers (n)</th>
<th>% with PC10 ≤16 mg/ml</th>
<th>% with PC20 ≤8 mg/ml</th>
<th>POR for PC10 ≤16 mg/ml</th>
<th>POR for PC20 ≤8 mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptom</td>
<td>100</td>
<td>17</td>
<td>3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>66</td>
<td>42*</td>
<td>15*</td>
<td>2.8*</td>
<td>4.0**</td>
</tr>
<tr>
<td>Chronic phlegm</td>
<td>55</td>
<td>36*</td>
<td>7</td>
<td>2.2**</td>
<td>1.5</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>28</td>
<td>37*</td>
<td>43*</td>
<td>3.8*</td>
<td>10.9*</td>
</tr>
<tr>
<td>Ever wheezing</td>
<td>70</td>
<td>46*</td>
<td>19*</td>
<td>2.6*</td>
<td>4.4*</td>
</tr>
<tr>
<td>Frequent wheezing</td>
<td>37</td>
<td>43*</td>
<td>19*</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Chest tightness (asthma)</td>
<td>27</td>
<td>63*</td>
<td>26*</td>
<td>8.1*</td>
<td>8.9*</td>
</tr>
<tr>
<td>≥1 symptom</td>
<td>96</td>
<td>45*</td>
<td>16*</td>
<td>2.9*</td>
<td>3.5**</td>
</tr>
</tbody>
</table>

*P < 0.05, **P between 0.05 and 0.10


Table 2  Multivariate associations between farm characteristics and the prevalence of mild bronchial responsiveness (PC_{10} \leq 16 \text{ mg/ml}) to histamine among 194 pig farmers, adjusted for age and smoking

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Farmers (n)</th>
<th>POR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of disinfectants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disinfectants</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quaternary ammonium compounds</td>
<td>19</td>
<td>6.7</td>
<td>1.4–32.8</td>
</tr>
<tr>
<td>Other disinfectants</td>
<td>146</td>
<td>2.4</td>
<td>0.7–8.4</td>
</tr>
<tr>
<td><strong>Use of bedding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bedding</td>
<td>162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood-shavings</td>
<td>7</td>
<td>13.3</td>
<td>1.3–136.7</td>
</tr>
<tr>
<td>Sawdust</td>
<td>23</td>
<td>0.7</td>
<td>0.2–2.5</td>
</tr>
<tr>
<td><strong>Feeding method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other methods</td>
<td>169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automated dry feeding</td>
<td>25</td>
<td>2.8</td>
<td>1.0–7.8</td>
</tr>
<tr>
<td><strong>Feeding material</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other materials</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellets</td>
<td>169</td>
<td>4.8</td>
<td>1.1–21.1</td>
</tr>
<tr>
<td><strong>Location of air exhaust</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Via side of building</td>
<td>141</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Via pit or roof</td>
<td>52</td>
<td>2.7</td>
<td>1.2–6.3</td>
</tr>
</tbody>
</table>

between mild bronchial responsiveness and other aspects of the ventilation system, aspects of the heating system, type of floor and degree of contamination (not shown). In the separate analyses for farmers with and without chronic symptoms, associations with farm characteristics tended to be stronger for the group without symptoms (not shown). No odds ratios could be calculated, as for a number of variables the associations between responsiveness and farm characteristics for asymptomatic farmers were too strong and based upon too small numbers.

Differences in mean exposure to dust, endotoxin and ammonia of the farmers with and without mild bronchial responsiveness were not statistically significant. Likewise, correlations between exposure to dust, endotoxin and ammonia and bronchial responsiveness as a continuous variable, were low (<0.1) and not statistically significant (not shown). Analysis only on farmers who showed reactions to histamine above threshold (PC_{10} \leq 16 \text{ mg/ml}) revealed no distinct effects for this group.

**Discussion**

In this study we showed that mild bronchial responsiveness (PC_{10} \leq 16 \text{ mg/ml}) was associated with the use of QACs and other disinfectants, use of wood-shavings as bedding material, use of an automated dry feeding system, feeding with pellets and location of air exhaust other than at the side. These results cannot be explained by differences in smoking behaviour, as these were adjusted for in multivariate analysis. No such associations with measured and modelled exposure to dust, endotoxins and ammonia were present.

As shown in Table 1, the associations between responsiveness and chronic symptoms are consistent for different symptoms, and not restricted to asthma-like symptoms. Furthermore, in this group of pig farmers, the association between responsiveness and symptoms could not be explained by the presence of airway obstruction only [46]. This indicates that bronchial responsiveness in pig farmers might be a factor associated with the development of progressive airway disease, independent of the diameter of the airways (the latter as indicator of the severity of disease at the present moment).

We demonstrated an association between the use of disinfectants and mild bronchial responsiveness. This was especially true if the farmer used QACs as the principal active component. In an earlier study among 1504 pig farmers we showed self-reported use of disinfectants to be associated with chronic respiratory symptoms [49]. In that study, use of disinfectants related most strongly with symptoms consistent with asthma. We also studied the repercussions of various aspects of the disinfecting procedure on symptoms and baseline lung function [39]. Duration of exposure to disinfectants was clearly associated with symptoms and lung function in that study. Disinfectants are often applied with spraying instruments using low (<20 bar) to high (>50 bar) pressure. The amount of pressure applied in spraying disinfectants proved to be strongly related to chronic symptoms [39]. We found atopic sensitization (defined as IgE to common allergens) more often in farmers who used disinfectants containing QACs [40]. Associations remained consistent in these studies, supporting the case for a contributory role of disinfectants in the development of respiratory morbidity. Some supporting evidence for such a role can be found in the literature: two case studies contain reports on the development of occupational asthma after exposure to disinfectants containing QACs [6, 11]. In a report on binding inhibition studies with five different QACs [51], it was concluded that QACs may be both sensitizers and histamine releasers. In line with our results, Zhang and coworkers [53] showed increases in bronchial respon-
siveness after exposure to QACs. Other disinfectants regularly used by pig farmers include chloramine-T and aldehydes, the latter often in combination with QACs. Several reports on respiratory effects of chloramine-T and aldehydes have been published so far.

Equally consistent as is the case with disinfectants are the associations found in our studies between adverse health outcomes and the use of wood-shavings as bedding material. Farmers reported more chronic symptoms and a tendency towards lower FEV₁ if they used wood-shavings [49]. In the present study we found a strong association between mild bronchial responsiveness and the use of wood-shavings as bedding, though not with the use of other bedding materials. In the literature wood-shavings have been shown to be a source of increased mould exposure and a cause of respiratory symptoms [19, 28]. Its use is also associated with high allergen concentration in the air [20]. An odds ratio of 2.8 was found in pig farmers who used automated dry feeding systems, an obvious source of high levels of dust-exposure. This is in accordance with the association found between automated feeding systems and chronic symptoms in our former study [49] and with the slightly lower lung function for farmers with automated systems found in that study and earlier by Bongers and coworkers [9]. In another part of our study [37] we showed that wet feeding is associated with lower exposure to dust, as reported also by Attwood and coworkers [2]. Both in this and former studies, there is evidence that the combination of automation with dry feed is associated with adverse health effects. Although other aspects of feeding showed associations with exposure to dust and endotoxins [37], we cannot confirm such associations for health effects. The association between use of pellets as feeding material and mild bronchial responsiveness of the farmer is not supported by other parts of our study [39, 49] and therefore probably inconsequential. We found a somewhat higher prevalence of mild bronchial responsiveness in farmers who worked mainly in confinement units in which the air exhaust was either situated in the roof or in the pit, compared with exhaust via the side of the building. This is not as expected, as air exhaust via the pit should lead to less exposure to environmental contaminants. We were able to confirm this as far as personal endotoxin exposure is concerned [37].

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