

# Sensitization and Symptoms Associated With Soybean Exposure in Processing Plants in South Africa

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**Background** Following the results of a previous study that highlighted the potential for significant levels of dust exposure in South African soybean processing plants, a clinical investigation was undertaken to study the respiratory health of workers in this industry.

**Methods** Workers from three soybean-processing plants were studied with a respiratory questionnaire and estimation of atopy and specific soybean IgE.

**Results** A total of 144 of the 181 (79.6% participation rate) plant employees completed the questionnaire and 136 (75.1%) gave blood samples for analysis of specific IgE. There was a significant association between work-related chest tightness (OR 4.0 [95% CI 1.3–12.6]), work-related nasal symptoms (OR 4.3 [95% CI 1.3–14.6]) and cough or chest tightness after handling soybean (OR 3.6 [95% CI 1.1–11.6]) and soybean sensitization. There was a significant association between current exposure to dust during soybean off-loading and “flu-like” illness (OR 2.7 [95% CI 1.0–7.2]), and cough or chest tightness after such work (OR 7.4 [95% CI 2.4–23.6]). The strongest predictor of work related nasal symptoms was sensitization to soybean, the latter strongly predicted by the presence of atopy (OR 34.7 [95% CI 6.6–182.5]).

**Conclusions** Exposure and sensitization to soybean were associated with the presence of work related symptoms, including flu-like symptoms, cough, chest tightness, and nasal symptoms. The aetiology of these symptoms and more particularly the best intervention strategies require more detailed investigation. *Am. J. Ind. Med.*

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**KEY WORDS:** allergy; occupational asthma; respiratory; agriculture; sensitizers

## INTRODUCTION

Soybean is used around the world in a wide range of products, particularly as an animal feed, as a relatively

cheap source of protein. The potential for soybean dust inhalation to induce allergic respiratory problems has long been recognized, causing both occupational asthma and hypersensitivity pneumonitis (HP) in workplaces [Bush et al., 1977; Zubeldia et al., 1995; Maggio et al., 2003] and epidemic asthma in exposed populations in Spanish cities associated with soybean unloading operations into harbor silos [Antó et al., 1989; Hernando et al., 1989]. A number of soybean allergens (mainly low molecular weight proteins concentrated in the hull) have been associated with the outbreaks [Rodrigo et al., 1990; González et al., 1992; Codina et al., 1999], although contamination of the beans with moulds such as *Aspergillus* and *Penicillium* has additionally been postulated as an suspected cause [Codina

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and Lockey, 1998]. Conversely, studies investigating respiratory symptoms caused by occupational exposure to soybean flour have identified high molecular weight proteins, that are identified both in the soybean flour and hull, as the causal allergens [Baur et al., 1996; Quirce et al., 2002; Green et al., 2011]. These data would suggest that there are a number of allergens associated with exposure to dust, from either the flour or hull, that may potentially cause respiratory ill-health.

Previous collaborative work between the National Institute for Occupational Health in Johannesburg (NIOH) and the Health and Safety Laboratory (HSL) highlighted the potential for significant levels of dust exposure in South African soybean-processing plants [Spies et al., 2008]. We therefore present the findings of a clinical investigation undertaken in three plants where soybeans are received, de-hulled, cooked, and processed, in order to better understand the origin of reported work related symptoms.

## METHODS

Three separate worksites (Companies A, B, and C) located in South Africa were identified and approached to participate. All employees at the three sites, regardless of their job title and/or area/section of the mill in which they work, were asked if they would undertake a respiratory questionnaire and provide a blood sample for analysis. Meetings were organized with management, company health, and safety committees and worker representatives in order to inform the workers about the study and to answer any questions.

An interviewer-led respiratory symptoms questionnaire, based on the original MRC questionnaire [Minette, 1962] was administered to all consenting participants. It focused on the presence or absence of a work relationship for each particular symptom and recorded the full work history. Work related symptoms were defined as those described as worse at work or improving on rest days (during the weekend or on holiday). Symptoms of work-related cough, shortness of breath, chest tightness, or wheeze were categorized as lower respiratory symptoms and work-related nose irritation was categorized as an upper respiratory symptom. Additional questions were also included to record constitutional symptoms following soybean handling, in order to identify acute febrile responses to organic dusts.

Ten milliliters of blood was collected from volunteers using untreated collection tubes (Becton Dickinson Vacutainer systems, Oxford, UK) to produce a clotted blood sample suitable for specific IgE immunoassay. Specific IgE to soybean (ImmunoCAP, Phadia UK, not containing hull allergens) was undertaken using an automated UniCAP 100 instrument. The test sample is assigned a specific IgE class from 0 to 6 (based on the fluorescence of the eluate

compared directly against a reference dilution curve), ranging from undetectable to very high levels of specific IgE. A result of class 1–6 was considered positive.

Radio-allergosorbant assay for atopy was performed as previously described [Harris-Roberts et al., 2009]. Atopy was defined as sensitization to a set of common environmental allergens. Results were expressed as a RAST score, based on the amount of radio labeled anti-IgE bound to the allergen disk incubated with the test serum, divided by the amount of radio labeled anti-IgE bound to the allergen disk incubated with negative (control) serum. A RAST score of 2 or more was considered positive.

Amongst the three worksites, job tasks were identified, observed, and categorized to define the potential risk they posed to workers as a result of the dust exposure. A walkthrough survey was carried out by an occupational hygienist and company production staff. This information was combined with previous dust measurements where available [Spies et al., 2008] and was used to classify jobs into low, medium, and high groups in terms of dustiness.

Although no measures of personal exposure to endotoxin were made, the endotoxin content of the soybeans was assessed. Samples of whole soybeans and separated hull collected at the worksites were eluted in endotoxin free phosphate buffered saline (50% w/v solution for whole soybeans and 20% w/v solution for hull) and tumble mixed for 2 hr at room temperature. Eluted extract solutions of the soybean suspensions were tested for endotoxin content using the BioWhittaker Kinetic QCL system (BioWhittaker, Wokingham, UK) and calculated against standard curves prepared from serial dilutions from known concentrations of an endotoxin standard (*Escherichia coli*) and presented as Endotoxin Units (EU). With the *E. coli* standard, 10 EU is equivalent to 1 ng endotoxin. Blanks and endotoxin free water formed negative controls.

All data analyses were performed using SPSS software (Statistical Package for Social Scientists v13.0, SPSS Inc., Chicago, IL). Descriptive statistical analyses were first performed on the data and Mantel–Haenszel common odds ratio estimates derived from cross-tabulations.

Logistic regression models were then used to estimate the independent effects of a variety of factors (including exposure to dust during bean off-loading, smoking, atopy, and exposure code) on a range of outcome variables, including the reporting of work-related upper and lower respiratory symptoms, flu-like illness consisting of fever, aching, and tiredness after working on the soybean mill and sensitization status. Odds ratios were also adjusted for the potential confounding effects of age, gender, and time in industry. Regression models were evaluated for goodness of fit using Hosmer and Lemeshow tests. In addition, Nagelkerke R Squares were derived allowing the proportion of the variation in the outcome variable explained by the model to be evaluated.

Ethical approval for the study to proceed was obtained from the Human Research Ethics Committee, University of Witwatersrand, South Africa and all workers gave written informed consent.

## RESULTS

The processes in all three worksites were based on similar soybean milling techniques. Soybeans arrived by truck, were off-loaded, and stored in silos. The beans were then de-hulled, subjected to a cooking process, milled, and bagged [Spies et al., 2008].

A total of 144 of the 181 (79.6% participation rate) plant employees completed the questionnaire and 136 (75.1%) gave blood samples for analysis of specific IgE.

The demographic characteristics of the study cohort by worksite and exposure group are summarized in Table I. 86.8% (125:144) of the volunteers were male. The mean age for the total population was 35.6 years (standard deviation (SD) 9.9 years, range 20–61 years). The mean time working at the current company was 4.3 years (SD 4, range <1–36.3 years). 30.6% of workers were current smokers, 20.8% ex smokers, while 48.6% had never smoked.

38:144 (26.4%) individuals reported either an upper or lower work-related respiratory symptom. Eight of these individuals reported an upper respiratory symptoms (nasal irritation) in the absence of any lower respiratory symptoms, 22 reported lower symptoms only (cough, wheeze, or chest tightness) and 8 reported both upper and

**TABLE I.** Worker Characteristics by Site

| Characteristics                                         | All<br>N = 144 | Worksite A<br>n = 8 | Worksite B<br>n = 51   | Worksite C<br>n = 85 |
|---------------------------------------------------------|----------------|---------------------|------------------------|----------------------|
| Age (years)                                             |                |                     |                        |                      |
| Mean (SD)                                               | 35.6 (9.9)     | 37.9 (13.3)         | 35.9 (10.7)            | 35.2 (9.0)           |
| Median                                                  | 33             | 39.5                | 34                     | 32                   |
| Range                                                   | 20–61          | 21–53               | 20–60                  | 20–61                |
| Duration of work at company (years)                     |                |                     |                        |                      |
| Mean (SD)                                               | 4.3 (4.3)      | 8.5 (11.5)          | 3.2 (5.0)              | 4.6 (1.8)            |
| Median                                                  | 4.3            | 4.5                 | 1.4                    | 5                    |
| Range                                                   | <1–36.3        | 1–36.3              | <1–29.0                | <1–9.3               |
| Current exposure to dust during soybean off-loading     |                |                     |                        |                      |
| Yes (%)                                                 | 84 (58.3)      | 7 (87.5)            | 31 (60.8)              | 46 (54.1)            |
| No (%)                                                  | 60 (41.7)      | 1 (12.5)            | 20 (39.2)              | 39 (45.9)            |
| Past exposure to dust during soybean off-loading        |                |                     |                        |                      |
| Yes (%)                                                 | 58 (42.3)      | 6 (75)              | 18 (36.7) <sup>a</sup> | 34 (42.5)            |
| No (%)                                                  | 79 (57.7)      | 2 (25)              | 31 (63.3)              | 46 (57.5)            |
| Exposure category                                       |                |                     |                        |                      |
| Low (%)                                                 | 30 (20.8)      | 0                   | 17 (33.3)              | 13 (15.3)            |
| Medium (%)                                              | 48 (33.3)      | 0                   | 10 (19.6)              | 38 (44.7)            |
| High (%)                                                | 66 (45.8)      | 8 (100)             | 24 (47.1)              | 34 (40.0)            |
| Gender                                                  |                |                     |                        |                      |
| Male (%)                                                | 125 (86.8)     | 8 (100)             | 41 (80.4)              | 76 (89.4)            |
| Female (%)                                              | 19 (13.2)      | 0 (0)               | 10 (19.6)              | 9 (10.6)             |
| Smoking                                                 |                |                     |                        |                      |
| Current (%)                                             | 44 (30.6)      | 2 (25.0)            | 10 (19.6)              | 32 (37.6)            |
| Ex (%)                                                  | 30 (20.8)      | 1 (12.5)            | 13 (25.5)              | 16 (18.8)            |
| Never (%)                                               | 70 (48.6)      | 5 (62.5)            | 28 (54.9)              | 37 (43.5)            |
| Ever suffered from asthma                               |                |                     |                        |                      |
| Yes (%)                                                 | 10 (6.9)       | 0 (0)               | 2 (3.9)                | 8 (9.4)              |
| No (%)                                                  | 134 (93.1)     | 8 (100)             | 49 (96.1)              | 77 (90.6)            |
| Ever suffered from eczema, hay fever or other allergies |                |                     |                        |                      |
| Yes (%)                                                 | 47 (32.6)      | 2 (25.0)            | 18 (35.3)              | 27 (31.8)            |
| No (%)                                                  | 97 (67.4)      | 6 (75.0)            | 33 (64.7)              | 58 (68.2)            |

<sup>a</sup>Percentages expressed relative to number exposed (excluding missing data).

lower symptoms. Cough and chest tightness were the most commonly reported symptoms (both 19:144 or 13.2%), followed by nasal irritation (16:114 or 11.1%) then wheeze (9:144 or 6.3%). 23.8% (25:105, this denominator representing those with available and interpretable data relating to this question) of workers reported flu-like illness consisting of fever, aching, and tiredness after working on the soy mill and 25.7% (27:105) reported cough or chest tightness after handling soybean. Altogether 33.1% (45:136) of workers were atopic and 19:136 (14%) of workers exhibited sensitization to soybean allergens.

Unadjusted risk factors for reported work-related respiratory symptoms were initially investigated by examining the crude effects of sensitization to soybean. No association was found between the reporting of lower work-related symptoms and sensitization status using the commercially available soy ImmunoCAP (Table II). However, when each symptom was analyzed individually, there was a significant association between work-related chest tightness (odds ratio (OR) 4.0 [95% CI 1.3–12.6]), work-related nasal symptoms (OR 4.3 [95% CI 1.3–14.6]) and an association between workers reporting cough or chest tightness after handling soybean (OR 3.6 [95% CI 1.1–11.6]) and soybean sensitization.

Eighty-four workers were exposed to dust during soybean off-loading. This process involved the transfer of whole beans brought from farms in large transport vehicles, into the processing factory. The precise details of the process varied between sites, but involved tipping the beans into a designated catchment area and then elevating them into a silo for storage prior to processing. No association was found between the reporting of upper or lower work-related symptoms as a group and exposure to dust during soybean off-loading (Table III). However, there

was a significant association between current exposure to dust during soybean off-loading and “flu-like” illness consisting of fever, aching, and tiredness after working on soy mill (OR 2.7 [95% CI 1.0–7.2]), and cough or chest tightness after handling soybean (OR 7.4 [95% CI 2.4–23.6]). There was no association (chi-squared analysis— $P = 0.274$ ) between exposure to dust during soybean off-loading and soybean sensitization status.

Adjusted odds ratios for symptoms were derived for exposure code, past and current exposure to dust during soybean off-loading and sensitization status from logistic regression models. Adjusting for the effects of age, smoking, gender, and time in industry demonstrated that soybean sensitization was an independent risk factor for work-related nasal symptoms. It also identified exposure to dust during soybean off-loading as a risk factor for reporting certain respiratory and constitutional symptoms (flu-like) following soybean handling. Bulk samples of whole soybeans and hull were obtained from each of the three sites and analyzed for endotoxin concentration. Levels of endotoxin were higher in hull samples 727–13611 ng/g, than in whole soybean 132–174 ng/g.

## DISCUSSION

This study found that workers employed in three South African soybean-processing companies commonly reported work-related respiratory and constitutional symptoms, with workers exposed to dust during soybean off-loading being particularly at risk. This study also found atopy to be an independent risk factor for soybean sensitization, with sensitized workers being at significantly increased risk of reporting symptoms suggestive of occupational rhinitis.

**TABLE II.** Work-Related Symptoms and Sensitization to Soybean (Commercially Available Soy ImmunoCAP)

|                                                                                        | All                        | Not soybean sensitized     | Soybean sensitized       | Odds Ratio            |
|----------------------------------------------------------------------------------------|----------------------------|----------------------------|--------------------------|-----------------------|
|                                                                                        | n (%)                      | N (%)                      | N (%)                    | (95% CI)              |
| Any work-related respiratory symptoms                                                  | 38/144 (26.4)              | 27/117 <sup>a</sup> (23.1) | 8/19 <sup>a</sup> (42.1) | 2.4 (0.9–6.6)         |
| Work-related lower respiratory symptoms                                                | 30/144 (20.8)              | 22/117 (18.8)              | 6/19 (31.6)              | 1.99 (0.7–5.8)        |
| Work-related wheeze                                                                    | 9/144 (6.3)                | 6/117 (5.1)                | 3/19 (15.8)              | 3.5 (0.8–15.3)        |
| Work-related chest tightness                                                           | 19/144 (13.2)              | 12/117 (10.3)              | 6/19 (31.6)              | <b>4.0 (1.3–12.6)</b> |
| Work-related cough                                                                     | 19/144 (13.2)              | 15/117 (12.8)              | 3/19 (15.8)              | 1.3 (0.3–4.9)         |
| Work-related nasal symptoms                                                            | 16/144 (11.1)              | 9/117 (7.7)                | 5/19 (26.3)              | <b>4.3 (1.3–14.6)</b> |
| “Flu-like” illness consisting of fever, aching and tiredness after working on soy mill | 25/105 <sup>b</sup> (23.8) | 16/83 (19.3)               | 5/14 (35.7)              | 2.3 (0.7–7.9)         |
| Cough or chest tightness after handling soybean                                        | 27/105 (25.7)              | 18/83 (21.7)               | 7/14 (50)                | <b>3.6 (1.1–11.6)</b> |

n = number of workers. Bold used to denote statistically significant confidence limits.

<sup>a</sup>136 Study volunteers provided serum for analysis of soybean sensitization.

<sup>b</sup>105 Study volunteers answered questions regarding “flu-like” illness or cough or chest tightness after handling soybean (of these, only 97 had provided serum for analysis of soybean sensitization).

**TABLE III.** Work-Related Symptoms and Exposure to Dust During Soybean Off-Loading

|                                                                                        | Not currently exposed<br>to dust during<br>soybean off-loading | Currently exposed<br>to dust during<br>soybean off-loading | Odds Ratio<br>(95% CI) |
|----------------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------|------------------------|
|                                                                                        | No. (%)                                                        | No. (%)                                                    |                        |
| Any work-related respiratory symptoms                                                  | 11/60 (18.3)                                                   | 27/84 (32.1)                                               | 2.1 (0.9–5.0)          |
| Work-related respiratory lower symptoms                                                | 9/60 (15)                                                      | 21/84 (25)                                                 | 1.9 (0.9–4.5)          |
| Work-related wheeze                                                                    | 3/60 (5)                                                       | 6/84 (7.14)                                                | 1.5 (0.4–6.1)          |
| Work-related chest tightness                                                           | 6/60 (10)                                                      | 13/84 (15.5)                                               | 1.7 (0.6–4.6)          |
| Work-related cough                                                                     | 6/60 (10)                                                      | 13/84 (15.5)                                               | 1.7 (0.6–4.6)          |
| Work-related nasal symptoms                                                            | 7/60 (11.6)                                                    | 9/84 (10.7)                                                | 0.9 (0.3–2.6)          |
| “Flu-like” illness consisting of fever, aching and tiredness after working on soy mill | 7/57 (12.3)                                                    | 18/57 (31.6)                                               | <b>2.7 (1.0–7.2)</b>   |
| Cough or chest tightness after handling soybean                                        | 4/48 (8.3)                                                     | 23/57 (40.4)                                               | <b>7.4 (2.4–23.6)</b>  |

Bold used to denote statistically significant confidence limits.

Soybean is an important source of protein worldwide, and has long been recognized to be an asthmagen. Despite this, to our knowledge there have only been two other studies published relating to soybean processing workers [Zuskin et al., 1988, 1991; Cummings et al., 2010]. In the Yugoslavian study, acute work-related symptoms were common, with cough, nasal symptoms, and wheezing being reported by 56%, 41%, and 30% of workers, respectively. In the study by Cummings et al., workers with soy-specific IgE had a significant excess of current asthma or asthma-like symptoms, but whilst work-related sinusitis, nasal allergies, and rash were associated with reported workplace mould exposure, they did not relate to soy-specific IgE. This prevalence of symptoms is clearly much higher than we found in our study, where the corresponding figures for work-related symptoms were cough in 13%, nasal symptoms in 11%, and wheeze in 6%. This may in part be explained by differences in smoking prevalence, as most of the Yugoslav workers were current smokers, whereas only half of the South African workers smoked. Another key factor is likely to relate to the level of exposure to soybean dust in the different workplaces. In the Yugoslav study, total inhalable dust levels were high, with a mean (range) of 29.5 (7.7–59.9) mg/m<sup>3</sup>. This average level was approximately three-times higher than the recommended maximum exposure standard in that country at the time of the study. In general, the dust levels recorded in the South African workplaces were lower, with a median (range) total inhalable level of between 0.25 and 3.94 (0.02–35.02) mg/m<sup>3</sup> in the three participating plants [Spies et al., 2008]. Although we found high odds ratios for cough or chest tightness after handling soybean in the medium and high exposure categories, this effect was not significant in the regression model.

Another potential reason for the differences seen in symptom prevalences may relate to study size. The studies

by Zuskin et al. involved low numbers of workers introducing the potential for selection bias, whereas the more recent study [Cummings et al., 2010] had numbers of workers comparable to our study.

Whilst the previous study of Yugoslav soybean workers did not identify any clear risk factors for work-related symptoms, [Zuskin et al., 1988, 1991] atopy, past cigarette smoking, and soybean sensitization have previously been demonstrated to be risk factors for the development of soybean epidemic asthma [Sunyer et al., 1992]. Our study notes consistent findings with those from the recent study from the US [Cummings et al., 2010] demonstrating an increased risk of work-related symptoms in workers sensitized to soybean. In the regression model, sensitized workers were at an approximately 20-fold increased risk of reporting symptoms suggestive of occupational rhinitis. We also found that current smoking was an independent risk factor for reporting work-related wheeze, which interestingly was not the case for work-related cough or chest tightness.

Our study found that 14% of workers were sensitized to soybean allergen, a prevalence very similar to the 16% found in the Yugoslav study. This level of sensitization is approximately three-times higher than levels reported in South African non-exposed controls [Roodt and Rees, 1995].

Atopy has been associated with an increased risk of sensitization in workers exposed to a number of occupational allergens including; acid anhydrides; [Welinder et al., 2001] bakery allergens; [Houba et al., 1998] castor and green coffee beans; [Osterman et al., 1982; Romano et al., 1995] enzymes; [Zentner et al., 1997; Cullinan et al., 2000] laboratory animals; [Cullinan et al., 1999] and shellfish [Cartier et al., 1984; McSharry et al., 1994]. Our study demonstrated that atopy is also strongly associated with sensitization to soybean, with atopic workers having an

approximately 35-fold increased risk. Previous research has found conflicting results for smoking as a risk factor for allergen sensitization; smokers were not at significantly increased risk of soybean sensitization in our study. Whilst it is most plausible that atopic status dictates the increased risk of soybean sensitization, this cross sectional study cannot exclude a reverse causation hypothesis; that soybean sensitization per se increases the general response to other commonly encountered aeroallergens.

This study found an elevated risk of work-related airway symptoms and constitutional flu-like symptoms in workers exposed to dust during soybean off-loading, the aetiology of which is unclear. Previous work has not documented constitutional symptoms associated with this type of work. In general, this type of flu-like symptom following organic dust exposure may relate to one of two main aetiologies, that is organic dust toxic syndrome [ODTS; Von Essen et al., 1999] or HP. Whilst there has been a single case report of HP due to soybean exposure from handling animal feeds, [Zubeldia et al., 1995] soybean handling amongst farmers has not been identified as a risk factor for ODTS [Von Essen et al., 1999].

Although not fully understood, exposure to inhaled endotoxin has been implicated in the aetiology of ODTS [Kirkhorn and Garry, 2000]. Although personal exposures to inhaled endotoxin were not measured, the level of endotoxin in bulk samples of soybeans was assessed from the three worksites. This demonstrated that although the levels of endotoxin varied between samples from the different worksites, they were consistently higher in the soybean hulls than in the actual bean. The endotoxin concentration in the hulls was between 727 and 13,611 ng/mg, which is considerably higher than levels found in a range of agricultural seeds [grass 5.9–36 ng/mg, cereal 0.3–8.6 ng/mg, and maize 0.05–0.7 ng/mg] thought to be the cause of ODTS in seed inspection workers [Smit et al., 2006]. It is therefore possible that similar endotoxin exposures during off-loading unprocessed soybean may also be a cause of ODTS. Clearly this area requires further study, ideally linking symptoms with personal endotoxin exposure measurements, and including a more detailed assessment of unprocessed soybean for fungi and other inflammatory constituents.

This study has certain downsides that need to be considered. There are no data relating to worker turnover, and the healthy worker effect is likely to preferentially allow healthier workers to remain at work. This will reduce the magnitude of work causation identified, as certain workers with significant work related respiratory complaints may leave the work environment early. It is unlikely that a significant participation bias exists as the response rate was very high, although it is plausible that certain affected workers chose not to respond. This, again, would underestimate the magnitude of any work related effect measured.

In addition, there were insufficient data to allow duration of work at each site to be consistently entered into any regression analysis. The logistics of this study also prevented further clinical characterization of these workers, and in particular lack of information relating to respiratory protection, airway reactivity measures and detailed exposure measures make the construction of a dose response function more difficult. Additionally, no data were available on non-responders. Nevertheless, the good response rate in principle allows generalization of the findings to other similarly exposed populations. Ultimately and additionally, relatively low numbers of those with outcome of interest may also potentially affect the interpretation of the regression analysis.

In summary, this study has demonstrated that atopy is a risk factor for developing soybean sensitization amongst South African soybean processing workers, with sensitized workers being at increased risk of developing occupational rhinitis. Work off-loading unprocessed soybean as it arrives at the workplace was associated with a significantly increased reporting of work-related cough/wheeze, and constitutional symptoms, the aetiology of which was not clear from this study. These findings merit further study, in parallel with developing the most appropriate intervention strategies.

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## REFERENCES

- Antó JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M, Vazquez L. 1989. Community outbreaks of asthma associated with inhalation of soybean dust. *New England J Med* 320:1098–1102.
- Baur X, Pau M, Czuppon A, Fruhmann G. 1996. Characterisation of soybean allergens causing sensitization of occupationally exposed bakers. *Allergy* 51:326–330.
- Bush RK, Cohen M. 1977. Immediate late onset asthma from occupational exposure to soybean dust. *Clin Allergy* 7:369–373.
- Cartier A, Malo JL, Forest F, Lafrance M, Pineau L, St-Aubin JJ, Dubois JY. 1984. Occupational asthma in snow crab-processing workers. *J Allergy Clin Immunol* 74(3 Pt 1):261–269.
- Codina R, Lockey RF. 1998. Possible roles of molds as secondary etiologic agents of the asthma epidemics in Barcelona, Spain. *J Allergy Clin Immunol* 102:318–320.

- Codina R, Lockey RF, Fernández-Caldas E, Rama R. 1999. Identification of the soybean hull allergens responsible for the Barcelona asthma outbreaks. *Int Arch Allergy Immunol* 119(1):69–71.
- Cullinan P, Cook A, Gordon S, Nieuwenhuijsen MJ, Tee RD, Venables KM, McDonald JC, Taylor AJ. 1999. Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. *Eur Respir J* 13(5):1139–1143.
- Cullinan P, Harris JM, Newman Taylor AJ, Hole AM, Jones M, Barnes F, Jolliffe G. 2000. An outbreak of asthma in a modern detergent factory. *Lancet* 356(9245):1899–1900.
- Cummings KJ, Gaughan DM, Kullman GJ, Beezhold DH, Green BJ, Blachere FM, Bledose T, Kreiss K, Cox-Ganser J. 2010. Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. *ERJ* 36(5):1007–1015.
- González R, Polo F, Zapatero L, Caravaca F, Carreira J. 1992. Purification and characterization of major inhalant allergens from soybean hulls. *Clin Exp Allergy* 22(8):748–755.
- Green BJ, Cummings KJ, Rittenour WR, Hettick JM, Bledose TA, Blachere FM, Siegel PD, Gaughan DM, Kullman GJ, Kreiss K, Cox-Ganser J, Beezhold DH. 2011. Sensitization to soy allergens in workers at a processing facility. *Clin Exp Allergy* 41(7):1022–1030.
- Harris-Roberts J, Robinson E, Waterhouse JC, Billings CG, Proctor AR, Stocks-Greaves M, Rahman S, Evans G, Garrod A, Curran AD, Fishwick D. 2009. Sensitisation to wheat flour and enzymes and associated respiratory symptoms in British bakers. *Am J Ind Med* 52(2):133–140.
- Hernando L, Navorro C, Márquez M, Zapatero L, Galván F. 1989. Asthma epidemics and soybean in Cartagena (Spain). *Lancet* 1:502.
- Houba R, Doekes G, Heederik D. 1998. Occupational respiratory allergy in bakery workers: A review of the literature. *Am J Ind Med* 34(6):529–546.
- Kirkhorn SR, Garry VF. 2000. Agricultural lung diseases. *Environ Health Perspect* 108 (Suppl 4): 705–712.
- Maggio P, Monsó E, Baltasar M, Morera J. 2003. Occupational asthma caused by soyabean hull: A workplace equivalent to epidemic asthma. *Allergy* 58:350–351.
- McSharry C, Anderson K, McKay IC, Colloff MJ, Feyerabend C, Wilson RB, Wilkinson PC. 1994. The IgE and IgG antibody responses to aerosols of *Nephrops norvegicus* (prawn) antigens: The association with clinical hypersensitivity and with cigarette smoking. *Clin Exp Immunol* 97(3):499–504.
- Minette A. 1989. Questionnaire of the European Community for Coal and Steel (ECSC) on respiratory symptoms. 1987 updating of the 1962 and 1967 questionnaires for studying chronic bronchitis and emphysema. *Eur Respir J* 2:165–177.
- Osterman K, Zetterstrom O, Johansson SG. 1982. Coffee worker's allergy. *Allergy* 37(5):313–322.
- Quirce S, Fernandez-Nieto M, Polo F, Sastre J. 2002. Soyabean trypsin inhibitor is an occupational inhalant allergen. *J Allergy Clin Immunol* 109:178.
- Rodrigo MJ, Morell F, Helm RM, Swanson M, Greife A, Anto JM, Sunyer J, Reed CE. 1990. Identification and partial characterisation of the soybean-dust allergens involved in the Barcelona asthma epidemic. *J Allergy Clin Immunol* 85:778–784.
- Romano C, Sulotto F, Piolatto G, Ciacco C, Capellaro E, Falagiani P, Constable DW, Verga A, Scansetti G. 1995. Factors related to the development of sensitization to green coffee and castor bean allergens among coffee workers. *Clin Exp Allergy* 25(7):643–650.
- Roodt L, Rees D. 1995. Tests for sensitisation in occupational medicine practice—The soy bean example. *S Afr Med J* 85(6):522–525.
- Smit LAM, Wouters IM, Hobo MM, Eduard W, Doekes G, Heederik D. 2006. Agricultural seed dust as a potential cause of organic dust toxic syndrome. *Occup Environ Med* 63:59–67.
- Spies A, Rees D, Fourie AM, Wilson KS, Harris-Roberts J, Robinson E. 2008. Inhalable dust and protein exposure in soybean processing plants. *Int J Occup Environ Health* 14(3):187–192.
- Sunyer J, Anto JM, Sabria J, Rodrigo MJ, Roca J, Morell F, Rodriguez-Roisin R, Codina R. 1992. Risk factors of soybean epidemic asthma. The role of smoking. *Am Rev Respir Dis* 145:1098–1102.
- Von Essen S, Fryzek J, Nowakowski B, Wampler M. 1999. Respiratory symptoms and farming practices in farmers associated with an acute febrile illness after organic dust exposure. *Chest* 116(5):1452–1458.
- Welinder H, Nielsen J, Rylander L, Stahlbom B. 2001. A prospective study of the relationship between exposure and specific antibodies in workers exposed to organic acid anhydrides. *Allergy* 56(6):506–511.
- Zentner A, Jeep S, Wahl R, Kunkel G, Kleine-Tebbe J. 1997. Multiple IgE-mediated sensitizations to enzymes after occupational exposure: Evaluation by skin prick test, RAST, and immunoblot. *Allergy* 52(9):928–934.
- Zubeldia JM, Gil P, Miralles P, de Barrio M, Aranzábal A, Herrero T, Rubio M, Bouzas E, Baeza ML. 1995. Hypersensitivity pneumonitis caused by soybean antigens. *J Allergy Clin Immunol* 95:622–626.
- Zuskin E, Skuric Z, Kanceljak B, Pokrajac D, Schachter EN, Witek TJ, Jr. 1988. Respiratory symptoms and ventilatory capacity in soy bean workers. *Am J Ind Med* 14(2):157–165.
- Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Jr, Marom Z, Goswami S, Maayani S. 1991. Immunological and respiratory changes in soy bean workers. *Int Arch Occup Environ Health* 63(1):15–20.