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A Source-Specific Algorithm To Estimate Occupational (1→3)-**Β**-D-Glucan Exposure For Farmers In The Biomarkers Of Exposure And Effect In Agriculture Cohort

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A Source-specific Algorithm to Estimate Occupational (1→3)-β-D-glucan Exposure for Farmers in the Biomarkers of Exposure and Effect in Agriculture Cohort

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Abstract

Background: (1→3)-β-D-glucans, or simply known as glucans, are components of fungal cell walls and are associated with mold. The adverse health effects due to glucan inhalation exposure has not been well studied, but it is known that upper respiratory inflammation has been seen with glucan exposure. Farmers, especially those who work with animals, are exposed to glucans on a daily basis; however, there is no occupational exposure limit to glucans and the full extent of glucan exposure in this population is unclear due to the lack of exposure assessment. This study will utilize decision-rules and a source-specific method to create an algorithm that quantitatively estimates glucan exposure intensity and allows us to identify any farming activities associated with glucan exposure.

Methods: The study population consists of farmers in the Biomarkers of Exposure and Effect in Agriculture study (BEEA). Subjects participated in an in-home interview that gathered information on farming activities and the duration and frequencies of these activities. 32 of the BEEA farmers had an additional visit day where an industrial hygienist visited the farm to take personal air samples. Activities performed during each sample were noted by the industrial hygienist. Using this air sampling data, we derived glucan exposure levels and identified certain farming activities that had glucan exposures higher than background. Focusing on these particular tasks, we took the questionnaire data all the farmers in the BEEA population answered to figure out the duration and frequency they did these identified tasks. This information was used to find a glucan intensity score of exposure for the past 30 days, past 7 days, and past 1 day. We calculated the median glucan intensity score and median time spent doing these activities. To see how the activities compared to themselves and to others, we found the correlations between the different time frames and between the different tasks. Results were then compared in a validation assessment using full-shift data of the 32 farmers who participated in the air sampling study.

Results: We identified 6 tasks that had glucan exposures greater than background: working around moldy hay, spending time in poultry confinement, spending time in swine confinement, working around stored seed, cleaning grain bins, and working around wood dust. Highest median exposure and time spent was seen for swine confinement across all time frames: 9000 ng/m^3-hrs and 30 hours for the past 30 days, 4200 ng/m^3-hrs and 4 hours for the past 7 days, and 450 ng/m^3-hrs and 1.5 hours in the past 1 day. Within-task correlations comparing the different time frames were the highest in spending time in poultry confinement with a Spearman correlation of 0.94 between the past 30 day and 1 day exposure. The lowest within-task correlation was seen in cleaning grain bins with a Spearman correlation of 0.19 between the past 30 day and 1 day exposure. The correlations between tasks ranged from -0.23 to 0.25. The validation portion of the study showed that our calculated glucan scores for swine confinement (p-value=0.01) and cleaning grain bins (p-value=0.00) were statistically significant in being able to predict full-shift data.

Conclusions: From the algorithm, we were able to identify that animal activities, which are typically done on a daily basis, appear to contribute the most to glucan exposure. This study's usage of decision-rules for assessing glucan exposure has never been done before and begins to fill in the gap for glucan exposure assessment. While this algorithm created in this study is limited to a certain population, it provides the framework for further development of an algorithm for better glucan exposure assessment. This can then be used to link glucan exposure to adverse health effects and the development of an occupational exposure limit.

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1. Introduction

(1→3)-β-D-glucans, or most commonly referred to as glucans, are glucose polymers that originate from fungi, bacteria, and plants (Douwes et al., 2003). Glucans are components of these organisms' cell wall and are found in organic dusts or in mold (Fogelmark et al., 1994). The traditional way of assessing mold using culture-based quantification can be difficult due to easy contamination, differing growing rates, and variable environments between species (Borchers et al., 2017). Glucans have served as a way to more accurately assess mold exposure since it pinpoints one specific compound. The relationship between glucans and adverse health effects is not well established; however, studies have shown that exposure to airborne glucans play a role in bioaerosol-induced inflammatory responses and resulting respiratory symptoms (Douwes et al., 2003). Glucan exposure has been associated with an increase in the severity of symptoms of nose and throat irritation, which can be potentially due to its immune stimulatory properties as indicated by activation of neutrophils and stimulation of macrophages and eosinophils (Douwes, 2005; Rylander, 1999; Tischer et al., 2011).

Currently, there are no internationally or nationally accepted exposure limits for airborne concentrations of glucans in occupational environments despite studies showing certain working populations experience a higher exposure to glucans (Adhikari et al., 2011). High glucan exposure has been seen in metal plant workers, wastewater treatment workers, waste composting plant workers, composting facilities, greenhouse workers, poultry workers, farmers, cotton growers, veterinarians, and workers handling animal feed and grain (Cyprowski et al., 2011; Douwes et al., 2003; Madsen et al., 2014; Samadi et al., 2013; Sykes et al., 2011; Viegas et al., 2017; Wouters et al., 2006). Farmers, especially animal farmers, appear to be exposed the most to glucans as they live and work long hours on their farms. Understanding exposure levels can help evaluate potential risks in farming work, but the current work on glucan exposures in this population is limited. Excluding one paper (Sauvé et al., 2020), most studies looking at glucan exposure in agricultural settings have been conducted outside of the United States (Lawniczek-Walczyk et al., 2013; Viegas et al., 2017).

Glucan exposure assessment is typically performed in three ways: dust collection, biomonitoring, and air sampling. Dust collection studies include analyzing desposited dust for glucans and is typically used for indoor air exposure (Tischer et al., 2011). This method, however, does not give personal exposure. Biomonitoring includes analysis of serum immunoglobulin IgG but is not recommended as IgG responses are non-specific to glucans and can be elevated or decreased due to other exposures (Borchers et al., 2017). Air sampling includes using a personal or stationary air monitor to collect particulate matter and then is subsequently analyzed with an immunoassay (Madsen et al., 2014). For glucans in particular, personal air sampling seems to be most accurate in terms of assessing exposure; however, different laboratories may use different immunoassays which can result in varying outcomes (Brooks et al., 2013). Exposure assessment through these three methods can give variable glucan levels and are costly in terms of money and time.

There is both variation in what activities farmers do day to day and between different farmers. This heterogeneity will result in differences in their estimated glucan levels. Although air sampling can be accurate in measuring exposure, this heterogeneity can lead to inaccurate conclusions on actual exposure. Other methods to assess exposure that account for variability and utlize existing exposure data include job exposure matrices, individual job-by-job assessment by experts, and decision-rules. In this study, we will be using the decision-rules approach which links subject-reported information to quantitative measures. The decision-rules approach is a middle-ground approach that is a compromise between job exposure matrices and job-by-job assessments as it both aims to increase between-subject contrast while also assigning exposure with greater consistency, transparency, and reproducibility (Sauvé & Friesen, 2019). This method is a new but growing field of exposure assessment and methodological research has been going into the creation of exposure decision rules (Friesen et al., 2015). Although this particular approach has not been done for glucans, other studies have successfully used similar methods. For example, a study used data and questionnaire answers from a case-control study of childhood acute lymphoblastic leukemia to assess parental occupational exposures (Peters et al., 2014).

This study will utilize the decision-rules method to create an algorithm that quantitatively estimates glucan exposure intensity for participants in the Biomarkers of Exposure and Effect in Agriculture (BEEA) study. Decision rules were developed to assign estimates of exposure intensity and incorporated participants' answers to questions regarding certain farming activities involving glucan exposure. The purpose of this study is to describe the approach in developing these decision rules to estimate glucan exposure for BEEA participants and to help future occupational epidemiology research with similar exposure studies.

2. Methods: Algorithm Development and Application

2.1. Study Population

BEEA is a subset of the Agricultural Health Study (AHS) which is a prospective cohort study of 52,394 farmers and pesticide applicators from Iowa and North Carolina that were recruited into the study between 1993 and 1997 (Alavanja et al., 1996). BEEA was created to better understand the biological mechanisms underlying agricultural exposures and adverse health outcomes. 1,681 AHS participants that had completed phases 1 (1993-1997), 2 (1999-2003), and 3 (2005-2010) of follow-up questionnaires were recruited to BEEA in 2010 (Hofmann et al., 2015). These eligible participants were male, aged 50 years or older, never diagnosed with a primary site of cancer, and agreed to a home visit that included an interviewer-administered questionnaire and biospecimen collection (Sauvé et al., 2020). Two subsets of the BEEA population participated 2-3 times in the home-visit. The first subset was the air monitoring group that was created to assess bioaerosol exposure (32 farmers) and the second subset was the recently exposed group that assessed permethrin exposure (30 farmers). Participants were visited during different seasons from 2014 to 2017.

The BEEA specific questionnaire included information on general participant characteristics and questions regarding frequency and duration of pesticide use, crops grown, animals raised, time spent in animal confinements, and performance of specific farming tasks (Hofmann et al., 2015). The questionnaire changed mid-study so 1,011 participants got earlier versions (versions 1 and 2) and 317 participants got newer versions (versions 3 and 4) that included more detailed questions on bioaerosol-related tasks. This study was restricted to only those who completed versions 3 and 4 of the questionnaire.

2.2. Exposure Assessment

Exposure level data was taken via air sampling for those in the air monitoring group. A total of 32 out of the 1,681 BEEA farmers were recruited to participate in this bioaerosol sampling study the day before their BEEA interview/phlebotomist visit (Sauvé et al., 2020). These participants lived within approximately 1 hour of Iowa City and needed to be available for air sampling the day before the comprehensive interview. On the day of air sampling, an industrial hygienist visited the farm to collect these samples. Samples were collected using Button aerosol samplers (SKC Inc, No. 225-360, Eighty Four, PA) with 25 mm binder-free glass fiber filters connected to air sampling pumps (BGI OMNI-400, MesaLabs, Butler, NJ, or SKC model 224-PCXR4, SKC Inc, Eighty Four, PA) at a 4 L/min flow rate. Air samplers were in a backpack or waist-pack that the farmers carried, and the inlet was located in the farmer's breathing zone. Sampling devices were calibrated before and after the visit and field blanks were collected after every 10 samples. Two types of personal inhalable dust samples were collected: short-term samples representing exposure for a single activity (i.e., task-based sample) and samples to characterize time-weighted average exposure that spanned for the entire day (full-shift sample). The industrial hygienist recorded the activity type corresponding to each short-term sample. Samples were then analyzed for glucans by using the *Limulus* Amebocyte Lysate (LAL) factor G pathway.

The BEEA questionnaire that was used in the interview the day following air sampling included questions that asked about bioaerosol related farming tasks. See Appendix A for a list of all the full questions and their tasks relating to bioaerosols. Using the questions as a guide as to what tasks to focus on, we looked through our existing data to see whether or not we had air sampling information associated with that particular task. To supplement our existing air sampling data as well as information for tasks we did not have measurements for, we did a literature search to see if other studies did something similar and to combine with our data.

2.3. Algorithm Development: Task-Specific Exposure Intensity

Next, we wanted to identify which of the bioaerosol related tasks had glucan levels above background. A numerical exposure value was identified, and this value was categorized as background, low, medium, or high glucan exposure. To find this numerical exposure value, we used two different methods.

The first method utilized models from the Sauvé et al., 2020 paper. These models were developed from the task-based samples from air sampling day and used multilevel models to estimate coefficients and standard errors of glucan exposure levels. The model outputs provided the EXP(β) of the intercept and variables relating to the tasks. We calculated predicted glucan geometric means (GM) from these model coefficients. In order to obtain the GM glucan exposure information from the paper, we used Table 3 for livestock-related tasks, Table 4 for crop-related tasks, and Table 2 for tasks that we could not derive the proper variables for from the other tables. Table 3 provided results from a model that considered location on the farm, number of animals, sampling duration, temperature, relative humidity, and season. Table 4 provided results from a model that considered location on the farm, production phase, crop type, sampling duration, temperature, relative humidity, and season. Table 2 provided results from a model that considered task, sampling duration, temperature, relative humidity, and season. We picked the variables that contributed to each individual BEEA task and multiplied the coefficients together to get a GM. See Appendix B for the variables used for each task.

The second method used the air sampling data directly to calculate GMs. We identified the geometric mean from raw air sampling data if the task we were looking at was not well represented in the model (for instance, a task was a subset of a broader activity in the model; e.g. mixing animal feed was a subset of the general feed work category) or was taken from outside literature.

Numbers from the two methods outlined were used to estimate exposure intensities. Once we had the exposure intensities, we then determined exposure categories. From these categories, we were able to identify glucan specific tasks. We assumed that all farmers had a background exposure to glucans, so we focused on tasks with an estimated GM greater than 20 ng/m^3, a value derived based on the calculated exposure intensities. Low, medium, and high exposure categories were assigned based on expert opinion from industrial hygienists.

2.4. Algorithm Development: Task Frequencies and Duration

The last part of the algorithm development was to figure out timing elements for each task based on the BEEA questionnaire. There were four different types of questions and answers that were included in the questionnaire. For each type of question, we decided on a midpoint within each frequency category to standardize the time performed for each task.

For the first question type, the farmer was asked about the frequency and duration at which they did an activity in the past 30, 7, and 1 day in terms of days. The farmer was given 3 frequency categories to choose from. For the second and third type of question, the farmer was asked about frequency and duration at which they did an activity in the past 30, 7, and 1 day in terms of hours and minutes. The farmer was given 4-5 frequency categories to choose from. For the fourth type of questions, the farmer was asked about the number of times at which they performed a certain task in the past 30, 7, and 1 day. The farmer was given 4 frequency categories to choose from. Since the fourth type of question only asked about the number of times a farmer performed an activity, an additional part to the question was asked to capture the full duration the farmers performed these particular tasks. This needed to be standardized as well. See Table 1 for question formats and final midpoints used.

[Table 1: BEEA questionnaire question types - format and midpoints]

Question	**Frequency Category Options**	**Midpoints**
Question Type 1		
"How many days have you [performed an activity] in the last 30 days?"	None 1-3 Days 4-7 Days 8 or More Days	0 days 2 days 5 days 10 days
"How many days have you [performed an activity] in the last 7 days?"	None 1-3 Days 4-7 Days	0 days 2 days 5 days
"Did you [perform an activity yesterday or today"	Yes No	N/A
Question Type 2		
"How much time did you spend [performing an activity] in the past 30 days?"	None <=7 hours >7-20 hours >20-40 hours >40 hours	0 hours 4 hours 14 hours 30 hours 60 hours
"How much time did you spend [performing an activity] in the past 7 days?"	None <=7 hours >7-20 hours >20-40 hours	0 hours 4 hours 14 hours 30 hours
"How much time did you spend [performing an activity] yesterday/today?"	None <30 min 30-60 min 1-2 hours >2 hours	0 minutes 15 minutes 45 minutes 90 minutes 150 minutes
Question Type 3		
"How much time did you spend [performing an activity] in the past 30 days?"	None <= 7 hours >7-20 hours >20-40 hours >40 hours	0 hours 4 hours 14 hours 30 hours 60 hours

"How much time did you spend [performing an activity] in the past 7 days?"	<= 7 hours >7-20 hours > 20 hours	0 hours 4 hours 14 hours 30 hours
"How much time did you spend [performing an activity] yesterday/today?"	None <30 min 30-60 min 1-3 hours > 3 hours	0 minutes 15 minutes 45 minutes 120 minutes 200 minutes
	Question Type 4 - Frequency	
"In the last month, how many times have you [performed and activity]?"	Not at all 1-3 times 4-20 times >20 times	0 times 2 times 12 times 25 times
"How many times have you [performed an activity] in the last 7 days?"	Not at all 1-3 times 4-7 times >7 times	0 times 2 times 5 times 8 times
"Did you [perform an activity] yesterday?"		N/A
	Question Type 4 - Duration	
"Each time you did this, on average how long did you spend [performing an activity?"	<10 min 10-30 min 30 min-1hr >1 hr	5 minutes 20 minutes 45 minutes 90 minutes

2.5. Application to Population

We developed equations that calculated a glucan intensity score (in ng/m^3-hrs) based on the exposure intensity, frequency, and duration components of each task that we found previously. These equations were applied to the BEEA farmers in order to find task-specific and total glucan exposure for the past 30 days, 7 days, and 1 day. For example, the swine confinement glucan intensity score for the past 30 days was equal to exposure estimate times the hours indicated by the questionnaire response on the number of hours they spent on that activity.

$$Glucan\ exposure\ swine\ confinement\ 30days = exposure\ intensity\ *\ hours[Question\ Response\ for\ past\ 30\ days]$$

See Appendix C for the rest of the equations developed and used. If the farmer indicated that they did not perform a particular task, we assumed that their glucan exposure for that task would be zero.

2.6. Statistical Analysis

2.6.1. Descriptives Analyses

We calculated the median and interquartile range (IQR) of the time spent doing an activity if the activity was identified as having an exposure level above background (20 ng/m^3). This was calculated from participant responses to the questionnaire and the midpoints outlined previously. We also found the median and IQR glucan exposure level for farmers that participated in any of the glucan-related tasks. The equations detailed in the previous section were used to calculate these values. Both medians and IQRs were calculated only if the participant had a glucan intensity score greater than zero for that particular task.

2.6.2. Correlation Analyses

Correlations between the glucan intensity scores for a task done in the past 30 days, 7 days, and 1 day (within-task correlation) and the glucan exposures between the tasks (between-task correlation) were assessed using a Spearman correlation. This was done if the participant had a total exposure level in the past 30 days that was greater than 0. Within-task correlations were found to see if 1 day exposure measurements could predict 7 day or 30 day exposure. Between-task correlations were calculated to see if any of the tasks were related to each other. The correlation was also found between individual tasks and the total intensity score in order to see which tasks contributed the most to total exposure.

2.6.3. Statistical modeling of total glucan exposure

After developing the algorithm, we wanted to see how well it predicted actual glucan exposure levels and to validate our algorithm. As mentioned in the exposure assessment section, we had available time-weighted average (TWA) full-shift data from the 32 farmers in the bioaerosol sampling study. There were a total of 56 samples since 24 of these farmers were visited twice. We compared the full-shift data to the algorithm calculation for each task as well as for the total glucan score in the past 1 day.

Four multilevel mixed effects model were performed with glucan TWA level as the dependent level. All models included individual subjects as a random effect due to most pariticpants having 2 visits. The first model was the null model with no independent variables; the second model had the algorithm glucan total as the independent variable; the third model had task-specific glucan levels as the independent variable; and the independent variable in the fourth model was a dichotomous variable indicating whether the farmer did the activity during the sampling day. All analyses were performed in STATA.

3. Results

3.1. Exposure Assessment

We had 10 bioaerosol related questions that referred to 19 specific tasks in the BEEA questionnaire. See Appendix A again for list of full questions and their tasks. We did not have any air sampling data associated with harvesting cotton and hauling cotton. We decided to search for other glucan exposure studies to supplement this gap in data and as well as to bolster our existing data.

We identified 5 studies that included glucan exposure assessment (Burch et al., 2010; Halstensen et al., 2007; Lawniczek-Walczyk et al., 2013; Roy & Thorne, 2003; Singh et al., 2011). However, all 5 studies were not ultimately included along with our measurements. Roy and Throne, 2003 and Halstensen et al., 2007 used a different immunoassay for analyzing glucan levels since they used an inhibition enzyme immunoassay rather than LAL. The samples in the Burch et al., 2010 study were not task-based. Singh et al., 2011 and Lawniczek-Walczyk et al., 2013 utilized area samples and did not do any personal sampling.

Due to the lack of data from our own air sampling measurements and other studies, the harvesting cotton and hauling cotton tasks were dropped from further analysis. Only 1 BEEA participant harvested cotton and none hauled cotton.

3.2. Algorithm Development: Task-Specific Exposure Intensity

The Sauvé et al., 2020 model provided sufficient information to estimate exposure intensity for the following tasks: harvesting grain/soy/corn, hauling grain/soy/corn, baling alfalfa/hay, spending time in poultry confinement, spending time in poultry confinement, cleaning poultry confinement, mixing poultry feed, spending time in swine confinement, cleaning swine confinement, mixing swine feed, working around stored seed, grinding animal feed, cleaning grain bins, working around moldy hay, milking animals, and cleaning barns. See Appendix B again for the exposure variables considered for the estimate. For the remaining two tasks, hauling alfalfa/hay and working around wood dust, there was not a clear way to derive an estimate from the model so the raw air sampling data was used. See Table 2 for all task-specific exposure estimates. These estimates were only to 1 significant figure due to the data only coming from one air sampling study.

Once we figured out an intensity estimate for glucan exposure, we derived four different exposure level categories with the help of an industrial hygienist and assigned each task a level (see Table 2). Glucan estimates below 20 ng/m3 were considered background, estimates from 20-80 ng/m3 were considered low exposure, estimates from 80-200 ng/m3 were considered medium exposure, and estimates over 200 ng/m3 were considered high exposure.

6 tasks had levels higher than background: working around moldy hay, spending time in poultry confinement, spending time in swine confinement, working around stored seed, cleaning grain bins, and working around wood dust. These were the tasks that will be put in the algorithm and further analyzed for the rest of the study.

[Table 2: Task-specific exposure estimates and exposure category]

Task	**Exposure Estimate (ng/m^3)**	**Exposure Category**
Working around moldy hay	500	High
Spending time in poultry confinement	300	Medium
Spending time in swine confinement	300	Medium
Working around stored seed	50	Low
Cleaning grain bins	50	Low
Working around wood dust	30	Low

3.3. Application to Population

3.3.1. Descriptives

There were 317 participants included in our analysis and a total of 534 BEEA questionnaire responses. Spending time in swine confinement was the task that was performed for the greatest number of hours. For the past 30 days, the median time spent was 30 hours; for the past 7 days, the median time spent was 4 hours; and for the past 1 day, the median time spent was 1.5 hours.

Spending time in swine confinement had the highest median glucan score for all timepoints. For the past 30 days, the median glucan score was 9000 ng/m^3-hrs; for the past 7 days, the glucan score was 4200 ng/m^3-hrs; and for the past 1 day, the glucan score was 450 ng/m^3-hrs.

Working around stored seed had the highest number of farmers who performed the task. For the past 30 days, 265 (50%) of farmers performed the task; for the past 7 days, 182 (34%) of farmers performed the task; and for the past 1 day, 115 (22%) of farmers performed the task.

See table 3 below for full descriptives of median time spent, median exposure based on the algorithm glucan level, and number of farmers who responded "yes" for each task.

[Table 3: Time spent, glucan exposure level, and number of BEEA participants for each task]

Task		**Number Yes**	**%**	**Median Time Spent (hrs)**	**IQR Time Spent**	**Median Exposure Exp > 0 (ng/m^3-hrs)**	**IQR Exposure**
Working with or around moldy hay or straw							
	Past 30 Days	109	20	1.5	(0.7-4)	750	(333-2000)
	Past 7 Days	79	15	0.7	(0.4-1.7)	333.3	(208-833)
	Past 1 Day	46	9	0.3	(0.1-0.8)	166.7	(42-375)
Spending time in poultry confinement area							
	Past 30 Days	6	1	9	(4-26)	2700	(1200-9000)
	Past 7 Days	5	1	4	(4-12)	1200	(1200-4200)
	Past 1 Day	5	1	1.5	(0.8-1.5)	450	(75-450)
Spending time in the swine confinement area							
	Past 30 Days	42	8	30	(14-60)	9000	(4200-18000)
	Past 7 Days	37	7	4	(4-14)	4200	(1200-4200)
	Past 1 Day	32	6	1.5	(0.3-2.5)	450	(338-900)

Working around stored seed or grain							
	Past 30 Days	265	50	8.3	(2.1-18)	416.7	(104-900)
	Past 7 Days	182	34	1.7	(0.7-3.8)	83.3	(42-188)
	Past 1 Day	115	22	0.8	(0.3-1.5)	37.5	(17-75)
Cleaning grain bins							
	Past 30 Days	111	21	3	(1.5-3)	150	(75-150)
	Past 7 Days	48	9	1.5	(1.5-3)	75	(75-150)
	Past 1 Day	18	3	0.8	(0.3-1.5)	37.5	(17-75)
Working around wood dust							
	Past 30 Days	197	37	4	(4-14)	120	(120-420)
	Past 7 Days	112	21	4	(4-14)	120	(120-420)
	Past 1 Day	44	8	45	(0.3-2)	60	(8-120)
Total							
	Past 30 Days	388	73			666.3	(200-1995)
	Past 7 Days	334	63			120	(120-900)
	Past 1 Day	195	37			75	(38-204)

3.3.2. Correlations

For the correlations looking at the relationship between exposure scores in the past 30 days, 7 days, and 1 day for individual tasks, the highest correlation was seen within the spending time in poultry confinement task. The past 7 day and 1 day exposure score had a correlation of 0.91; the past 30 day and 1 day exposure score had a correlation of 0.94; and the past 30 day and 1 day exposure score had a correlation of 0.87. The lowest within-task correlation was seen in the working with stored seed task. The past 7 day and 1 day exposure score had a correlation of 0.45; the past 30 day and 1 day exposure score had a correlation of 0.14; and the past 30 day and 1 day exposure score had a correlation of 0.19. See table 4 for all within-task correlations.

[Table 4: Within task correlations if 30 day glucan exposure was greater than 0]

	Spearman's Correlation Coefficients		
Task (N's if Exp>0 for Past 30 Days)	**Past 30 vs 7 Days**	**Past 30 vs 1 Day**	**Past 7 Days vs 1 Day**
Working around moldy hay (N=109)	0.70	0.52	0.63

Spending time in poultry confinement (N=6)	0.87	0.94	0.91
Spending time in swine confinement area (N=42)	0.83	0.58	0.71
Working around stored seed (N=265)	0.65	0.45	0.66
Cleaning grain bins (N=111)	0.19	0.14	0.45
Working around wood dust (N-197)	0.47	0.33	0.54
Total Glucan Exposure (N=388)	0.77	0.63	0.74

For the correlations looking at the relationship between exposures of all the tasks, the correlations were very low, ranging from -0.23 to 0.25. Spending time in swine confinement and working around stored seed had the highest correlation with total exposure with a Spearman correlation of 0.48 and 0.40 respectively. See table 5 for all between-task correlations.

[Table 5: Between task correlation if total glucan exposure was greater than 0]

	Spearman's Correlation Coefficients						
	Poultry confinement	Swine confinement	Stored seed/grain	Cleaning grain bins	Moldy hay	Wood dust	Total
Poultry confinement	1.00						
Swine confinement	0.02	1.00					
Stored seed/grain	-0.10	0.01	1.00				
Cleaning grain bins	-0.02	0.08	0.25	1.00			
Moldy hay	-0.03	-0.08	0.01	-0.08	1.00		
Wood dust	-0.09	-0.06	-0.23	-0.19	-0.05	1.00	
Total	0.14	0.48	0.40	0.17	0.41	0.14	1.00

3.3.3. Statistical modeling of total glucan exposure

Before preceding with the models, the total TWA glucan exposure had to first be log-transformed since the data was skewed. See table 6 for all model results. There was very little between-subject variability in all models but very large within-subject variability between the 32 farmers we had TWA data for. In model 2, the total glucan algorithm level had a p-value of 0.31, indicating score was not significantly associated with measured glucan concentration. In model 3, the predicted glucan concentration increased 1.5 times for every 100 unit increase in score for the swine confinement glucan score (p-value of 0.01). Similarly, the predicted glucan concentration increased 1.1 times for every unit increase in cleaning grain bin glucan score (p-value of 0.00). Swine confinement was looked at per 100 units to emphasize the predictiveness of the beta value. In model 4, the predicted glucan concentration increased 4.2 times for every time the farmer worked in swine confinement (p-value of 0.06). Similarly, the predicted glucan concentration increased 13.2 times for every time the farmer cleaned grain bins (p-value of 0.00).

[Table 6: Multilevel model with the logarithm of TWA glucan exposure as the dependent variable]

Model	**Independent Variable**	**N**	**β**	**SE**	**EXP(β)**	**P-value**	**Prob > chi2**	**Between Subj. Var**	**Within Subj. Var**
				Model 1					
Null								9.22E-24	4.06
	Intercept	56	2.9	0.3	18.2				
				Model 2					
Glucan Total (continuous scale)							0.31	1.16E-23	3.99
	Intercept		2.7	0.001	15.5				
	Total Glucan Score	56	0.0015	0.3	1.0	0.31			
				Model 3					
By Task-Specific Levels (continuous scale)							0.0003	2.84E-25	2.89
	Intercept		2.5	0.3	12.1				
	Moldy Hay Score	5	-0.0016	0.01	1.0	0.43			
	Swine Confinement Score (per 100 units)	3	0.42	0.200	1.5	0.01			
	Stored Seed Score	19	-0.0059	0.009	1.0	0.53			
	Cleaning Grain Bins Score	7	0.053	0.1	1.1	0.00			
	Wood Dust Score	4	0.0082	0.01	1.0	0.40			
				Model 4					
By Task (Yes/No)							0.01	1.29E-21	3.22
	Intercept		2.5	0.3	12.2				

	Moldy Hay Yesterday = Yes	5	-0.43	0.9	0.6	0.61			
	Swine Confinement Yesterday = Yes	3	1.4	0.7	4.2	0.06			
	Stored Seed Yesterday = Yes	19	-0.42	0.5	0.7	0.31			
	Cleaning Grain Bins Yesterday = Yes	7	2.6	0.7	13.2	0.00			
	Wood Dust Yesterday = Yes	4	0.64	0.9	1.9	0.50			

4. Discussion

This study adds to the limited work on glucan exposure in farmers. We were able to identify 6 different tasks that showcased glucan levels above background and could be targeted for exposure mitigation: working around moldy hay, spending time in poultry confinement, spending time in swine confinement, working around stored seed, cleaning grain bins, and working around wood dust.

4.1. Descriptives

Duration and glucan intensity information has allowed us to see that although working with moldy hay was categorized as a high exposure task, the median exposure score was moderately high due to the little amount of time the farmers performed this task. This could also be due to the fact that actually working with moldy hay is very hard to know. Unless one can very visibly spot or easily smell it, it will be difficult to assess whether or not a farmer is working with moldy hay. Questionnaire responses to this question may not accurately reflect exposure. In addition, the industrial hygienist during the observation time may not have categorized the air sample to be associated with working with moldy hay.

On the other hand, the duration and glucan intensity information allowed us to spot that spending time in swine confinement, although not categorized as high exposure, was the biggest contributor to glucan exposure. The high median exposure score and greater amount of time the farmers performed this task was most likely due to working with animals being typically a daily task. Daily tasks result in longer periods of time spent doing the activity and therefore higher exposure even if the task itself is not categorized as a high source of glucan exposure.

While there is no data to directly compare our intensities and glucan exposure scores to, other studies have showcased that glucans are found in the feed industry and poultry houses (Viegas et al., 2017). This aligns with our algorithm output that spending time in swine confinement was the biggest contributor to glucan exposure and in general, animal-related tasks will be associated with glucan exposure.

4.2. Correlations

Correlations within task were able to show us if 1 day measurements were correlated with 7 day measurements and 30 day measurements. Correlations within tasks were the highest for spending time in poultry confinement, spending time in swine confinement, working around stored seed and working around moldy hay which are typically done every day. This shows that the 1 day exposure can only predict potentially daily tasks. The other tasks, cleaning grain bins and working with wood dust, are not typically daily activities and therefore a 1 day exposure most likely cannot predict an exposure for a longer period of time as reflected by the lower correlations.

The correlations between tasks were very low (range -0.23 to 0.25), indicating that they were not related and that each of the final 6 tasks were unique contributors to the total exposure level of glucans. The correlations between the task and the total glucan score also showed us what tasks were contributing the most to the total glucan exposure level. Spending time in swine confinement and working around stored seed had higher correlations with the total glucan exposure, indicating that these were tasks that contributed the most to the total exposure level in this population.

4.3. Statistical modeling of total glucan exposure

The purpose of these models was to give some assessment of validity for our glucan scores using the TWA data. The high within-subject variability seen in all four models may be explained by the fact that participants who were visited twice were visited during two different seasons. Farming activity may differ between season so their glucan exposure levels will be different as a result. 24 out of the 32 participants were visited twice so this could be why the within-subject variability was so high. This within-subject variability is also reflected in the within-task correlations since the 1 day measurements were not entirely reflective of their 7 day or 30 day exposure, further demonstrating the variability farmers have in the tasks they do.

The models also showed that the total glucan score was not associated with the TWA data. In the model looking at the continuous glucan score, there were only two variables that were able to predict the TWA glucan total. Swine confinement glucan algorithm level and cleaning grain bin glucan algorithm level were the only two activities that were statistically significant to predict TWA glucan levels. The model with the dichotomous variables showcased that doing the cleaning grain bins activity was statistically significant in predicting TWA levels. While this validity analysis gives us a sense of how well our algorithm predicts actual glucan exposure levels, it was assessed in a very small dataset with low prevalence and the TWA data did not reflect the farmer's entire workday. These are factors that can contribute to the lack of statistically significance in this validity analysis.

4.4. Strengths and Limitations

The method of using decision rules and a source-specific approach in this study has not been seen with glucan exposure. While other studies have used a similar approach, nothing has been done for glucans specifically. Source-specific studies typically utilize self-reported questionnaire data on job and activities and then derive a source-specific estimate based on that and an existing measurement of exposure level (Callahan et al., 2018). This study was able to use not only reported data, but also actual air sampling data to determine exposure levels. In addition, the air sampling data and activities associated with exposure were evaluated and determined by an industrial hygienist rather than self-reporting of data. This was a major strength for this study as it was able to use a range of data.

The biggest limitation of this study was that we can only apply the algorithm to animal farmers in Iowa. The data for both the air sampling and validation were taken from the 32 farmers in Iowa and our glucan intensity measures were only from this one specific source, not allowing us to extend it to other types of crop practices or geographic regions. Our algorithm was not able to characterize glucan exposure to crops since our sampling data demonstrated an exposure level close to background, which is why we ultimately decided to eliminate it from the algorithm. As a verification for dropping crop activities from the algorithm, a verification analysis not shown demonstrated that crop-related variables were not statistically associated with glucan measurements. Despite the fact that crop exposure may be low and our study eliminated these variables from the algorithm, crop activities are usually done for a long duration, which can result in a high exposure over time. Additional information and studies on crop-related glucan exposure is needed for development of another algorithm. Another limitation was that exposure levels that we calculated were only estimates and not an exact reading. As mentioned before, these exposure estimates were only at 1 significant figure due to our data coming only from one source. This prevented us from getting a more accurate assessment of exposure. Despite all of these limitations and our inability to measure glucans with precision, we think we have identified agricultural activities with broad contrast of exposure to glucans.

4.5. Future direction

While the conclusions in this study are only applicable to the BEEA population, the method of using a source-specific approach can be further fine-tuned for glucan exposure with the help of additional studies and data. Algorithms such as this one identify broad contrasts in exposure for several time windows in an agricultural population that can be used in epidemiologic analyses. Additional epidemiological studies investigating the respiratory effects of glucan exposure can be done after better understanding of exposure. Although the algorithm is limited to our population, it will be good for exposure mitigation for the BEEA population itself. This can be through more education on proper protective equipment or on proper ventilation in places such as animal confinements. In addition, since there is not an occupational exposure limit (OEL) for glucans, studies such as these can help towards developing one.

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Appendix A: List of BEEA questionnaire questions used and their tasks associated with glucans

Task	Question Number	Question Type[a]	Question
Harvesting grain/soy/corn	22	Type 1	How many days have you spent harvesting grain/soybeans/corn field/corn seed in the last 30 days?
			How many days have you spent harvesting grain/soybeans/corn field/corn seed in the last 7 days?
			Did you harvest grain/soybeans/corn field/corn seed yesterday or today?
Hauling grain/soy/corn	23	Type 1	How many days have you spent hauling grain/soybeans/corn field/corn seed in the last 30 days?
			How many days have you spent hauling grain/soybeans/corn field/corn seed in the last 7 days?
			Did you haul grain/soybeans/corn field/corn seed yesterday or today?
Harvesting cotton	24	Type 1	How many days have you spent harvesting cotton in the last 30 days?
			How many days have you spent harvesting cotton in the last 7 days?
			Did you harvest cotton yesterday or today?
Hauling cotton	25	Type 1	How many days have you spent hauling cotton in the last 30 days?
			How many days have you spent hauling cotton in the last 7 days?
			Did you haul cotton yesterday or today?
Baling alfalfa/hay	26	Type 1	How many days have you spent baling alfalfa or hay in the last 30 days?
			How many days have you spent baling alfalfa or hay in the last 7 days?
			Did you bale alfalfa or hay yesterday or today?
Hauling alfalfa/hay	27	Type 1	How many days have you spent hauling alfalfa or hay in the last 30 days?
			How many days have you spent hauling alfalfa or hay in the last 7 days?
			Did you haul alfalfa or hay yesterday or today?
Spending time in poultry confinement	33	Type 2	How much time did you spend in the poultry confinement area? In the past 30 days?
			How much time did you spend in the poultry confinement area? In the past 7 days?
			How much time did you spend in the poultry confinement area? Yesterday or today?
Cleaning poultry confinement	33	Type 2	How much time did you spend cleaning the poultry confinement area? In the past 30 days?
			How much time did you spend cleaning the poultry confinement area? In the past 7 days?
			How much time did you spend cleaning the poultry confinement area? Yesterday or today?

Mixing poultry feed	33	Type 2	How much time did you spend mixing poultry feed and feeding poultry? In the past 30 days?
			How much time did you spend mixing poultry feed and feeding poultry? In the past 7 days?
			How much time did you spend mixing poultry feed and feeding poultry? Yesterday or today?
Spending time in swine confinement	34	Type 2	How much time did you spend in the swine confinement area? In the past 30 days?
			How much time did you spend in the swine confinement area? In the past 7 days?
			How much time did you spend in the swine confinement area? Yesterday or today?
Cleaning swine confinement	34	Type 2	How much time did you spend cleaning the swine confinement area? In the past 30 days?
			How much time did you spend cleaning the swine confinement area? In the past 7 days?
			How much time did you spend cleaning the swine confinement area? Yesterday or today?
Mixing swine feed	34	Type 2	How much time did you spend mixing swine feed and feeding swine? In the past 30 days?
			How much time did you spend mixing swine feed and feeding swine? In the past 7 days?
			How much time did you spend mixing swine feed and feeding swine? Yesterday or today?
Working around stored seed	35	Type 4	[In the last month] how often have you worked with or around stored seed or grain on your farm or elsewhere (such as grain elevators or feed mills)?
			How many times have you worked with or around stored seed or grain in the last 7 days?
			Did you work with or around stored seed or grain yesterday?
			Each time you did this, on average how long did you spend working with or around stored seed or grain?
Grinding animal feed	35	Type 4	[In the last month] how often have you ground animal feed?
			How many times have you ground animal feed in the last 7 days?
			Did you grind animal feed yesterday or today?
			Each time you did this, on average how long did you spend grinding animal feed?
Cleaning grain bins	35	Type 4	[In the last month], how often have you cleaned grain bins?
			How many times have you cleaned grain bins in the last 7 days?
			Did you clean grain bins yesterday or today?
			Each time you did this, on average how long did you spend cleaning grain bins?
Working around moldy hay	35	Type 4	[In the last month], how often have you worked with or around moldy hay or straw?
			How many times have you worked with or around moldy hay or straw in the last 7 days?
			Did you work with or around moldy hay or straw yesterday or today?

			Each time you did this, on average how long did you spend working with or around moldy hay or straw?
Milking animals	35	Type 4	[In the past month], how often have you milked cows or other animals?
			How many times have you milked cows or other animals in the last 7 days?
			Did you milk cows or other animals yesterday or today?
			Each time you did this, on average how long did you spend milking cows or other animals?
Cleaning barns	35	Type 4	[In the past month], how often have you cleaned barns or other animal facilities?
			How many times have you cleaned barns or other animal facilities in the last 7 days?
			Did you work clean barns or other animal facilities yesterday or today?
			Each time you did this, on average how long did you spend cleaning barns or other animal facilities?
Working around wood dust	37	Type 3	Have you worked around wood dust, such as at a saw mill, in furniture-making, or other wood-working activities? How many hours in the past 30 days?
			Have you worked around wood dust, such as at a saw mill, in furniture-making, or other wood-working activities? How many hours in the past 7 days?
			Have you worked around wood dust, such as at a saw mill, in furniture-making, or other wood-working activities? How many hours yesterday or today?

[a] See table 1 for the response categories for each question type.

Appendix B: Exposure variables used to extract information from Sauve et al. 2020 paper]

Task	Exposure Variables	Exp B Exposure Equation	Exposure Level GM (ng/m3)	Table Used
Harvesting grain	Location on the farm, Production phase, Crop type	intercept * field * harvest * grain	15	Table 4
Harvesting soybeans	Location on the farm, Production phase, Crop type	intercept * field * harvest * soy	33	Table 4
Harvesting corn	Location on the farm, Production phase, Crop type	intercept * field * harvest * corn	18	Table 4
Hauling grain	Location on the farm, Production phase, Crop type	intercept * field * post-harvest * grain	32	Table 4
Hauling soybeans	Location on the farm, Production phase, Crop type	intercept * field * post-harvest * soy	72	Table 4
Hauling corn	Location on the farm, Production phase, Crop type	intercept * field * post-harvest * corn	38	Table 4
Baling alfalfa or hay	Location on the farm, Production phase, Crop type	intercept * field * field work * hay	3	Table 4
Hauling alfalfa or hay	N/A - used raw data	N/A - used raw data	46	N/A
Spent time in poultry confinement area	Location on the farm, Number of animals	intercept * confinement * <100 animals	275	Table 3
Spent time in poultry confinement area	Location on the farm, Number of animals	intercept * confinement * 100-999	292	Table 3
Spent time in poultry confinement area	Location on the farm, Number of animals	intercept *confinement * ≥1000 animals	305	Table 3
Spent time cleaning the poultry confinement area	Task	intercept * clean building	70.584	Table 2
Spent time mixing poultry feed and feeding poultry	Task	intercept * feed work	28	Table 2
Spent time in the swine confinement area	Location on the farm, Number of animals	intercept * confinement * <100 animals	275	Table 3
Spent time in the swine confinement area	Location on the farm, Number of animals	intercept * confinement * 100-999	292	Table 3

Spent time in the swine confinement area	Location on the farm, Number of animals	intercept *confinement * ≥1000 animals	305	Table 3
Spent time cleaning the swine confinement	Task	intercept * clean building	70.584	Table 2
Spent time mixing swine feed and feeding swine	Task	intercept * feed work	28	Table 2
Worked with or around stored seed or grain	Location on farm, Production phase, Crop type	intercept * grain bin * other phase * grain	47	Table 4
Ground animal feed	Task	intercept * feed work	28	Table 2
Cleaning grain bins	Location on farm, Production phase, Crop type	intercept * grain bin * other phase * grain	47	Table 4
Working with or around moldy hay or straw	Task	intercept * bedding work	532	Table 2
Milking cows or other animals	Task	intercept * cow/dairy task	12	Table 2
Cleaning animal confinements	Task	intercept * clean manure	2	Table 2
Worked around wood dust	N/A - used raw data	N/A - used raw data	37.45	N/A

Appendix C: Equations used to determine glucan exposure level for tasks identified to have glucan levels above background

[Working with/around Moldy Hay or Straw Source-Specific Equations – High Exp]
Gmoldyhay,30days (in ng/m3-hrs) = 50 * Ntimes[Q35,30days] * Duration[Q35] / 60
Gmoldyhay,7days (in ng/m3-hrs) = 50 * Ntimes[Q35,7days] * Duration[Q35] / 60
Gmoldyhay,1days (in ng/m3-hrs) = 50 * Yes=1/N=0,yesterday/today * Duration[Q35] / 60

[Poultry Confinement Source-Specific Equations – Medium Exp]
Gpoultryconfinement,30days (in ng/m3-hrs) = 300 * hours[Q33,30days]
Gpoultryconfinement,7days (in ng/m3-hrs) = 300 * hours[Q33,7days]
Gpoultryconfinement,1days (in ng/m3-hrs) = 300 * minutes[Q33,yesterday/today] / 60

[Swine Confinement Source-Specific Equations – Medium Exp]
Gswineconfinement,30days (in ng/m3-hrs) = 300 * hours[Q34,30days]
Gswineconfinement,7days (in ng/m3-hrs) = 300 * hours[Q34,7days]
Gswineconfinement,1days (in ng/m3-hrs) = 300 * minutes[Q34,yesterday/today] / 60

[Worked with/around Stored Seed or Grain Source-Specific Equations – Low Exp]
Gseed,30days (in ng/m3-hrs) = 50 * Ntimes[Q35,30days] * Duration[Q35] / 60
Gseed,7days (in ng/m3-hrs) = 50 * Ntimes[Q35,7days] * Duration[Q35] / 60
Gseed,1days (in ng/m3-hrs) = 50 * Yes=1/N=0,yesterday/today * Duration[Q35] / 60

[Cleaning Grain Bins Source-Specific Equations – Low Exp]
Gcleanbin,30days (in ng/m3-hrs) = 50 * Ntimes[Q35,30days] * Duration[Q35] / 60
Gcleanbin,7days (in ng/m3-hrs) = 50 * Ntimes[Q35,7days] * Duration[Q35] / 60
Gcleanbin,1days (in ng/m3-hrs) = 50 * Yes=1/N=0,yesterday/today * Duration[Q35] / 60

[Worked Around Wood Dust Source-Specific Equations – Low Exp]
Gwooddust,30days (in ng/m3-hrs) = 30 * hours[Q37,30days]
Gwooddust,7days (in ng/m3-hrs) = 30 * hours[Q37,7days]
Gwooddust,1days (in ng/m3-hrs) = 30 * min[Q37,yesterday/today] / 60