# FINAL PERFORMANCE REPORT

**Title of Project**: Grain Dust Exposure: Physiologic and Biologic Correlates

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# I. FINAL PERFORMANCE REPORT

## A. LIST OF PUBLICATIONS

1. Clapp WD, Becker S, Quay J, Watt JL, Thorne PS, Frees KL, Zhang X, Koren HS, Lux CR, Schwartz DA. Grain dust-induced airflow obstruction and inflammation of the lower respiratory tract. Am J Respir Crit Care Med 1994; 150:611-617.

2. Schwartz, DA, Thorne PS, Jagielo PJ, White GE, Bleuer SA, Frees KL. Endotoxin responsiveness and grain dust-induced inflammation in the lower respiratory tract. Am J Physiol: Lung Cell Mol Physiol 1994; 11:L609-L617.

3. Jagielo PJ, Thorne PS, Watt JL, Frees KL, Quinn TJ, Schwartz DA. Grain dust and endotoxin inhalation produce similar inflammatory responses in normal subjects. Chest 1996; 110:263-270.

4. Blaski CA, Clapp WD, Thorne PS, Quinn TJ, Watt JL, Frees K, Yagla SJ, Schwartz DA. The role of atopy in grain dust-induced airway disease. Am J Respir Crit Care Med 1996; 154:334-340.

5. Jagielo PJ, Watt JL, Quinn TJ, Knapp HR, Schwartz DA. Pentoxifylline does not alter the response to inhaled grain dust. Chest (in press).

6. Jagielo PJ, Watt JL, Quinn TJ, Schwartz DA. Is bronchial hyperreactivity protective in grain dust induced airway inflammation? (submitted).

7. Jagielo PJ, Quinn TJ, Qureshi N, Schwartz DA. Grain dust induced lung inflammation is reduced by *Rhodobacter sphaeroides* diphosporyl lipid A. (submitted).

## B. SIGNIFICANT FINDINGS

The significant findings of our investigation, "Grain Dust Exposure: Physiologic and Biologic Correlates" may be outlined as follows:

1. Inhalation of aqueous extracts of grain dust (GDE) cause acute airflow obstruction and airway inflammation in non-atopic, non-asthmatic, health adult volunteers. Following exposure to GDE, acute declines in $FEV_1$ occur as early as 10 minutes post-inhalation challenge and persist for at least four hours post exposure. Furthermore, acute GDE inhalation causes increased concentrations of acute inflammatory cells in the lower respiratory tract as well as inflammatory proteins (cytokines) such as tumor necrosis factors alpha (TNF-$\alpha$), interleukin 1 beta (IL-1$\beta$), interleukin 6 (IL-6), and interleukin 8 (IL-8).

2. Endotoxin appears to be the principal component in grain dust associated with the development of airflow obstruction and airway inflammation. Exposure studies performed in non-atopic, non-asthmatic health adult volunteers demonstrated that inhalation of GDE or *E. coli* lipopolysaccharide solutions (LPS), each containing equivalent endotoxin activity, produce similar respiratory symptoms, reductions in airflow, and concentrations of inflammatory cells and inflammatory cytokines (TNF-$\alpha$, IL-1$\beta$, IL-6, and IL-8). Furthermore, a dose-response relationship exists between the level of endotoxin in GDE and the magnitude of the inflammatory cells and cytokines following inhalation of GDE.

3. Atopy, as a specific host factor, alone does not appear to effect the physiologic and biologic response to GDE inhalation. Volunteer subjects who are atopic but with normal airway reactivity do not have any significant differences in spirometric changes, BAL cellularity, or concentrations of inflammatory mediators in comparison to non-atopic subjects following exposure to GDE.

4. Airway hyperreactivity, as a specific host factor, does appear to affect the physiologic response to GDE inhalation. Volunteer subjects demonstrating bronchial hyperreactivity (as measured by histamine challenge) developed significantly greater respiratory symptoms as well as greater decline s in $FEV_1$. However, subjects with bronchial hyperreactivity appeared to develop significantly lower concentrations of inflammatory cells in comparison to subjects with normal airway reactivity. Thus, it appears that bronchial hyperreactivity as a specific host factor may lead to an exaggerated physiologic response to GDE but this exaggerated response could also be protective by reducing the magnitude of airway inflammation following GDE inhalation.

5. Pentoxifylline, a medication known to possess anti-TNF-$\alpha$ properties, does not alter the acute physiologic or inflammatory events following exposure in GDE in normal volunteers.

## C. USEFULNESS OF FINDINGS

The results of the clinical investigations performed as described above are all important in the understanding of grain dust induced airway disease. These inhalation studies, performed under controlled conditions, demonstrate that extracts of grain dust are biologically active, capable of producing acute physiologic changes (airflow obstruction) as well as causing acute airway inflammation. Therefore, individuals exposed to grain dust during the handling or processing of grain are at increased risk for the development of acute airflow obstruction and airway inflammation if exposed to significant levels of grain dust. Of particular importance is the observation that the acute physiologic and inflammatory response following grain dust inhalation is associated with the concentration of endotoxin contained in the bioaerosol. Because a dose-response relationship exists between the level of endotoxin in the grain dust and the magnitude of the inflammatory response, it may be more important to monitor airborne levels of endotoxin in the work setting rather than total dust levels in order to minimize the risk of airway injury due to grain dust. We have characterized the initial biologic and physiologic events associated with acute grain dust exposure, and the results of this investigation may be relevant in developing interventions leading to the prevention of the chronic manifestations of this environmental lung disease. Although the results of the pentoxifylline study demonstrated no therapeutic benefit in

reducing the physiologic and inflammatory events associated with acute GDE inhalation, other anti-inflammatory agents may be studied using our present model of grain dust induced lung inflammation. Our study also investigated whether specific host factors were important in affecting the host's physiologic and biologic response to GDE. Our results suggested that while atopy alone plays a minor role in the development of grain dust induced airway disease, bronchial hyperreactivity as a host factor significantly affects the physiologic and biologic response to grain dust.

## D. SPECIFIC AIMS

The specific aims of this project are listed below. The references noted after each aim refer to the publications listed above that fulfill the specific aim.

1. Inhalation of aqueous grain dust extract causes inflammation primarily localized in the airways and is associated with airflow obstruction (1,2).

2. Host factors, such as age, ethnic background, gender , atopic status, asthma, and cigarette smoking modulate the duration, intensity, and severity of those effects (3,5).

3. Repeated exposure results in physiologic and biologic tolerance occurring within days of onset of exposure. This tolerance is modulated by one or several host factors which will be investigated in specific aim 2 (2,6,7).

II. **FINANCIAL STATUS REPORT**: SF269 will be sent under a separate cover from the University of Iowa Grants Accounting Office.

III. **EQUIPMENT INVENTORY** - No equipment was purchased under this grant.

IV. **FINAL INVENTION STATEMENT** - No inventions were conceived under this grant.