USDA-ARS/
U.S. Wheat and Barley Scab Initiative
FY07 Final Performance Report (approx. May 07 – April 08)
July 15, 2008

Cover Page

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Fiscal Year:	2007
USDA-ARS Agreement ID:	59-0790-4-119
USDA-ARS Agreement Title:	Human Susceptibility to Trichothecene Mycotoxins.
FY07 ARS Award Amount:	$ 93,991

USWBSI Individual Project(s)

USWBSI Research Area*	Project Title	ARS Adjusted Award Amount
FSTU-R	Human Susceptibility to Trichothecene Mycotoxins.	$93,991
	Total Award Amount	**$ 93,991**

James J Pestka 7/14/2008

Principal Investigator Date

* CBCC – Chemical, Biological & Cultural Control
EEDF – Etiology, Epidemiology & Disease Forecasting
FSTU – Food Safety, Toxicology, & Utilization of Mycotoxin-contaminated Grain
GET – Genetic Engineering & Transformation
HGR – Host Genetics Resources
HGG – Host Genetics & Genomics
IIR – Integrated/Interdisciplinary Research
PGG – Pathogen Genetics & Genomics
VDUN – Variety Development & Uniform Nurseries

Project 1: *Human Susceptibility to Trichothecene Mycotoxins.*

1. What major problem or issue is being resolved and how are you resolving it?

During head blight of wheat and barley, deoxynivalenol (DON or "vomitoxin") and other trichothecene mycotoxins are elaborated that might adversely affect human health. Two aspects related to trichothecene exposure and human health were addressed. First, since DON can potentially cause adverse health effects in individuals who consume the infected grain, this mycotoxin DON is regulated in the U.S. at 1 ppm in finished food. Recently, the European Economic Union have established lower limits based on a a limited number of rodent studies as well as the concern that children have greater sensitivity to DON. A second concern is that agricultural workers are exposed to airborne DON during harvest, threshing and milling of infected wheat and barley, however, we do not understand the potential for adverse effects from inhalation of this toxin. Overall, serious questions remain relative to the true risks presented to consumers and grain handlers posed by DON and other trichothecenes elicited during outbreaks head blight. Our research is addressing this gap by providing data on effects of DON on toxicity biomarkers using the young (weanling) mouse model and a mouse intranasal instillation model.

2. List the most important accomplishment and its impact (how is it being used?). Complete all three sections (repeat sections for each major accomplishment):

Accomplishment #1: We determined that the initial plasma and tissue DON concentrations in young mice were approximately twice that of adult mice given identical doses of the toxin but that clearance was rapid in both groups of mice. DON induction of TNF-α, IL-1β and IL-6 in young animals were two to three times greater in spleens, a primary source of systemic proinflammatory cytokines, whereas differences in proinflammatory cytokine expression were less robust or not apparent in the liver or lung between the two age groups.

Impact: This is the first report comparing the effects of age on trichothecene uptake and molecular endpoints of toxicity. Mice have been previously used to model potential adverse effects of DON to humans and large safety factor (100X) for species differences (10X) and human variability (10X) have been employed in Tolerable Daily Intake (TDI) estimates. The differences seen in young mice compared to adult mice relative to uptake and toxicity are likely accounted for in this large safety factor.

As a result of that accomplishment, what does your particular clientele, the scientific community, and agriculture as a whole have now that they didn't have before?: The effects of age on DON uptake and toxicity biomarkers were quite modest. They do not support the need to lower the level of concern for DON in U.S.food because of special risks to children. These findings are being published in Food and Chemical Toxicology.

Accomplishment #2: We have determined that DON distributes rapidly throughout mouse organs and reaches peak plasma concentration within 30 minutes of exposure regardless of whether mice are exposed to the toxin via gut or respiratory route. However, plasma and tissue DON concentrations in mice exposed by intranasal route were 1.5 to 3 times that of mice orally exposed to DON. Relative inductions of cytokine biomarkers were 2 to 10 times that observed in the tissues of orally exposed mice. Taken together, these data suggest that DON is more toxic when inhaled than when ingested, and further suggest the potential for adverse human health effects from inhalation of DON-contaminated grain dust.

Impact: Quantification of kinetic differences between nasal and oral routes provides a basis for characterization of potential risk(s) associated with DON inhalation. These observations show for the first time a potential health effect with respiratory exposure to DON suggesting the need for adequate risk characterization and risk management for grain handlers. Overall this brings us closer to understanding the effects of DON inhalation in a quantifiable manner

As a result of that accomplishment, what does your particular clientele, the scientific community, and agriculture as a whole have now that they didn't have before? There is a possible hazard to agricultural workers handling Fusarium-contaminated grain containing very high DON levelshas been identified. This is an important consideration in for establishing safety measures for workers occupationally exposed to DON during grain handling. These findings are being published in Toxicology Letters.

Accomplishment #3: The eukaryotic ribosome has long been known to be a target of DON and other trichothecenes. We employed cell-free and the clonal macrophage models to test the hypothesis that DON and T-2 exposure mediates cleavage of rRNA. The results suggest that while these trichothecenes did not possess the inherent enzymatic activity in a cell-free model, DON and T-2 evoked 28S rRNA cleavage in the macrophage, possibly by facilitating the action of constitutive and induced RNases.

Impact: This is the first report of specific ribosomal rRNA cleavage by trichothecenes. Pending further work, this lesion has potential use as a biomarker of for DON exposure and toxicity on animals and humans.

As a result of that accomplishment, what does your particular clientele, the scientific community, and agriculture as a whole have now that they didn't have before: A cell-specific type of damage due to DON has been identified in cells of the immune system- a central tissue target for this toxin.. These findings are being published in Toxicology Sciences. This information has the potential to be used safety studies employing animals as well as measuring in human exposure.

Include below a list of the publications, presentations, peer-reviewed articles, and non-peer reviewed articles written about your work that resulted from all of the projects included in the grant. Please reference each item using an accepted journal format. If you need more space, continue the list on the next page.

(1) Pestka JJ, Islam Z, Amuzie CJ. Immunochemical assessment of deoxynivalenol tissue distribution following oral exposure in the mouse. Toxicol Lett 2008 May 5; 178(2):83-7, PM:18395371

(2) Pestka JJ, Amuzie CJ. Tissue distribution and proinflammatory cytokine gene expression following acute oral exposure to deoxynivalenol: Comparison of weanling and adult mice. Food and Chemical Toxicol (in press) 2008

(3) Amuzie CJ, Harkema JR, Pestka JJ. Tissue distribution and proinflammatory cytokine induction by the trichothecene deoxynivalenol in the mouse: Comparison of nasal vs. oral exposure. Toxicology 2008 Jun 3; 248(1):39-44, PM:18433975

(4) Li M, Pestka JJ. Comparative induction of 28S ribosomal RNA cleavage by ricin and the trichothecenes deoxynivalenol and T-2 toxin in the macrophage. Toxicol Sci 2008 Jun 4; PM:18535001

(5) Pestka JJ. Mechanisms of deoxynivalenol-induced gene expression and apoptosis. Food Addit Contam (in press) 2008;

(6) Pestka JJ. Deoxynivalenol: Toxicity, mechanisms and animal health risks. Animal Feed Science and Technology 2007; 137:283-98

(7) Gray JS, Pestka JJ. Transcriptional regulation of deoxynivalenol-induced IL-8 expression in human monocytes. Toxicol Sci 2007 Oct; 99(2):502-11, PM:17636245

(8) Gray JS, Bae H-K, Li JCB, Lau AS, Pestka JJ. Double-stranded RNA-activated proteiin kinase (PKR) mediates induction of IL-8 expression by deoxynivalenol, Shiga toxin 1 and ricin in monocytes. Toxicol Sci (in press) 2008;