USDA-ARS/
U.S. Wheat and Barley Scab Initiative
FY06 Final Performance Report (approx. May 06 – April 07)
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Cover Page

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Fiscal Year:	2006
USDA-ARS Agreement ID:	59-0790-4-119
USDA-ARS Agreement Title:	Human Susceptibility to Trichothecene Mycotoxcins.
FY06 ARS Award Amount:	$ 92,594

USWBSI Individual Project(s)

USWBSI Research Area*	Project Title	ARS Award Amount
FSTU-R	Human Susceptibility to Trichothecene Mycotoxcins.	$ 92,594
	Total Award Amount	**$ 92,594**

James J Pestka July 9, 2007
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
PGG – Pathogen Genetics & Genomics
VDUN – Variety Development & Uniform Nurseries

Project 1: *Human Susceptibility to Trichothecene Mycotoxcins.*

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

Two issues are being addressed in this project. First, during head blight of wheat and barley, deoxynivalenol (DON or "vomitoxin") and other trichothecene mycotoxins are elaborated that can potentially cause adverse health effects in individuals who consume the infected grain. Although DON is regulated in the U.S. at 1 ppm in finished food, the European Economic Union and Codex Alimenterius have proposed much lower limits based on a few rodent studies and assumptions that their greater sensitivity of children to DON. Our work has identified specific indicators or biomarkers of DON toxicity that can be applied to risk assessment.

A second issue is that although agricultural workers are exposed to airborne DON during harvest, threshing and milling of infected wheat and barley, virtually nothing is known about the adverse effects of inhaling this toxin. Thus, a critical knowledge gap exists relative to the true risks presented to consumers and grain handlers by DON and other trichothecenes elicited during outbreaks head blight. Our research is addressing this gap by providing data on effects of DON inhalation using the rodent 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 have determined that DON is absorbed similarly by young and adult mice. Ingestion of DON also causes marked proinflammatory cytokine induction (a marker for DON toxicity) in spleen, liver and lung in adults but a much reduced response occurs in young mice. We have further determined that DON is capable of rapidly and transiently upregulating suppressors of cytokine signaling ("SOCs") in the murine liver. SOCs are capable of downregulating food intake and weight gain and then induction might explain DON's metabolic effects.

Impact:. DON-induced upregulation of SOCS might represent an unrecognized mechanism for chronic effects like growth retardation. A characterization of the physiological role of SOCS upregulation in DON treated might hold promise for precise human comparability of murine DON data. The understanding of growth retardation mechanisms will reduce uncertainties in risk assessment for this toxin.

Accomplishment #2: We have determined that the mycotoxin deoxynivalenol distributes rapidly throughout mouse organs and reaches peak plasma concentration within 30 minutes of exposure regardless of whether exposed via gut or respiratory route. We have determined that plasma concentration of DON is 2-3 fold higher in respiratory-exposed mice, resulting in a greater tissue distribution. We have determined that proinflammatory markers of DON toxicity are higher in tissues of nasally exposed mice given the same quantities of DON.

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?

- DON regulations are largely based on its effects on growth retardation and potential effects of young children. Critical new information is now available to enhance science –based risk assessment and for establishing/modifying DON tolerances.
- A potential hazard for agricultural workers handling Fusarium-contaminated grain has been identified. This might be an important consideration in for establishing safety measures for workers occupationally exposed to DON during grain handling.

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, J.J.,Amuzie, C.J., and Harkema, J.R., 2006. Tissue distribution and pro-inflammatory cytokine induction by the trichothecene deoxynivalenol in the mouse: comparison of nasal *vs.* oral exposure. . Abstract Meet Fusarium Head Scab Inititiative. (Raleigh, NC)

2. Pestka, J. J. 2006, Mycotoxins: the ever-lower regulatory standards and toxicological significance. World Mycotoxin Forum, Nov. 2006, Cincinnatti OH

3. Pestka, J. J. 2006. Ribosome-mediated stress response to trichothecene mycotoxins. U.S. Japan Natural Toxin Research Program. Am. Meeting, (Washington DC)

4. Islam, Z., Gray, J. S., and Pestka, J. J. (2006). p38 Mitogen-activated protein kinase mediates IL-8 induction by the ribotoxin deoxynivalenol in human monocytes. *Toxicol. Appl. Pharmacol.* **213**(3), 235-244.

5. Pestka, J., and Zhou, H. R. (2006). Toll-like receptor priming sensitizes macrophages to proinflammatory cytokine gene induction by deoxynivalenol and other toxicants. *Toxicol. Sci.* **92**(2), 445-455.

6. Islam, Z., and Pestka, J. J. (2006). LPS priming potentiates and prolongs proinflammatory cytokine response to the trichothecene deoxynivalenol in the mouse. *Toxicol. Appl. Pharmacol.* **211**(1), 53-63.

7. Mbandi, E., and Pestka, J. J. (2006). Deoxynivalenol and satratoxin G potentiate proinflammatory cytokine and macrophage inhibitory protein 2 induction by Listeria and Salmonella in the macrophage. *J. Food Prot.* **69**(6), 1334-1339.

8. Li, M., Harkema, J. R., Cuff, C. F., and Pestka, J. J. (2007). Deoxynivalenol exacerbates viral bronchopneumonia induced by respiratory reovirus infection. *Toxicol. Sci.* **95**(2), 412-426.

9. Li, M., Harkema, J. R., Islam, Z., Cuff, C. F., and Pestka, J. J. (2006). T-2 toxin impairs murine immune response to respiratory reovirus and exacerbates viral bronchiolitis. *Toxicol. Appl. Pharmacol.* **217**(1), 76-85.

10. Li, M., Cuff, C. F., and Pestka, J. J. (2006). T-2 toxin impairment of enteric reovirus clearance in the mouse associated with suppressed immunoglobulin and IFN-gamma responses. *Toxicol. Appl. Pharmacol.* **214**(3), 318-325.

11. Amuzie, C.J., Harkema, J.R., and Pestka, J.J. (2007). Tissue distribution and pro-inflammatory cytokine induction by the trichothecene deoxynivalenol in the mouse: comparison of nasal *vs.* oral exposure. Society of Toxicology Annual Meeting (Charlotte, SC) The Toxicologist. P 13.

12. Li, M., Harkema, J.R., Cuff, C.F., and Pestka J.J. (2007). Deoxynivalenol impairs resistance to respiratory reovirus infection and promotes viral bronchopneumonia. Society of Toxicology Annual Meeting (Charlotte, SC) The Toxicologist. P 67.

13. Pestka, J.J., Bae, H.B., and Li, M. (2007). Ribosome-mediated stress response to biological toxins in the macrophage. Society of Toxicology Annual Meeting (Charlotte, SC) The Toxicologist. P 139.

14. Harris, A.J., and Pestka, J.J. (2007). Molds, mycotoxins and damp building-related illnesses. Society of Toxicology Annual Meeting (Charlotte, SC) The Toxicologist. P 446.

15. Pestka, J.J., Islam, Z., Harkema, J.R., Bae, H., and Li, M. (2007). Trichothecene-induced inflammation and apoptosis: cellular targets and molecular mechanisms. Society of Toxicology Annual Meeting (Charlotte, SC) The Toxicologist. P 447.