USDA-ARS/
U.S. Wheat and Barley Scab Initiative
FY13 Final Performance Report
July 15, 2014

Cover Page

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Fiscal Year:	FY13
USDA-ARS Agreement ID:	59-0206-9-058
USDA-ARS Agreement Title:	Mechanisms and Biomarkers for Deoxynivalenol-induced Growth Retardation.
FY13 USDA-ARS Award Amount:	$ 56,851

USWBSI Individual Project(s)

USWBSI Research Category*	Project Title	ARS Award Amount
FSTU-R	Hormonal Biomarkers for Deoxynivalenol Risk Assessment.	$ 56,851
	FY13 Total ARS Award Amount	**$ 56,851**

July 15, 2014

Principal Investigator Date

* MGMT – FHB Management
FSTU – Food Safety, Toxicology, & Utilization of Mycotoxin-contaminated Grain
GDER – Gene Discovery & Engineering Resistance
PBG – Pathogen Biology & Genetics
BAR-CP – Barley Coordinated Project
DUR-CP – Durum Coordinated Project
HWW-CP – Hard Winter Wheat Coordinated Project
VDHR – Variety Development & Uniform Nurseries – Sub categories are below:
SPR – Spring Wheat Region
NWW – Northern Soft Winter Wheat Region
SWW – Southern Soft Red Winter Wheat Region

Project 1: *Hormonal Biomarkers for Deoxynivalenol Risk Assessment.*

1. What major problem or issue is being resolved relevant to Fusarium head blight (scab) and how are you resolving it?

During Fusarium head blight of wheat and barley, deoxynivalenol (DON or "vomitoxin") and other trichothecenes are elaborated. These mycotoxins potentially cause illness in individuals who consume the infected grain and thus are an important public health concern. DON is regulated in the U.S. at 1 ppm in finished food, but the European Food Safety Administration has enacted much lower limits (200 ppb for infant food) largely based on reduced weight gain (ie. growth retardation) observed in mouse studies.

This project addressed Goal #2 of the FSTU Action plan " Provide requisite information on DON/trichothecene safety issues to producers, millers, researchers, risk assessors and regulators." Although DON-induced growth impairment has long been observed in many animal species, a critical research gap exists relative to understanding the mechanisms for this effect, thus creating a source of uncertainty in human risk assessment. We the tested the hypothesis that the gut satiety hormones CCK and PYY can be used as biomarkers of DON toxicity. We see to accomplish this by: (1) Relating DON-induced anorexia to plasma elevation in the gut satiety peptides CCK and PYY and (2) Relating gender- and age-related susceptibility differences in DON-induced anorexia to gut satiety hormone responses.

2. List the most important accomplishments and their impact (i.e. how are they being used) to minimize the threat of Fusarium Head Blight or to reduce mycotoxins. Complete both sections; repeat sections for each major accomplishment:

Accomplishment: We have successfully demonstrated that both CCK and PYY mediated DON-induced anorexia in the mouse model thus confirming the validity that these are two sensitive biomarkers of DON's growth effects that can also complement biomarkers of exposure in human studies. We have now used these markers to compare toxicity of other 8-ketotrichothecenes. We have further determined that young mice do not differ from adult mice in terms of sensitivity to DON-induced anorexia. However, elderly mice were extremely sensitive.

Impact: This research has improved knowledge of mechanisms and thresholds for DON-induced food refusal and growth retardation. This knowledge reduces uncertainties in risk assessment and ensure better quantification of human susceptibility. Over the long term, knowledge from our studies will bring precision to tolerable daily intake values of DON. The resulting data can be directly applied safety assessments and enable determination of the accuracy of existing hazard data being used for establishing and harmonizing practical and achievable international guidelines In February 2013, Currently Codex Alimentarius Commisssion has issued a "Proposed Draft Maximum Levels For Deoxynivalenol In Cereals And Cereal-Based Products And Associated Sampling Plan" that is under discussion for world trade (ftp://ftp.fao.org/codex/meetings/cccf/cccf7/cf07_07e.pdf) .We

have presented our findings in the U.S. and 5 other countries the last few years . Our new data is being used in these ongoing discussions.

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 FY13 grant. Please reference each item using an accepted journal format. If you need more space, continue the list on the next page.

Papers

1. Wu W, Zhou HR, He K, Pan X, Sugita-Konishi Y, Watanabe M, Zhang H, Pestka JJ. 2014. Role of cholecystokinin in anorexia induction following oral exposure to the 8-ketotrichothecenes deoxynivalenol, 15-acetyldeoxynivalenol, 3-acetyldeoxynivalenol, fusarenon x and nivalenol. Toxicol. Sci. 138:278-289. PMID: 24385417

2. Wu F, Groopman JD, Pestka JJ. 2014. Public health impacts of foodborne mycotoxins. Ann. Rev. Food Sci. Technol. 5:351-372. PMID: 24422587

3. Miller, JD, Schaafsma AW, Bhatnagar D, Bondy G, Carbone I, Harris LJ, Harrison G, Munkvold GP, Oswald IP, Pestka JJ, Sharpe L, Sumarah MW, Tittlemier SA, Zhou T. 2014. Mycotoxins that affect the North American agri-food sector: state of the art and directions for the future. World Mycotoxin J. 7:63-82.

4. Flannery BM, He K, Pestka JJ. 2013. Deoxynivalenol-induced weight loss in the diet-induced obese mouse is reversible and PKR-independent. Toxicol. Lett. 221:9-14. PMID: 23707852

5. Pan X, Whitten DA, Wu M, Chan C, Wilkerson CG, Pestka JJ. 2013. Early phosphoproteomic changes in the mouse spleen during deoxynivalenol-induced ribotoxic stress. Toxicol. Sci. 135:129-143. PMID: 23811945

6. Pan X, Whitten DA, Wilkerson CG, Pestka JJ. 2014. Dynamic changes in ribosome-associated proteome and phosphoproteome during deoxynivalenol-induced translation inhibition and ribotoxic stress. Toxicol. Sci. 138:217-233. PMID: 24284785

7. Wu W, Bates MA, Bursian SJ, Flannery B, Zhou HR, Link JE, Link, J. E. Zhang, H. Pestka, J. 2013. Peptide YY3-36 and 5-hydroxytryptamine mediate emesis induction by the trichothecene deoxynivalenol (vomitoxin). Toxicol. Sci. 133:186-195. PMID: 23457120

8. Flannery BM, Amuzie CJ, Pestka JJ. . 2013. Evaluation of insulin-like growth factor acid-labile subunit as a potential biomarker of effect for deoxynivalenol-induced proinflammatory cytokine expression. Toxicology 304:192-198. PMID: 23298694

9. He, K., Pan X, Zhou HR, Pestka, JJ. 2013. Modulation of inflammatory gene expression by the ribotoxin deoxynivalenol involves coordinate regulation of the transcriptome and translatome. Toxicol. Sci. 131:153-163. PMID: 22968694

10. Pan X, Whitten DA, Wu M, Chan C, Wilkerson CG, Pestka JJ. 2013. Global protein phosphorylation dynamics during deoxynivalenol-induced ribotoxic stress response in the macrophage. Toxicol. Appl. Pharmacol. 268:201-211. PMID: 23352502

Presentations

1. Clark ES, Bates M, Doan CJ, Pestka JJ. 2014. Elderly male mice display impaired clearance of deoxynivalenol. The 53rd Annual Meeting of the Society of Toxicology, Phoenix, AZ , March 23-27.

2. Pan X, Whitten DA, Wilkerson CG, Pestka JJ. 2014. Dynamic changes in ribosome-associated proteome and phosphoproteome during deoxynivalenol-induced translation inhibition and ribotoxic stress. The 53rd Annual Meeting of the Society of Toxicology, Phoenix, AZ , March 23-27.

3. Zhou, H., Pestka, J. 2013. Deoxynivalenol (DON)-induced secretion of the gut satiety hormone cholecystokinin (CCK) in the STC-1 enteroendocrine cell model is mediated by the calcium sensing receptor (CaSR) and transient receptor potential ankyrin-1 (TRPA1). The 52nd Annual Meeting of the Society of Toxicology, San Antonio, TX, March 10-14.

4. Bates, M., Wu, W., Bursian, S., Flannery, B., Zhou, H., Link, J., Zhang, H., Pestka, J. 2013. Role of peptide YY3-36 (PYY) and 5-hydroxytryptamine (5-HT) in emesis induction by deoxynivalenol (vomitoxin). The 52nd Annual Meeting of the Society of Toxicology, San Antonio, TX, March 10-14.

5. Pan, X., Whitten, D., Wilkerson, C., Pestka, J. 2013. Quantitative phosphoproteomic analysis of the dynamic signaling network mediating proinflammatory response in the spleen of mice under deoxynivalenol-induced ribotoxic stress. The 52nd Annual Meeting of the Society of Toxicology, San Antonio, TX, March 10-14.