

PI: Jim Pestka**PI's E-mail: pestka@msu.edu****Project ID: FY14-PE-031****ARS Agreement #: New Agreement (Expiring Agreement # 59-0206-9-058)****Research Category: FSTU****Duration of Award: 1 Year****Project Title: Hormonal Biomarkers for Trichothecene Risk Assessment.****PROJECT 1 ABSTRACT**

(1 Page Limit)

During Fusarium head blight of wheat and barley, deoxynivalenol (DON or “vomitoxin”) and other trichothecenes are produced. When DON is elaborated within the kernel, varying amounts of the toxin are glycosylated to DON-3-glucoside (DON-3-G) rendering it non-toxic to the plant. DON-3-G has been demonstrated in cereal products and beer to contain DON glucoside and its concentration can increase during dough fermentation and malting process beer making. Interestingly, bacterial flora from the gut are able to convert DON-3-G to DON which could increase its bioavailability. Currently, there is active discussion by CODEX on how to best harmonize regulations for DON and its congeners. Because of its potential for toxicity, the Joint Expert Committee on Food Additives (JECFA) has recommended consideration that DON-3-G glucosides be added to the group tolerable daily intake for the DON which could lead to added testing for this and other trichothecene glycoside conjugates. The two main toxicological effects of DON in sensitive species are anorexia and vomiting. Several research studies suggest these effects are mediated by neuroendocrine hormones. Thus any evaluation of DON-3-G toxicity should include measurement of these responses. Enteroendocrine cells (EECs) are one of the four primary intestinal cell subtypes that populate the epithelial layer of the GI tract. EEC normally sense the contents of the gut lumen and respond by secreting a range of peptide and amine hormones that can act on adjacent cells, afferent enteric neurons and more distal cells. These hormones control numerous digestive and physiologic functions. We have established robust animal models for DON-induced anorexia (mouse) which corresponds to the secretion of CCK and PYY by “I” cell EEC lineage in the duodenum and “L” cell EEC lineage of the ileum and colon, respectively and emesis (mink) which corresponds to increased plasma PYY and 5-HT which is produced by the “EC” cell EEC lineage found throughout the GI tract. We propose to test the guiding hypothesis that DON and DON-3-G differentially regulate hormone secretion by EEC cells. In AIM 1 we will compare the effects of DON and DON-3-G on (1) $[Ca^{2+}]_i$ elevation and CCK release in the cloned STC1 EEC model and (2) $[Ca^{2+}]_i$ elevation and 5-HT secretion in cloned EC cell models. In AIM 2 we will compare the effects of DON and DON-3-G on (1) CCK release in primary murine I-cell-containing models, (2) PYY release in primary murine L-cell-containing models and (3) 5-HT secretion from intestinal whole mount preparations from mice and mink. This research will be important because it will help discern whether DON-3-G is sufficiently toxic to be included in the TDI for DON. The resulting data can be directly applied to DON safety assessments and enable determination of the accuracy of existing hazard data being used for establishing international guidelines. This will ensure precision to DON regulation and balance consumer protection and food supply and is consistent with the goals of the Food Safety, Toxicology and Utilization of Mycotoxin-Contaminated Grain Research Area.