

**PI: Pestka, James****PI's E-mail: pestka@msu.edu****Project ID: FY07-PE-057****FY06 ARS Agreement #: 59-0790-4-119****Research Area: FSTU-R****Duration of Award: 1 Year****Project Title: Human Susceptibility to Trichothecene Mycotoxins.****PROJECT 1 ABSTRACT**

(1 Page Limit)

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 Alimentarius have proposed much lower limits based on a few rodent studies. Since children were identified as being at greatest risk, the most stringent limits have set for infant foods. A further concern 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 adult and infant consumers as well as grain handlers by DON and other trichothecenes elicited during outbreaks head blight. Our *in vitro* data suggest that the keys steps for DON toxicity induction are induction of ribosomal RNA damage, stress signaling and cytokine expression in human and mouse leukocytes (white blood cells) which ultimately mediate acute and chronic illness. To accurately measure the hazardous potential of trichothecene to humans, it is now essential to relate these *in vitro* studies to threshold dose, duration of exposure, exposure route, and magnitude of toxic effect in the mouse model. To do this, we propose to use ribosomal RNA cleavage as a biomarker of DON toxicity. Our guiding hypothesis is that the minimal tissue concentrations of DON required for ribosomal RNA damage will correlate with stress activation and cytokine induction in (1) murine immune tissue in vivo and (2) mouse and human leukocytes in vitro. Two specific objectives are proposed: (1) *Compare the threshold oral doses of DON required for ribosomal RNA damage and cytokine gene upregulation in infant and adult mice and relate these to DON tissue levels;* (2) *Determine threshold intranasal doses of DON required for ribosomal RNA damage and cytokine gene upregulation in the mouse and relate these to DON tissue levels.* In both objectives, we will identify the lowest observed adverse effect level (LOAEL) and the no observed adverse level (NOAEL) for DON toxicity and these will be further related to DON tissue concentrations in the exposed animals. Finally, DON tissue levels corresponding to these thresholds will be compared to *in vitro* studies with human and mouse leukocytes conducted previously under the USWBSI grants program. The resultant data from this and follow-up studies will be used to estimate the true risks of DON and related trichothecenes to humans following exposure via diet or occupational exposure. Over the long term, these data will be used (1) by the U.S. and other governments in improved accurate, safety assessments relative to consumption of grain products and (2) wheat and barley industries for enhanced safety of their workers.