PI: James Pestka **PI's E-mail: pestka@msu.edu**

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PROJECT 1 ABSTRACT

(1 Page Limit)

The **long term goal** of this research is to improve understanding of mechanisms and toxic thresholds for trichothecene-induced health effects for application to risk assessment. During head blight of wheat and barley, deoxynivalenol (DON or "vomitoxin") and other 8-ketotrichothecenes such as 3-acetyldeoxynivalenol (3-ADON) and 15-acetyldeoxynivalenol (15-ADON) 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 have enacted much lower limits (200 ppb for infant food) largely based on reduced weight gain (ie. growth retardation) observed in mouse studies. 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. Previous studies have suggested that DON impairs food intake by interfering with intestinal motility and the desire to eat possibly via serotonin (5-hydroxytryptamine [5-HT]) release in the gut and subsequent signaling within enteric nervous systems. We have observed in mice that acute intraperitoneal exposure to DON causes feed refusal which corresponds to increased serum 5-HT. The objective of this proposal is to establish the validity of using 5-HT and its metabolite 5-hydroxylindoleacetic acid (5-HIAA) as biomarkers of DON-induced feed refusal. Our guiding hypothesis that the hormone 5-HT mediates induction of feed refusal by DON and therefore can be used a biomarker of effect. We will use a mouse model to test our hypothesis in two Specific Aims: *(1)Characterize the dose response effects of acute oral exposure to DON on feed refusal* and *(2)Relate DON-induced feed refusal to 5-HT release and 5-HIAA.* At least two positive **outcomes** are anticipated to result from this work. First, these studies should enable us to identify the no observed adverse effect level (NOAEL) and lowest observed-adverse effect level (LOAEL) relative to food refusal for DON**.** Resultant data can be applied to DON safety assessments thus enabling determination of veracity of existing hazard assessment data being used for establishing U.S. and international guidelines. Second, validation of serum 5-HT and urinary 5-HIAA as "biomarkers of effect" will have applicability to human epidemiological studies employing "biomarkers of exposure" in regions of the world where there is high DON ingestion. Collectively, this research will result in improved toxicological data on DON that will help ensure current guidelines are providing the appropriate safety factors for the consumer and is thus consistent with the goals of the **Food Safety, Toxicology and Utilization of Mycotoxin-Contaminated Grain Research Area**.