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(1 Page Limit)

The **long term goal** of this research is to improve understanding of mechanisms, biomarkers, and thresholds for trichothecene-induced health effects for application to risk assessment. During head blight of wheat and barley, deoxynivalenol (DON or “vomitoxin”) and other trichothecene mycotoxins are elaborated; and can cause adverse health effects in individuals who consume the infected grain. DON is regulated in the U.S. at 1 ppm in finished food, but the European Union have recently 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, and identifying biomarkers for this effect, thus creating uncertainty in human risk assessment. In **recent studies**, we have observed that oral DON exposure rapidly induces proinflammatory cytokine, and suppressor of cytokine signaling-3 (SOCS-3), a protein known to downregulate the liver’s responses to growth hormone (GH). Here we propose to test the **hypothesis** that *DON-induced growth retardation results from DON-induced cytokine-mediated SOCS-3 upregulation, which inhibits hepatic GH signaling, leading to reductions of growth factor(s) and weight gain.* This will be accomplished by achieving **three objectives**: 1) Relate acute DON-induced SOCS upregulation to GH impairment by (a) assessing the capacity of DON to inhibit GH-induction of acid-labile subunit (ALS) of the insulin-like growth factor 1 (IGF-1) ternary complex and (b) demonstrating DON’s impairment of GH’s activation of its receptor, and (c) relating post DON exposure kinetics SOCS-3 upregulation to ALS downregulation kinetics; 2) Determine the sensitivity of SOCS-3, ALS, IGF-1 proteins to act as biomarkers of DON’s growth effects by (a) comparing the minimal dietary DON concentrations required to alter these biomarkers and (b) identifying the NOAEL for the most sensitive biomarker; and 3) Determine the influence of age and gender on DON-induced biomarker alteration. These studies should enable us to identify the no-adverse effect level (NOAEL) relative to growth dysregulation for this mycotoxin. Several positive **outcomes** are anticipated to result from this work. First, we will confirm the validity of one or more sensitive biomarkers of DON’s growth effects that can also complement biomarkers of exposure in human studies. Second, we will relate the biomarker(s) to potential age and gender sensitive effects of DON. Collectively, this research will update the science on which DON regulation is based, resulting in quantitative data that can be applied to DON-specific safety factors. 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.**