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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 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 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. In **recent studies**, we have observed that oral exposure to DON results in its rapid uptake in the liver where it induces proinflammatory cytokine and chemokine expression. Cytokine induction is followed by the hepatic upregulation of suppressor of cytokine signaling-3 (SOCS-3) - a protein well-known to downregulate cellular responses to growth hormone as well as cytokines. Here we propose to test the **hypothesis** that *DON-induced growth retardation is caused by cytokine-induced hepatic growth hormone resistance and is mediated by suppressors of cytokine signaling (SOCS).* This will be accomplished by achieving **two objectives**. First, we will relate DON-induced SOCS upregulation to growth impairment in the mouse by (1) assessing the capacity of DON-induced SOCS to inhibit growth hormone (GH) signal transduction pathways and (2) demonstrating the capacity of sub-chronic DON feeding to induce SOCS mRNA expression and reduce GH-induced plasma insulin-like growth factor (IGF-1). Second, we will relate the effects in mice of (1) acute and (2) sub-chronic exposure to a range of DON doses on SOCS expression and plasma IGF-1 to weight gain in the mouse. These studies should enable us to identify the no-adverse effect level (NOAEL) and lowest observed-adverse effect level (LOAEL) relative to growth dysregulation for this mycotoxin**.** Several positive **outcomes** are anticipated to result from this work. First, 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 SOCS expression and IGF-1 as biomarkers might also have applicability to human epidemiological studies 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 are thus consistent with the goals of the **Food Safety, Toxicology and Utilization of Mycotoxin-Contaminated Grain Research Area**.