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PROJECT 1 ABSTRACT
(1 Page Limit)

During head blight, deoxynivalenol (DON or "vomitoxin") and other trichothecenes are elaborated that can potentially pose a threat to human health. Although regulated in the U.S. at 1 ppm in finished food, the European Economic Union and Codex are considering to establish much lower limits which could threaten the ability of U.S wheat, barley and resultant products to compete in the national and global economies. It is absolutely necessary that accurate data be available relative to human sensitivity to DON. Based on studies in the mouse immune system, we believe that the most critical step for DON toxicity induction is its action on cell signaling in leukocytes (white blood cells) and cytokine induction which then mediate acute and chronic illness. During the previous grant period, we have found that DON concentrations required to for induction of cytokines in blood leukocytes from the most sensitive human donors were indeed as sensitive as leukocytes from the mouse. To accurately measure the hazard of these toxins to humans, it is now essential that these in vitro studies be related to the in vivo mouse with respect to threshold dose, magnitude and duration of toxic effect. We hypothesize that the *minimal tissue concentrations of DON required for stress activation and cytokine induction in murine immune tissue in vivo correlate with concentrations for the same effects in vitro in human and mouse leukocytes*. Two specific objectives are proposed.. In Objective 1, we will complete studies on the sensitivity of blood leukocytes from different human donors to DON-induced stress activation and cytokine upregulation . Specifically, we will compare the concentrations of DON required for MAPK activation and cytokine mRNA response profile in the absence and presence of specific co-stimuli. These data will also be related to antiproliferative effects of DON. In Objective 2, we will identify the threshold doses of DON required for stress activation and cytokine upregulation in the mouse and corresponding DON tissue levels. Here, the lowest observed adverse effect level (LOAEL) and the no observed adverse level (NOAEL) for DON required to induce MAPK and cytokine production in the mouse will be determined in acute and chronic exposure models. These thresholds 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 of human described in Objective 1 and previous investigations with mouse leukocytes. The resultant data from this study will be used to assess the potential hazard of DON and related trichothecenes to humans and, ultimately, incorporated into future safety assessments employed by the U.S. and other governments.