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Project ID: 0506-PE-038
FY04 ARS Agreement #: 59-0790-4-119
Research Area: FSTU
Duration of Award: 1 Year
Project Title: Human Susceptibility to Trichothecenes.

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 Alimenterius have proposed much lower limits based on a few rodent studies. 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 consumers and 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 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. We hypothesize that the *minimal tissue concentrations of trichothecenes 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*. Three specific objectives are proposed: (1) Complete studies comparing the effects of DON and other trichothecenes on stress activation and cytokine upregulation in human leukocytes; (2) Determine threshold doses of acute and subchronic oral DON exposure required for stress activation and cytokine upregulation in the mouse and corresponding DON tissue levels; and (3) Determine the threshold doses of acute and subchronic intranasal DON exposure required for stress activation and cytokine upregulation in the mouse and corresponding DON tissue levels. In the latter two 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 of human described in Objective 1 and previous investigations with mouse leukocytes. The resultant data from this study 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