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PROJECT 1 ABSTRACT

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DON plant metabolites and congeners are perplexing to regulators. During *Fusarium* head blight of wheat and barley, deoxynivalenol (DON or "vomitoxin"), 3-acetyl-DON, and 15-acetyl DON are produced. When DON is elaborated within the kernel, varying amounts of the toxin are metabolized to new products rendering it non-toxic to the plant. One example is DON-3-glucoside (DON-3-G). Interestingly, gut microflora are able to convert DON-3-G to DON increasing its bioavailability. Currently, there is active discussion by JECFA and CODEX on how to best harmonize regulations for DON and its metabolites/congeners which could lead to added testing these compounds.

DON's main toxicological effects are anorexia and vomiting. Several research studies suggest these effects are mediated by neuroendocrine hormones produced by enteroendocrine cells (EECs), one of the four primary intestinal cell subtypes that populate the epithelial layer of the GI tract. DON-induced anorexia (mouse) corresponds to the CCK and PYY secretion by "I" cell EEC lineage in the duodenum and "L" cell EEC lineage of the ileum and colon, respectively. Emesis (mink) which corresponds to increased plasma PYY and 5-HT which is produced by the "EC" cell EEC lineage found throughout the GI tract. Current available cell culture models have limitations for assessing the toxicity of DON metabolites and congeners.

Comparative toxicity of DON plant metabolites and congeners can be assessed in mini-gut cultures. There has been much recent progress on the propagation of adult intestinal stem cells from animals making it now feasible to generate ever-expanding, three-dimensional epithelial organoid structures in mini-gut cell culture that replicate the *in vivo* epithelium of the intestine. We propose here to test the guiding hypothesis that DON, DON plant metabolites and DON congeners differentially regulate hormone secretion in mini-gut organoid cultures. In AIM 1, we will determine effects of DON on CCK, PYY and 5-HT secretion mini-gut cultures. In AIM 2, we will compare the differential effects of DON, DON plant metabolites and DON congeners on hormone secretion by mini-gut cultures.

Mini-gut data can be used to resolve regulatory conundrum. The resulting cutting-edge data can be directly applied to DON metabolite/congener safety assessments for establishing international guidelines. This will ensure precision in DON risk assessment/regulation that balances consumer protection and an adequate food supply. This research will be important because it will help discern whether DON plant metabolites and congeners are sufficiently toxic to be included in the tolerable daily intake (TDI) for DON. Taken together, this project is highly consistent with the goals of the FST Action Plan