Cover Page

<table>
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<tr>
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<tbody>
<tr>
<td>Institution:</td>
<td>Michigan State University</td>
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| Year:              | FY2003 (approx. May 03 – April 04) |
| FY03 ARS Agreement ID: | 59-0790-9-060                |
| FY03 ARS Agreement Title: | Human Susceptibility to Trichothecene Mycotoxins. |
| FY03 ARS Award Amount: | $ 74,218                     |

USWBSI Individual Project(s)

<table>
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<tr>
<th>USWBSI Research Area*</th>
<th>Project Title</th>
<th>ARS Adjusted Award Amount</th>
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<tr>
<td>FSTU</td>
<td>Human Susceptibility to Trichothecene Mycotoxins.</td>
<td>$ 74,218</td>
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Total Amount Recommended $ 74,218

Principal Investigator

Date

* BIO – Biotechnology  
CBC – Chemical & Biological Control  
EDM – Epidemiology & Disease Management  
FSTU – Food Safety, Toxicology, & Utilization  
GIE – Germplasm Introduction & Enhancement  
VDUN – Variety Development & Uniform Nurseries

(Form – FPR03)
Project 1: *Human Susceptibility to Trichothecene Mycotoxins.*

1. **What major problem or issue is being resolved and how are you resolving it?**

   Deoxynivalenol (DON or vomitoxin) and other trichothecenes are elaborated during head blight and thus pose a potential threat to human health. There have been several European studies that have suggested that a lower action level for DON be considered rather than the 1-2 ppm being employed by most countries. Based on the report of the Joint Expert Committee on Food Additives (JEFCA) on safety concerns for DON and other mycotoxins, the CODEX Alimentarius Commission has proposed the following maximum levels for DON are proposed for discussion: a) raw cereal grains, to be subjected to sorting or other physical treatment (e.g. starch production) before human consumption or use as an ingredient in foodstuffs (after which the DON levels should comply with the other relevant maximum level): 2000 µg/kg b) all products derived from cereals (e.g. flour, processed cereal products) including cereal grains intended for direct human consumption, except infant food: 500 µg/kg c) cereal-based infant food: 100 µg/kg. Also mixing of lots with the aim to decrease the contamination level below the maximum level would not be allowed.

   Based on studies in the mouse immune system, we believe that the most critical step for toxicity induction is its action on cell signaling in leukocytes (white blood cells). We currently evaluating whether human leukocyte cytokine production and/or apoptosis induction are indeed targeted by the same levels of DON and related 8-ketotrichothecenes as are the mouse equivalents. If this is true, then the risk of low ppm levels of DON to humans will be extremely small when one considers the diversity of the human diet and the actual potential level of DON exposure in human tissues. Such evidence is critical because it would support the argument against establishing lower action levels than those currently set for DON.

2. **What were the most significant accomplishments?**

   a. We have demonstrated novel kinases involved in trichothecene-induced cell death in cloned human macrophage and T cell models. We submitted evaluation of the structure function effects trichothecene effects on a cloned human T lymphocyte model (Jurkat cells) for publication.

   b. We are continuing studies using the direct culturing of human blood obtained from volunteers and measuring key mediators of DON-induced toxicity by highly sensitive real-time PCR. The results suggest that some people may be resistant to DON whereas others are sensitive. DON sensitivity can vary within an individual perhaps due to non-genetic factors (e.g. prior/ongoing infections diet, medication,). We are continuing to expand our donor pool and collecting multiple samples to validate these findings relative to multiple cytokines.

   c. We have developed a rapid method for measuring DON in blood and tissue.

   d. We have written three major reviews on the toxicology of DON and related trichothecenes. One covers all aspects of DON toxicology and will be published in the Journal of Toxicology and Environmental Health this year. The second is based on a presentation at the DON Workshop in Dublin in September 2003, Ireland that is funded by the European International Life Sciences Institute. The third is based on a presentation at the International Mycotoxin Meeting in Kagawa, Japan in November, 2003.
Include below a list of the publications, presentations, peer-reviewed articles, and non-peer reviewed articles written about your work that resulted from all of the projects included in you grant. Please reference each item using an accepted journal format. If you need more space, continue the list on the next page.


