U.S. Wheat and Barley Scab Initiative
FY00 Final Performance Report (approx. May 00 – April 01)
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Cover Page

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Year:	**FY2000 (approx. May 00 – April 01)**
Grant Number:	**59-0790-9-060**
Grant Title:	**Fusarium Head Blight Research**
2000 ARS Award Amount:	**$58,140**

Project

Program Area	Project Title	Requested Amount
Food Safety, Toxicology, & Utilization	Human susceptibility to trichothecene mycotoxins.	$59,594.00
	Requested Total	$50,000.00[1]

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Principal Investigator Date

[1] Note: The Requested Total and the Award Amount are not equal.

Project 1: Human susceptibility to trichothecene mycotoxins.

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

Vomitoxin (VT or deoxynivalenol) 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 VT be considered (120 ppb) rather than the 1-2 ppm being employed by most countries. The Joint Expert Committee on Food Additives (JEFCA) met in 2001 to review safety concerns for VT and other mycotoxins. I worked with this group and the International Life Sciences Research Institute to provide a state-of-the-art review on toxicological issues related to VT.

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

2. What were the most significant accomplishments?

a. We completed evaluation of trichothecene effects on a cloned human macrophage model (U-937 cells). We found that VT at 100 to 1000 ng/ml stimulate production of three critical proinflammatory mediators, namely, the proinflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-- " (TNF- "), and for the chemokine, interleukin-8 (IL-8). Four other 8-ketotrichothecenes, fusarenon X, nivalenol, 3-acetyl DON, and 15-acetyl DON, were also capable of up-regulating or suppressing TNF-" , IL-6, and IL-8 production at similar concentrations to VT. Interestingly, the higher trichothecene concentrations were markedly cytotoxic. This work has been written up and accepted for publication (Sugita-Kinoshi et al., 2001).

b. We just completed evaluation of trichothecene effects on a cloned human T lymphocyte model (Jurkat cells). Although VT at concentrations of 60 to 500 ng/ml could stimulate interleukin 2 production, the four other trichothecenes were not stimulatory. VT and 15-acetyl DON at 60 to 500 ng/ml and 3-acetyl DON at 600 to 5000 ng/ml could induce interleukin-8 production. Again, the higher trichothecene concentrations were markedly cytotoxic. This work is currently being written up for publication.

c. We have optimized conditions for the primary culture of human leukocytes and conducted preliminary experiments on the effects of VT. Two culture approaches are being used. The first involves direct culturing of human blood obtained from volunteers. For the second approach, we have established an agreement with the Red Cross to provide us with human blood cells that are a by-product of donor blood processing. In both approaches, we have observed that VT will directly induce interleukin-6 and –8. However, the doses required for these effects in primary appear to be lower that for cloned cell models suggesting that human primary cells are highly sensitive to VT and potentially other trichothecenes.

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 the grant. Please reference each item using an accepted journal format. If you need more space, continue the list on the next page.

a. Sugita-Kinoshi, Y and Pestka, J.J. Differential. 2001 Up-regulation of TNF- , IL-6 and IL-8 Production by Deoxynivalenol (Vomitoxin) and Other 8-Ketotrichothecenes in a Human Macrophage Model. J. Toxicol. Environ. Health. (in press)
b. Pestka, J.J. Deoxynivalenol: Toxicology and Potential Effects on Humans. 2001. Report submitted to the International Life Sciences Institute
c. Chung, Y-H., G-H. Yang, and J.J. Pestka. 2001. Up-regulation of macrophage inflammatory protein-2 and complement 3A receptor by trichothecenes. Abstr. 40th Ann. Meet. Soc. Toxicol. (San Francisco, CA).
d. Zhou, H.R. and J.J. Pestka. 2001. Activation of JNK, ERK and P38 mitogen-activated protein kinases by the trichothecene vomitoxin (deoxynivalenol): Role of translational arrest and double stranded RNA-dependent protein kinase R (PKR). Abstr. 40th Ann. Meet. Soc. Toxicol. (San Francisco, CA).
e. Hinton, D.M., M.J. Myers, A. Perltoni, F. Hines, R. Raybourne, R.E. Sotomayor, J. Shaddock, A. Warbritton, M. Chou and J.J. Pestka 2001. Enhanced histopathology with morphometry, immuno- and in-situ staining in immunotoxicity studies of the mycotoxins aflatoxin B_1 and deoxynivalenol. Abstr. 40th Ann. Meet. Soc. Toxicol. (San Francisco, CA).
f. Uzarski, R. and J.J. Pestka. 2001. Upregulation of mitogen-activated protein kinases (MAPKs) and caspase-3 by vomitoxin (deoxynivalenol) in Jurkat T cells. Abst. 40th Ann. Meet. Soc. Toxicol. (San Francisco, CA)
g. Zhou, H.R. and J.J. Pestka. 2001. Essential role of non-receptor tyrosine kinase Hck in vomitoxin-induced phosphorylation of JNK, ERK, and p38 mitogen-activated protein kinases. Abstr. Soc. Exp. Biol. Ann Meet. (Orlando, FL).
h. Islam, Z. and J.J. Pestka. 2001. Role of corticosteroids in LPS-mediated potentiation of trichothecene-induced lymphocyte apoptosis. Abstr. Soc. Exp. Biol. Ann. Meet. (Orlando, FL).
i. Pestka, J.J. 2000. Toxic effects of deoxynivalenol on cellular and immune function. Annual Meeting for Fusarium Head Scab Initiative (Cincinnati, OH).
j. Pestka, J.J. 2000. Deoxynivalenol. Symposium on Significance of Mycotoxins to the Global Food Supply. Sponsored by the International Life Sciences Institute in conjunction with the International Association for Food Protection 87th Annual Meeting (Atlanta, GA).
k. Uzarski, R., Clarke, J., Uzarski, D. and Pestka, J.J. 2000. Trichothecene-induced apoptosis in B cell lymphomas: Quantitative structure activity relationships. Cancer and Molecular Genetics in the 21st Century. Van Andel Research Institute. (Grand Rapids, MI).