

MICROBIOLOGICAL TOXINS

FUMONISIN-INDUCED LIVER TOXICITY IN MICE IS INDEPENDENT OF THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR α (K. A. Voss, J. Liu, J.D. Miller, J.R. Owen, R.T. Riley, C.W. Bacon, J.C. Corton)

Fumonisin mycotoxins occur worldwide in corn and foods made from corn. Fumonisin B₁ (FB₁) causes liver and kidney cancer in rodents and is a suspected human carcinogen. It inhibits the enzyme ceramide synthase and disrupts sphingolipid metabolism and function. The events linking ceramide synthase inhibition to toxicity are not understood and their elucidation is important for understanding fumonisin's mode of action. Sphinganine (Sa) and sphingosine (So) accumulate in tissues of fumonisin-exposed animals as a result of ceramide synthase inhibition and they have been shown to bind mouse recombinant peroxisome proliferator-activated receptor α (PPAR α) *in vitro*. Activation of PPAR α by peroxisome proliferator compounds alters the expression of genes involved in lipid metabolism, peroxisome proliferation, and cell proliferation. Therefore, to explore whether PPAR α -dependent pathways are involved in fumonisin toxicity, genetically modified mice lacking PPAR α (PPAR α -null) and their genotypic wild types (WT) were fed for one week control diets or diets containing 300 ppm FB₁, *F. verticillioides* culture material (CM=fungus-contaminated corn produced under controlled laboratory conditions) providing 300 ppm FB₁, or 500 ppm of the peroxisome proliferator WY-14,643. WT but not PPAR α -null mice responded to WY-14,643, exhibiting enlarged livers and hepatocyte proliferation in the absence of increased Sa and So concentrations. FB₁ and CM were toxic to both mouse strains and the liver effects were different from those induced by WY14,643 in WT mice. They included, in addition to cell proliferation, increased Sa concentrations and hepatocyte cell death by apoptosis. Gene expression profiles of WT mice fed FB₁, CM or WY14,643 were also compared. FB₁ and CM elicited similar expression patterns of genes involved in cell proliferation, signal transduction, and glutathione metabolism. In addition, this gene expression pattern differed from that induced by WY-14,643 and involved PPAR α -independent alterations of genes involved in lipid metabolism. The findings indicate that FB₁-induced liver toxicity in mice does not require PPAR α and that *F. verticillioides* does not produce metabolites that have significant peroxisome proliferator activity.

REPRODUCTIVE TOXICITY OF FUMONISIN-PRODUCING *FUSARIUM VERTICILLIOIDES* IN THE LM/Bc AND CD1 MOUSE STRAINS (K. A. Voss, J. B. Gelineau-van Waes, R. T. Riley, T. D. Burns, and C. W. Bacon)

Fumonisin mycotoxins are produced by *Fusarium verticillioides*, a fungus commonly found in corn. Their health effects in humans are not known, however, recent findings suggest that they might be a risk factor for neural tube defects (NTDs) in populations consuming large quantities of contaminated corn. Fumonisin B₁ (FB₁) was not teratogenic when given orally to pregnant CD1 mice during gestation days (GD) 7-15. Intraperitoneal injection of ≥ 5 mg/kg body weight FB₁ to pregnant mice of the inbred LM/Bc strain on GD 7.5-8.5 caused NTDs in the fetuses. To compare the susceptibility of these strains to fumonisin-induced NTDs, female LM/Bc and CD1 mice were fed diets containing 0 (control), 50 or 150 ppm FB₁ (provided by *F. verticillioides* culture material) beginning 5 weeks before mating to unexposed males. The pregnant females and their fetuses were examined after GD16. Microscopic examination of the livers established that the 150 ppm diet was maternally toxic to both strains, however, no significant effects on fertility and litter size were noted. No NTDs or evidence of fetotoxicity was found in LM/Bc or CD1 groups fed the control or 50 ppm diets. At 150 ppm, one of five (20%) LM/Bc litters was positive for NTDs. While no NTDs were found in fetuses of the CD1 group fed 150 ppm, fetotoxicity occurred in two high-dose CD1 litters; the incidence of dead fetuses therein ranged from 40 to 64%. These findings

suggest that the dietary no observed effect level for NTDs in the LM/Bc strain is ≥ 50 ppm FB1, NTDs develop at maternally toxic doses, and strain-dependent differences in sensitivity to fumonisin-induced fetotoxicity and NTDs exist.

