



## Texas Department of Health

William R. Archer III, M.D.  
Commissioner of Health

Patti J. Patterson, M.D., M.P.H.  
Executive Deputy Commissioner

1100 West 49th Street  
Austin, Texas 78756-3199  
(512) 458-7111  
<http://www.tdh.state.tx.us>

### TEXAS BOARD OF HEALTH

Walter D. Wilkerson, Jr., M.D., Chairman  
Mary E. Ceverha, M.P.A., Vice-Chair  
Mario R. Anzaldua, M.D.  
J. C. Chambers  
David L. Collins, P.E.  
Ruth F. Stewart, M.S., R.N.C.

August 7, 2000

Dr. Jane Henney  
Food and Drug Administration  
Dockets Management Branch (HFA-305)  
Docket No. 00D-1277  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

Dear Dr. Henney:

We are submitting this letter to comment on the proposed "Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds" and to request a participatory role in developing the scientific basis for any necessary regulation and control of these natural toxins.

The Texas Department of Health (TDH) has a long history of interest in the possible health risks specifically, those involving neural maturation and development and liver toxicity, associated with fumonisins. We first expressed our concerns to the Food and Drug Administration (FDA) in September of 1992, in a letter addressed to Dr. David Kessler (copy attached). We had noted a temporal relationship between high levels of fumonisins in corn-based animal feed, an unusual epizootic of equine leukoencephalomalacia (ELEM), and an unusual cluster of anencephalic babies born to Hispanic mothers along the Texas-Mexico border. We were not able to identify any plausible environmental cause; however, we did note that border Hispanics traditionally consume large quantities of corn-based products in the form of corn tortillas. In our letter we asked the FDA a number of questions and urged that a preliminary decision be made regarding acceptable levels of fumonisins in corn intended for human consumption and/or animal feed. Replying for your agency, Dr. Fred Shank, the Director of the Center for Food Safety and Applied Nutrition, wrote "...[we] hope to work with you and other organizations in developing the scientific basis for any necessary regulation and control of these natural toxins in foods and feeds."

Since we first voiced our concerns, a great deal of progress has been made towards answering some of the questions we posed in our letter. Some of the data, particularly those that address the distribution of the compound in animal-based human foods, has been reassuring. Other data published since 1992 have been less reassuring.

00D-1277

An Equal Employment Opportunity Employer

C 6

As early as 1991, researchers noted that fumonisins appear to cause liver cancer in rodents (Gelderblom 1991). While there is evidence that fumonisins may not be genotoxic, there is other evidence that at dietary levels below those necessary to induce significant changes in sphingolipid concentrations, fumonisins may have a cancer promoting effect (Gelderblom 1996). Additionally, there is evidence that at higher levels, they might act as cancer inducers (Hirschberg 1996). Recently, the National Center for Toxicologic Research (NCTR) concluded that there is "clear evidence of carcinogenic activity of fumonisin B<sub>1</sub> in ...male F344/N rats [and]...in female B6C3F<sub>1</sub> mice" (NTP technical report 1999). As impressive as the long-term feeding studies that NCTR used to come to this conclusion, the issue of exposures to multiple hepatotoxins were not addressed. In addition, questions remain regarding the effects of fumonisin exposure in a population potentially exposed to alcohol, chronic hepatitis C or B infection, or aflatoxins.

In Texas, Hispanics (a population with a high per capita consumption of corn products) have some of the highest liver cancer rates in the United States (TDH unpublished data). During the years 1995-1996, the age adjusted liver cancer rates for Hispanic males was 12.8 per 100,000; a rate three times the rate observed in non-Hispanic males. Hispanic females also have rates two to three times those of non-Hispanic white and African-American females.

While the "Background Paper in Support of Fumonisin Levels in Corn and Corn Products Intended For Human Consumption" addressed some of the cancer research, it did not address the potential for developmental effects. Some of the developmental work may have been discounted because of the belief that fumonisins do not cross the placenta. While there is experimental evidence that fumonisins do not cross the placenta (Reddy 1996, LaBorde 1996), there also is experimental evidence suggesting developmental toxicities both in cultured ex-utero rat fetuses and in maternally exposed hamsters (Floss 1994, Penner 1998) and mice (Gross 1994, Gross 1994, Reddy 1996). Rat fetuses exposed ex-utero to the aminopentol hydrolysis product (such as would be formed during the nixtamilization process during the production of tortillas) developed neural tube defects (Flynn 1994). One possible explanation for this seeming paradox is the fact that the placenta concentrates folate in favor of the fetus and fumonisins appear to inhibit cellular uptake of folate in both a time- and concentration-dependent fashion (Stevens 1997). Since adequate concentrations of the water-soluble vitamin folate are needed for proper neural tube formation, any toxin that interfered with folate uptake by the placenta could effect development. Unfortunately none of the published developmental work addresses folate issues. Ideally, in such experiments, folate intake would be carefully controlled and fetal folate levels would be assessed. Since fetal resorptions were so common in the developmental settings, it also might be useful to terminate the pregnancies of the experimental animals immediately after closure of the neural tube, rather than later in the gestation.

There is, in addition, clinical evidence to support a role for fumonisins in neural tube defects. Texas Hispanics, have the distinction of having some of the highest neural tube defects (NTD) in the United States. For instance, the NTD rate for Hispanic women living in the 14 Texas counties that border Mexico was 13.8 per 10,000 live births for the years 1993-1998 (TDH

Dr. Jane Henney  
August 7, 2000  
Page 3

unpublished data). Between 1990-1991 (TDH unpublished data), the period when the levels of fumonisins in corn were reported to be high, NTD rates in Cameron County were 27.1 per 10,000 live births (TDH unpublished data); this is a level three times higher than the national rates which are generally less than 10 per 10,000.

Since fumonisins are common in corn-based food, the likelihood that a population is exposed to fumonisins depends on the prevalence of fumonisins in corn-based foods and the population-specific consumption of corn-based foods. Worldwide, there is wide variation in consumption of corn-based foods. Per capita daily consumption ranges from 4-17 grams for Switzerland, Germany and Canada to 450 grams for the Transkei area of South Africa (Solfrizzo 1997 and Kuiper-Goodman 1996). In Texas, Hispanic women living along the border consume a substantial amount of corn (primarily in the form of tortillas); women of childbearing age eat, on average, 110 corn tortillas per month (or about 86 grams per day). When one also considers the consumption of fresh and canned corn, corn chips, corn flakes, and tortillas in foods, the grams consumed per day would likely be in the range of 95-100 grams per day for women.

In summary, there is clear evidence that fumonisins are carcinogenic in some animal species and sufficient evidence indicating that these compounds may be able to affect the neural development of the fetus. The Hispanic population in Texas is likely exposed to fumonisins through diet. This information, coupled with Texas-Hispanic-specific mortality and morbidity data, lead us to conclude that the four (4) ppm maximum fumonisin level recommended for masa and other corn products may be too high. We would highly recommend that any risk assessment performed to determine appropriate levels for humans take into consideration the consumption patterns of the Texas Hispanic population.

Sincerely,



William R. Archer, M.D.  
Commissioner of Health

Attachment

Floss JL, Casteel SW, Johnson GC, Rottinghaus GE, Krause GF. Developmental toxicity of fumonisin in Syrian hamsters. *Mycopathologia*. 1994;128(1):33-38.

Flynn TJ, Pritchard D, Bradlaw J, Eppley R, Page S. Effects of the mycotoxin fumonisin B<sub>1</sub> and its alkaline hydrolysis product on presomite rat embryos in vitro [abstract]. *Teratology*. 1994;49:404. Abstract P74.

Gelderblom WCA, Smuts CM, Abel S, Snyman SD, van der Westhuizen, Huber WW, Swanevelder S. Effect of fumonisin B<sub>1</sub> on the levels and fatty acid composition of selected lipids in rat liver *in vivo*. *Food Chem Toxicol*. 1997;35(7):647-656.

Gelderblom WCA, Snyman SD, Lebepe-Mazur S, van der Westhuizen L, Kriek NPJ, Marasas WFO. The cancer-promoting potential of fumonisin B<sub>1</sub> in rat liver using diethylnitrosamine as a cancer initiator. *Cancer Letters*. 1996;109(1-2):101-108.

Gelderblom WCA, Kriek NPJ, Marasas WFO, Thiel PG. Toxicity and carcinogenicity of the *Fusarium moniliforme* metabolite, fumonisin B<sub>1</sub> in rats. *Carcinogenesis*. 1991;12:1247-1251.

Gross SM, Rajasekhar VR, Rottinghaus GE, Johnson G, Reddy CS. Developmental effects of fumonisin B<sub>1</sub>-containing *Fusarium moniliforme* culture extract in CD1 mice. *Mycopathologia*. 1994;128(2):111-118.

Gross SM, Reddy CS, Reddy RV, Johnson G, Rottinghaus GE. Maternal mediation of the developmental toxicity of fumonisin B<sub>1</sub> in CD1 mice [abstract]. *FASEB*. 1994;8:A407. Abstract 2357.

Hirschberg K, Zisling R, van Echten-Deckert G, Futerman AH. Ganglioside synthesis during the development of neuronal polarity. *J Biol Chem*. 1996;271(25):14876-14882.

Kuiper-Goodman T, Scott PM, McEwen NP, Lombaert GA, NG W. Approaches to the risk assessment of fumonisins in corn-based foods for Canada. In: Jackson LS, DeVries JW, Bullerman LB, eds. *Advances in Medical Biology, Volume 392, Fumonisins in Food*. New York: Plenum Press; 1996:369-393.

LaBorde JB, Terry KK, Collins TXF, Schackelford ME, Hansen DK. Developmental toxicity of fumonisin (FB<sub>1</sub>) in New Zealand white (NZW) rabbits [abstract]. *Teratology*. 1996;53:114. Abstract P42.

NTP technical report on the toxicology and carcinogenesis studies of fumonisin B<sub>1</sub> in F344/N rats and B6C3F<sub>1</sub> mice (feed studies). Washington DC: National Institutes of Health; 1999. Publication No. 99-3955. Case No. 116335-83-0.

Penner JD, Casteel SW, Pittman L Jr, Rottinghaus GE, Wyatt RD. Developmental toxicity of purified fumonisin B<sub>1</sub> in pregnant Syrian hamsters. *J Appl Toxicol*. 1998;18:197-203.

Reddy RV, Johnson G, Rottinghaus GE, Casteel SW, Reddy CS. Developmental effects of fumonisin B<sub>1</sub> in mice. *Mycopathologia*. 1996;134(3):161-166.

Solfrizzo M, Avantaggiato G, Visconti A. Rapid method to determine sphinganine/sphingosine in human and animal urine as a biomarker for fumonisin exposure. *J Chromatogr B*. 1997;692(1):87-93.

Stevens VL, Tang J. Fumonisin B<sub>1</sub>-induced sphingolipid depletion inhibits vitamin uptake via the glycosylphosphatidylinositol-anchored folate receptor. *J Biol Chem*. 1997;272(2):18020-18025.

