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Background Paper in Support of Fumonisin Levels in Corn and Corn Products Intended for Human Consumption

Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds

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Center for Food Safety and Applied Nutrition
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This background paper discusses the basis for CFSAN's guidance on fumonisin levels in corn and corn products intended for human consumption.

BACKGROUND

Fumonisins are environmental toxins produced mainly by the molds *Fusarium moniliforme* (*F. verticillioides*), *F. proliferatum*, and several other *Fusarium* species that grow on agricultural commodities in the field or during storage. These mycotoxins have been found worldwide, primarily in corn. More than ten types of fumonisins have been isolated and characterized. Of these, fumonisin B1 (FB_1), B2 (FB_2), and B3 (FB_3) are the major fumonisins produced. The most prevalent of these mycotoxins in contaminated corn is FB_1, which is believed to be the most toxic (Thiel *et al*., 1992, Musser and Plattner, 1997).

OCCURRENCE IN RAW CORN

The levels of fumonisins in raw corn are influenced by environmental factors such as temperature, humidity, drought stress, and rainfall during pre-harvest and harvest periods. For example, high levels of fumonisins are associated with hot and dry weather, followed by periods of high humidity (Shelby *et al*., 1994). Fumonisin levels in raw corn are also influenced by storage conditions. For example, optimal growth of fumonisin-producing mold that leads to increased levels of fumonisin in the raw corn can occur when the moisture content of harvested raw corn during storage is 18-23 percent (Bacon and Nelson, 1994).
High levels of fumonisins may also occur in raw corn that has been damaged by insects (Miller, 1999, Bacon and Nelson, 1994). However, corn hybrids genetically engineered with genes from the bacterium *Bacillus thuringiensis* (*Bt* corn) that produce proteins that are toxic to insects, specifically the European corn borer, have been found to be less susceptible to *Fusarium* infection and contain lower levels of fumonisins than the non-hybrid corn in field studies (Munkvold *et al.*, 1997, Munkvold *et al.*, 1999).

OCCURRENCE IN PROCESSED CORN PRODUCTS

One of the major factors that determines the level of fumonisins in processed corn products is whether a dry- or wet-milling process is used. The whole corn kernel consists of the following major constituents:

Starch - the most abundant constituent from which corn starches and corn sweetners are produced
Germ - located at the bottom of the center of the kernel from which corn oil is produced
Gluten - contains the majority of the protein found in corn kernel
Hull (Pericarp) - the outer coat of the kernel from which corn bran is produced

Dry milling of whole corn kernel generally results in the production of fractions called bran, flaking grits, grits, meal, and flour. Because the fumonisins are concentrated in the germ and the hull of the whole corn kernel, dry milling results in fractions with different concentrations of fumonisins. For example, dry milled fractions (except for the bran fraction) obtained from degermed corn kernels contain lower levels of fumonisins than dry milled fractions obtained from non-degermed or partially- degermed corn. Industry information indicates that dry-milling results in fumonisin-containing fractions in descending order of highest to lowest fumonisin levels: bran, flour, meal, grits, and flaking grits. Consequently, corn products such as corn bread, corn grits, and corn muffins made from the grits and flour fractions may contain low levels of fumonisins. Ready-to-eat breakfast cereals made from flaking grits, such as corn flakes and puffed type cereals, contain very low levels (non-detectable to 10 parts per billion (ppb)) of fumonisins (Stack and Eppley, 1992).

Data provided by the North American Millers' Association (NAMA) accumulated over two crop years (1997 and 1998) indicate that degermed corn meal in the U. S. has a mean level of total fumonisins of 0.15 parts per million (ppm) (Standard Deviation (SD) = 0.50). The mean levels of total fumonisins in corn meal prepared from partially degermed and whole non-degermed corn were 0.59 ppm (SD = 1.01) and 1.21ppm (SD = 1.71), respectively, according to NAMA data.

Wet milling of whole corn generally results in the production of fractions called starch, germ, gluten, and fiber. Data indicate that this process results in fumonisin-containing fractions in descending order of highest to lowest fumonisin levels: gluten, fiber, germ, and starch (Bennett and Richard, 1996). No fumonisins have been detected in the starch fraction obtained from wet milling of fumonisin contaminated corn. The starch fraction is further processed for the production of high fructose corn syrups and other corn sweeteners (Bennett and Richard, 1996). Therefore, these types of products do not contain any detectable levels of fumonisins. Corn oil, extracted from corn germ and refined, does not contain any detectable levels of fumonisins (Patel *et al*., 1997). The gluten and fiber fractions from the wet-milling process do contain fumonisins; however, these fractions are used to produce animal feed, such as corn gluten meal and corn gluten feed.

Another process that whole corn may be subjected to is nixtamalization, which consists of boiling the raw corn kernels in aqueous calcium hydroxide solution (lye), cooling, and washing to remove the pericarp and excess calcium hydroxide. The washed kernels are then ground to produce the masa, from which corn chips and tortillas are made. This process has been shown to reduce levels of fumonisins that may be present in raw corn kernels (Dombrink-Kurtzman and Dvorak, 1999). However, because information is lacking on the degree of fumonisin reduction that occurs, further studies (e.g., determining fumonisin levels at each stage of the nixtamalzation process) are needed.

Fumonisins may also be found at low levels (0.1 - 0.6 ppm) in whole kernels of unpopped popcorn (Bullerman and Tsai, 1994). However, recent data provided by The Popcorn Institute indicate that fumonisin levels in whole, cleaned kernels of unpopped popcorn ranged from non-detectable to 2.8 ppm. In addition, recent preliminary studies by the popcorn industry suggest popping corn results in significant reduction of fumonisins that may be present in cleaned kernels of unpopped popcorn.

Available data indicate the presence of low levels (4 - 82 ppb) of fumonisins in sweet corn (Trucksess *et al*., 1995). In addition, current data regarding beer show that fumonisins can be present, but at very low levels (0.3 to 12.7 ppb), and distilled spirits made from corn do not contain fumonisins (Hlywka and Bullerman, 1999; Bennett and Richard, 1996). Further, FDA recognizes that purple color additive, prepared either by expressing the juice from mature purple corn or by water infusion of the dried purple corn as provided in § 73.260 of Title 21 of the Code of Federal Regulations (21 CFR 73.260), may be expected to contain fumonisin levels that are similar to those present in purple corn. However, information on the occurrence of fumonisins in edible purple corn currently is lacking.

Broken kernels of corn which have been screened from bulk lots of corn prior to any milling process are higher in fumonisins than whole kernels, and are often used in animal feeds. It has been found that fumonisins in animal feeds are poorly absorbed by farm animals after ingestion. Fumonisin residues in milk (Richard *et al.*, 1996, Scott *et al.*, 1994, Maragos and Richard, 1994, Becker *et al.*, 1995), eggs (Vudathala *et al.*, 1994), and meat (Prelusky *et al.*, 1994, Prelusky *et al.*, 1996, Smith and Thakur, 1996) are therefore either undetectable or detected at extremely low levels.

Based on available occurrence information for fumonisins in processed corn products, FDA believes that the recommended fumonisin levels can be achieved with the use of good agricultural and good manufacturing practices. FDA recognizes that during a year with adverse weather conditions, high levels of fumonisins in corn may occur. However, until additional information on the year-to-year variability of fumonisin occurrence (especially for bad weather years) is available for further evaluation, FDA considers the recommended levels for fumonisins in corn and corn products for human consumption to be a prudent public health measure.

ANIMAL HEALTH EFFECTS

Substantial information exists on the adverse health effects of fumonisins in animals that serves as the basis for concern with the potential adverse effects of fumonisins on human health.

<u>Livestock Health Effects</u>

Ingestion of fumonisin-contaminated corn and corn screenings can result in a variety of adverse health effects in livestock.. *F. moniliforme* in moldy feed, particularly corn feed, has been associated with horse and pig deaths since the 1970's. The horse is known as the species most sensitive to fumonisins, and equine leukoencephalomalacia (ELEM) is the most frequently encountered disease associated with *F. moniliforme* (Kellerman *et al.*, 1990, Ross *et al.*, 1993, Wilson *et al*., 1992). ELEM is characterized by liquefactive necrosis of the cerebral hemispheres. Porcine pulmonary edema was produced within 3-4 days after pigs started consuming a diet that provided 20 mg of FB_1/kg body weight each day. (Smith *et al.*, 1999).

<u>Experimental Animal Health Effects</u>

Fumonisins have produced liver damage and changes in the levels of certain classes of lipids, especially sphingolipids, in all animals studied (Merrill *et al*., 1997). Kidney lesions were also found in many animals (Norred *et al*., 1998, Merrill *et al*., 1997). Feeding of *Fusarium* culture material containing fumonisins has also been associated with heart failure in baboons (Kriek *et al.*, 1981) and swine (Smith *et al*., 1999), with atherogenic effects in vervet monkeys (Fincham *et al.*, 1992), and with medial hypertrophy of pulmonary arteries in swine (Casteel *et al.*, 1994).

Chronic feeding of purified FB_1 (at levels of 50 ppm or more) produced liver cancer and decreased life span in female $B6C3F_1$ mice and kidney cancer in male F344/N rats without decreased life spans (NTP, 1999). At lower exposures, no carcinogenic effect was observed. However, in a smaller study using *Fusarium* culture material, the feeding of similar levels of fumonisins (50 ppm) to BD IX male rats resulted in liver cancer (Gelderblom *et al.*, 1991). Fumonisin was negative in genotoxicity assays (Norred *et al.*, 1992, Gelderblom *et al.,* 1992).

HUMAN HEALTH EFFECTS

Currently, there is no direct evidence that fumonisins cause adverse health effects in humans. Studies currently available demonstrate only inconclusive associations between fumonisins and human cancer. Investigators in South Africa suggested an association between high levels of fumonisin-producing molds on corn used to make alcoholic beverages and esophageal cancer in human subgroups (Rheeder *et al.*, 1992). However, those studies were limited by the lack of controlled conditions, particularly for established confounding risk factors (e.g., alcohol consumption), and therefore do not allow any definitive conclusions to be made about cancer causation in humans. Other studies associating high levels of fumonisin-producing molds on corn with esophageal cancer lacked similar controls (Chu and Li, 1994), or did not measure fumonisin levels (Franceschi *et al.*, 1990). Further, in an area of China with high incidence of gastric cancer, Groves *et al.* (1999) observed a lack of association between consumption of fumonisin contaminated corn with gastric or any other human cancer.

In a limited epidemiological study in India, an association between high levels of fumonisins (but not other mycotoxins) in moldy sorghum and corn and gastrointestinal symptoms (e.g., cramping and diarrhea) was noted (Bhat *et al.*, 1997). However, this study also lacked control of established risk factors. In addition, contaminants other than mycotoxins cannot be eliminated as causative factors, and a similar association was not detected in studies conducted in other countries.

Other factors that make it difficult to extrapolate the results of these studies are the differences in agricultural and nutritional conditions in those countries relative to those in the U.S. For example, the U.S. corn supply generally contains significantly lower levels of fumonisins than corn from the rural areas in the South African study. Further, in some instances the study populations significantly were malnourished in comparison with the U.S. population.

Limited studies (e.g., Flynn *et al.*, 1997, Collins *et al.*, 1997, Flynn *et al.*, 1996) have suggested potential developmental effects, such as neural tube defects (NTD), could be associated with exposure to fumonisins. However, the association of NTD with dietary exposure to fumonsins is only based on theoretical conclusions at this time. Indeed these studies also suggest that fumonisin B_1 is not teratogenic until general toxicity occurs and does not pass the placenta. A great deal more definitive scientific information is needed to elucidate further the role of other confounding factors, such as inadequate folate intake, which is an established NTD risk factor. In addition, further information on the dietary intake of corn products by specific population groups (e.g., Texas Hispanics) and the levels of fumonisins found in those corn products are needed to assess further the potential risk associated with dietary exposure to fumonisins.

Nevertheless, as discussed above and in the document entitled "Background Paper in Support of Fumonisin Levels in Animal Feed" prepared by FDA's Center for Veterinary Medicine (CVM), fumonisins have been shown to produce a variety of significant adverse health effects in livestock and experimental animals. Therefore, because human physiology is similar to the physiology of many animals (e.g., other primates, cardiovascular system of swine), an association between fumonisins and human disease is possible.

CONCLUSION: PUBLIC HEALTH CONCERNS

Currently, the available information on human health effects associated with fumonisins is not conclusive. However, based on the wealth of available information on the adverse animal health effects associated with fumonisins (discussed in this document and in the document entitled "Background Paper in Support of Fumonisin Levels in Animal Feed" prepared by FDA's CVM), FDA believes that human health risks associated with fumonisins are possible.

Based on the current available occurrence data, levels of fumonisins in human foods derived from corn are normally quite low. At the present time, FDA believes that these levels present a negligible public health risk. Nevertheless, FDA considers the fumonisin guidance levels to be a prudent public health measure during the development of a better understanding of the human health risk associated with fumonisins and the development of a long-term risk management policy and program by the agency for the control of fumonisins in human foods and animal feeds.

The recommended maximum levels for fumonisins in corn and corn products intended for human consumption (Table 1) are based on concerns associated with hazards shown primarily by animal studies. However, based on available information on the occurrence of fumonisins, FDA believes that typical fumonisin levels found in corn and corn products intended for human consumption are much lower than the recommended levels.

Table 1. Human Foods

Product	Total Fumonisins ($FB_1 + FB_2 + FB_3$) parts per million (ppm)
Degermed dry milled corn products (e.g., flaking grits, corn grits, corn meal, corn flour with fat content of < 2.25 %, dry weight basis)	2 ppm
Whole or partially degermed dry milled corn products (e.g., flaking grits, corn grits, corn meal, corn flour with fat content of ≥2.25 %, dry weight basis)	4 ppm
Dry milled corn bran	4 ppm
Cleaned corn intended for masa production	4 ppm
Cleaned corn intended for popcorn	3 ppm

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Pesticides, Metals, Chemical Contaminants & Natural Toxins
