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Fumonisins

Fumonisins are a significant health risk to livestock, and potentially also to humans

Fumonisins are naturally occurring toxins produced by several species of *Fusarium* fungi (moulds). A number of different types of fumonisin are known, but fumonisins B_1, B_2 and B_3 (also named FB_1, FB_2 and FB_3) are the major forms found in food. Fumonisins were first recognized in 1988.

Fumonisins can have significant health effects in livestock and other animals. While the evidence for adverse health effects in humans is currently inconclusive, there are concerns that exposure to fumonisins may contribute to various serious adverse health outcomes such as cancer and birth defects.

Maize and maize-based products contain the highest amounts of fumonisins

The fungi *Fusarium verticillioides*, *F. proliferatum* and *F. fujikuroi*, as well as some less widespread *Fusarium* species, are common contaminants of maize, and to a lesser extent of wheat and other cereals included their derived products. They occur worldwide but are most common in warm climate and warm tropical areas where maize is grown.

Maize and maize-based products were found to have the highest occurrence and mean concentrations of FB_1 than any cereal or cereal-based product in an evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2016; with higher mean concentrations of FB_1 reported in products from Africa, Central and South America and some countries in the Western Pacific Region.

FB_1 is rarely detectable in milk, dairy products, meat and meat products, indicating that transfer into animal products is negligible. However, FB_1 has been found in the urine of exclusively breastfed infants, suggesting that human breast milk may be a source of exposure in young children.

The majority of reported data reveal levels of the free forms of fumonisins (FB_1, FB_2 and FB_3), however the toxins can also be bound to proteins and complex carbohydrates. While some studies have shown that the level of bound fumonisins can be higher than the free forms, data on the occurrence of bound fumonisins in different cereals, as well as the impact of processing on these bound forms, and their bioavailability after consumption, are limited.

Dietary exposure can vary greatly

Fumonisin contaminated maize

In national evaluations from a few countries in 2011–2016 (JECFA, 2016), the mean exposure to FB_1 and total fumonisins was generally below 250 ng/kg body weight (bw) per day (a nanogram is one billionth [1×10^{-9}] of a gram) in European countries. High exposures to FB_1 were reported for Guatemala, Zimbabwe and China, with a maximum of 7700 ng/kg bw per day for adults living in one rural province of China, while for total fumonisins the highest mean exposures were reported in Malawi, ranging from 3000 to 15 000 ng/kg bw per day. The highest national exposures to FB_1 and total fumonisins were observed in the youngest age groups.

In recent international exposure estimates from all dietary sources, using occurrence data mapped to food consumption data of the 17 GEMS/Food cluster diets, lower bound mean exposure estimates for FB_1 ranged from 2 ng/kg bw per day (cluster G09; mainly East Asian countries) to 560 ng/kg bw per day (cluster G05: mainly South and Central America), and for total fumonisins, ranged from 13 ng/kg bw per day (cluster G09) to 820 ng/kg bw per day (cluster G05, which includes Guatemala).

Maize is the predominant source of exposure to FB_1 and total fumonisins in most cluster diets and can lead to very high exposures in areas where maize is the main food source and contamination levels can be very high. Wheat can be an important contributor to exposure to fumonisins in those clusters where wheat is an important food source and less maize is consumed.

In animals, fumonisins are associated with a wide range of health effects

In all animal species tested, fumonisin B_1 has been associated with a wide range of adverse health effects, particularly on the liver and kidney. A particular concern is the cancer causing potential of the toxins, thought to arise following disruption of fat metabolism by the toxins, resulting in depletion of the fats known as complex sphingolipids and accumulation of the fats known as sphingoid bases and sphingoid base metabolites. Another concern is the potential immunotoxicity; depression of specific and nonspecific immune response has been observed in pigs and mice at low oral doses, but the data are inconclusive. Other concerns include possible indirect mutagenicity (DNA damage), although to date the weight of evidence indicates that fumonisins are neither directly mutagenic nor metabolized into DNA reactive compounds. Fumonisins have been observed to have effects on reproductive performance in pigs and rabbits, and birth defects – neural tube defects – have been induced in mice in a few studies. Concerning the potential neurotoxicity of fumonisins, while the toxins can induce leukoencephalomalacia (softening of brain tissue) in horses (equids), it is considered unlikely that fumonisins cross the blood–brain barrier and induce neurotoxic effects in the brain; rather, in equids, they are thought to act via disruption of vascular function. In pigs, the pulmonary edema caused by fumonisins has also been linked to altered vascular function. The altered vascular function is likely to be caused by accumulation of sphingoid bases and their phosphorylated metabolites in the blood.

In humans, the potential to contribute to cancer is a main concern

There are various health concerns in humans:

- the toxins are considered to have the potential to induce regenerative cell proliferation in the liver and kidney, leading to cancer in animal models, but there is no evidence for this in humans – of the few reports on the effects of fumonisins in humans, one study found no significant association between fumonisin exposure and the risk of hepatocellular cancer, while another study indicated FB_1 contamination in rice was associated with increased risk of oesophageal cancer;
- a study in women conducted in Guatemala showed that fumonisin intake from maize-based foods was correlated with evidence indicative of disruption of fat metabolism as seen in carcinogenicity studies conducted with animal models;

- fumonisins may be a cause of stunting – of two studies in the United Republic of Tanzania investigating the association of mycotoxin exposure and childhood growth, one study indicated that exposure to fumonisin from maize-based foods was associated with impairment of growth while the other study showed no significant association with stunting or underweight among infants;
- a study of the incidence of neural tube defects (NTD) among Mexican Americans on the Texas/Mexico border, combined with toxicological and earlier epidemiological studies, suggests that fumonisin exposure in pregnant women may be a contributing factor to increased NTD risk in babies;
- evidence to date indicates that fumonisins are not acutely toxic.

Thus observations on the health effects of the toxins on humans are limited and further studies to investigate the association of fumonisin exposure with cancer risk, child growth impairment, and NTDs in humans are needed.

Improved procedures for detecting fumonisins are needed

Many methods have been developed to detect fumonisins in maize and maize by-products, such as various types of chromatography, electrophoresis, and immunosorbent assays. Some of these methods are expensive and laborious. However, studies to develop a fumonisin detection procedure that is simple, rapid, and inexpensive are ongoing. A few studies with a limited number of samples indicate that substantial amounts of bound fumonisins may be present in raw maize, but commonly used analytical methods are not able to measure their occurrence.

To estimate fumonisin exposure in humans, biomarkers are increasingly being used. Urinary FB_1 (UFB_1) is the most commonly used biomarker; it has been used to evaluate the effectiveness of dietary interventions designed to help decrease fumonisin exposure in humans. UFB_1 is reflective of recent fumonisin exposure, but in areas where maize is a dietary staple and exposure is likely to occur year round, UFB_1 levels may be indicative of chronic exposure; data from such areas have been used to verify the biochemical mechanism of action in human populations exposed daily to large amounts of fumonisin over the course of one year.

Methods for preventing and controlling fumonisins are being developed

Fusarium infection and fumonisin production on maize occurs predominantly in the field environment. Fumonisin production rarely occurs post-harvest.

For the field, transgenic crops are being developed. For example, significantly lower levels of fumonisin have been demonstrated in *Bacillus thuringiensis* (Bt) maize, through reduction of insect pest damage and subsequent fungal infection; other transgenic crops are being developed which would themselves detoxify mycotoxins. Antagonistic microorganisms have also been used. Other methods using essential oils or specific microorganisms (lactic and propionic acid bacteria) to control fumonisins are being investigated in the laboratory. The primary method to reduce risk of fumonisin development in the field however is to implement good agricultural practice; this involves rotating crops, using hybrids or plant varieties suitable for the soil and climate, minimizing factors that increase plant stress, and implementing good soil management.

There have been studies on the effects of various processing procedures – sorting, cleaning, thermal processing (including extrusion), milling, fermentation and alkaline treatment (nixtamalization) – on the levels of FB_1, FB_2 and FB_3 contamination in cereals, primarily maize. Reduction of fumonisin levels during sorting and cleaning depends on the initial contamination level. During the wet milling process, fumonisins are reduced in part due to the solubility of the toxins in the steep water. In dry milled products, toxin distribution is dependent on the milling strategy used. The traditional and commercial alkaline treatment of maize known as nixtamalization is a proven method for reducing fumonisin contamination and reducing or eliminating the toxic effects of fumonisin in animal models. Feed additives which accomplish the same result as nixtamalization are also effective at reducing fumonisin toxicity.

Further studies are required to analyse the bound fumonisins created during processing, including cooking, and to test the toxicity of bound fumonisins in animal models. The few studies so far have shown that some processes, such as extrusion, cooking with glucose and nixtamalization, produce feeds that are less or not toxic in the animal models used.

WHO supports countries in controlling fumonisins

WHO, in collaboration with FAO, evaluates the science and develops risk assessments to define safe exposure levels. Based on these risk assessments, maximum levels for fumonisins in different foods are recommended. These form the basis for national regulations to limit contamination.

Since first being noted in 1988, fumonisins have several times been the subject of toxicological evaluation and dietary exposure assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). These evaluations inform the Codex Alimentarius Commission[1] which has worked, since 1963, to create harmonized international food safety standards to protect the health of consumers and ensure fair trade practices.

Codex standards set the maximum levels for contaminants and natural toxins such as fumonisins in food, and are the reference for the international trade in food, so that consumers everywhere can be confident that the food they buy meets agreed standards for safety and quality, no matter where it was produced. The maximum levels for fumonisins in grain from raw maize and maize flour and meal are 4000 and 2000 µg/kg (a µgram is one millionths [1×10^{-6}] of a gram). respectively. To prevent and reduce the risk of fumonisins in food and feed, Codex has established codes of practice which describe preventive measures.

In support of this work, WHO collects food contamination data from nationally recognized institutions through the Food Contamination Monitoring and Assessment Programme of the WHO Global Environment Monitoring System, commonly known as GEMS/Food[2]. The GEMS/Food contaminants database informs governments, the Codex Alimentarius Commission and other relevant institutions, as well as the public, on levels and trends of contaminants in food.

The WHO GEMS/Food programme has also developed a Consumption Cluster Diets database, which provides an overview of food consumption patterns worldwide, through 17 dietary patterns (based on population food choices) covering more than 180 countries. These estimates, together with reported contamination levels, allow assessment of the potential exposure of populations to contaminants such as fumonisins in food. These diets are based on Food Balance Sheet data collected by FAO, and are routinely used by international risk assessment bodies.

The accuracy of the dietary exposure estimates at the country level, based on the input of data in the GEMS/Food contaminants and GEMS/Food cluster diets, is highly dependent on the quality/accuracy of the data in characterizing the conditions in specific countries which can be highly variable.

National authorities are developing regulations to limit contamination

Exposure to fumonisins needs to be kept as low as possible to protect the consumer. Many countries have regulations governing fumonisins in food with prescribed acceptable limits, and most have maximum permitted or acceptable levels for different foodstuffs. Fumonisins damage health and business opportunities, and importing countries are imposing increasingly more stringent regulations.

The Codex recommendations, maximum levels, and codes of practices mentioned above, serve as guidance for national authorities.

[1] a joint intergovernmental body of the Food and Agriculture Organization of the United Nations (FAO) and WHO with 187 member states and one member organization (EU): http://www. codexalimentarius.org

[2] http://www.who.int/foodsafety/areas_work/chemical-risks/gems-food/en/

The consumers can do

Maize will occasionally be contaminated with fumonisins and consumers living on a maize-based staple diet need to pay extra attention to minimize the risk of exposure to the toxins. Since most measures to avoid fumonisin contamination take place before harvest, the consumer has only a few opportunities to minimize the risk. The consumer is advised to:

- remove visibly infected or damaged kernels before eating and/or storing;
- buy maize, wheat and other grains as fresh as possible; that have been grown as close to home as possible, and which have not been transported over a long time;
- make sure that foods are stored properly – kept free of insects, dry, and not too warm – and ensure that grains are not kept for extended periods of time before being used;
- buy only reputable brands of maize, wheat etc.;
- discard food if it shows signs of mould. Mouldy foods are potentially contaminated with mycotoxins such as fumonisins and are potentially harmful when eaten, as moulds penetrate deep into the food and do not just grow on the surface. While reduction of fumonisin levels may occur after heating, results from different studies are variable and further work is required to determine what happens to fumonisins in heated food.
- try to ensure his/her diet is diverse; this not only helps to mitigate fumonisin exposure, but also improves health and nutrition.

Further reading (references)

Evaluation of certain contaminants in food (Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series:. WHO Technical Report Series, No.1002, 2017.

Evaluation of certain mycotoxins (Fifty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 906, 2002.

Evaluation of certain food additives and contaminants (Seventy-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 966, 2011

JECFA report and additional information are available at www.who.int/foodsafety/areas_work/chemical-risks/en/