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Aflatoxins: Latent danger in the daily diet

Aflatoxine: Latente Gefahr in der täglichen Ernährung

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Summary

Microorganisms can produce secondary metabolites that contaminate grains and seeds, and this way cause significant economic losses and serious damage to health in populations or entire countries. One of these microorganisms are fungi of the genus *Aspergillus,* which produce aflatoxins. The ingested of these mycotoxins are related to various types of cancer, mainly liver, in addition to that in children it can cause other ills. Due to their structure, aflatoxins are odorless, colorless, and tasteless, so they cannot be identified with the naked eye, together with these characteristics, these can tolerate various processes of cooking, fermentation and pH change, which makes us question whether can aflatoxins continue in foods ready to eat, be cumulative and represent a type of risk to health in the long term? For this reason, this review describes which are aflatoxins, the absorption and metabolism of AFB_1 inside the human body, the different types of aflatoxicosis they present, the regulations that exist in different countries regarding their consumption, the contamination present in different processed foods, including derivative products of animal origin and nixtamalized, and finally daily intake analyses of these metabolites in countries concerned with the health of their populations.

Keywords: Aflatoxins, Liver Cancer, Processed Foods, Aflatoxin Absorption, Aflatoxicosis

Introduction

Cooking food is an important process to avoid stomach diseases or infections because it eliminates or reduces the growth of different types of microorganisms (Gutierrez de Alva, 2012). These microorganisms include fungi, which can be found from the field to the storage of raw grains and seeds. However, the physical presence or absence of these microorganisms in food is not the real problem, but the possible production of secondary metabolites such as mycotoxins, which these can produce in response to the different climatic conditions they may be in subjected when they are in contact with grains or/and seeds, and in this way generate economic damage and serious health problems (Martínez-Padrón und Hernández-Delgado, 2013; Ismail et al., 2019; Pandey et al., 2019; Scharaarschmdt and Fauhl-Hassek, 2019).

Fungi of the genus *Aspergillus* have been extensively studied, especially *A. flavus* and *A. parasiticus,* which can produce mycotoxins known as aflatoxins. These species of fungi are saprophytes so they can found in grain crops and seeds basic for the daily diet, such as, maize *(Zea mays),* rice *(Oryza sativa),* sorghum *(Sorghum),* wheat *(Triticum),* chili *(Capsicum annuum),* almond *(Prunus dulcis),* sunflower seeds *(Helianthus annuus),* peanut *(Arachis hypogaea),* waltnuts *(Juglans regia),* pepper *(Piper nigrum),* nuts, among others (Martínez-Miranda et al., 2013; Martínez-Padrón und Hernández-Delgado, 2013; Martínez-Miranda et al., 2018; Ojiambo et al., 2018; Pandey et al., 2019).

Aflatoxins

Tropical and subtropical regions are the main incubation sites for aflatoxins with these areas offering ideal conditions, such as temperature and humidity for the growth of pathogenic fungi or molds (Shukla et al., 2017). Normally, fungi of the genus *Aspergillus* to grow need a relative humidity between 70 and 90% and a temperature range between 0 and 45 °C, when stressed by temperature and humidity conditions can generate aflatoxins. The first time it was known about these secondary metabolites was in England in the year 1960, this phenomenon was given the name „Turkey X Syndrome“, due to the death of more than 100,000 turkeys, ducks and chickens, fed peanuts from Brazil, which had been contaminated by a strain of *A. flavus* (Martínez-Padrón and Hernández-Delgado, 2013; Liew und Mohd-Redzwan, 2018; Spanjer, 2019).

Aflatoxins are nonprotein organic chemical compounds, low molecular weight, with low water solubility, soluble in organic polar solvents (e.as. chloroform, methanol, acetonitrile, etc.) especially dimethylsulfoxide (IARC, 1993). In the fungus, they are synthesized by the metabolic route of polycetics, involving at least 23 enzymatic reactions and 15 intermediaries, involving at least 25 genes, grouped into a 70kb DNA region, obtaining at the end, a basic structure molecule consisting of a dihydro-difuran ring or tetrahydro-difuran attached to a coumarin with a ring of five or six carbon atoms, this depends on the type of aflatoxin generated, usually *A. flavus* strains generate type B aflatoxins (AFB_1 and AFB_2), while *A. parasiticus* produces type B and G aflatoxins (AFB_1, AFB_2, AFG_1 and AFG_2) (Guzmán de Peña, 2007; Yu et. al., 2004; Pandey et al., 2019).

AFB_1 and AFB_2 take their characteristic name from the blue fluorescence showed under ultraviolet (UV) light, this color is generated thanks to the five-carbon ring, while those of type G, with the six-carbon ring, under UV light show green fluorescence. AFB_2 and AFG_2 are dihydro-derived from the compounds AFB_1 and AFG_1; as for other aflatoxins, such as AFM_1, AFM_2, AFP_1, AFQ_1, AFB_2a, AFG_2a, aflatoxicol (AFL), among others, are hydroxylated products from animal or microbial metabolism. More than 20 different types of aflatoxins are known (Martínez-Padrón und Hernández Delgado, 2013), however, the most studied and considered as carcinogens from group 1 by the International Cancer Research Institute (IARC), are AFB_1, AFB_2, AFG_1, AFG_2 and AFM_1, the latter for its importance in contamination in dairy and meat products, its fluorescence is blue-violet under UV light. AFB_1 is considered the most toxic aflatoxin due to a great affinity to DNA in contrast the others. The main attack organ is the liver, but they are similarly related to other carcinomas. In addition, these metabolites are related to other types of alterations, because of various studies have supported their effects as mutagenic, immunotoxic, teratogenic substances and are also related to hormonal disorders (IARC, 1993; Martínez-Miranda et al., 2013; Ornelas-Aguirre und Fimbre-Morales, 2015; Londoño-Cifuentes und Martínez-Miranda, 2017; Ostry et al., 2017; Global Cancer, 2018; Marchesse et al., 2018).

Absorption and metabolism of aflatoxins

When consumed, aflatoxins are absorbed by the small intestine (see Figure 1), and then transported in the blood, where red blood cells and plasma proteins lead it to the liver, due to its high liposolubility in liver cells, the toxin is metabolized in the endoplasmic reticulum and is biotransformed by microsomal enzymes of the cytochrome P450 superfamily, different studies have shown CYP3A4 and CYP1A2 as the most active isoenzymes of this complex, which activate AFB_1 and make it the stereoisomers AFB_1-exo-8,9-epoxy and AFB_1-endo-8,9-epoxid. In this step, the ingested aflatoxin concentration has great relevance, because when consumption of aflatoxin is high, CYP3A4 is the largest producer of AFB_1-exo-8,9-epoxide, whereas if it is low, CYP1A2 is the one that produces the most amount of this isomer. Additionally, CYP1A2 is the transformer from AFB_1 to AFM_1. On the other hand, CYP3A4 converts AFB_1 to AFQ_1. The concentration of total amount aflatoxin B_1 is processed into the metabolites AFM_1 and AFQ_1 in 1–4 % and 1–11 %, respectively. Aflatoxin P_1 is produced by other P450 enzymes, which are CYP2A13, CYP2A3, and CYP321A1, however, there is very little information on this aflatoxin as it is considered a detoxification product (Anguiano-Ruvalcaba et al., 2005; Bbosa et al., 2013; Martinez-Padron und Hernández-Delgado, 2013; Marchese et al., 2018; Rushing und Selim 2018).

With the cooperate of NADPH reductase, usually in the cytosol, another compound is formed from AFB_1, which is AFL, this metabolite is the only one capable of being transferred by the placenta and is a kind of reserve, since it can be converted into AFB_1 again by enzymatic reactions and thus preserved in the body for longer. It is known for a metabolite that resembles AFL but with a hydroxy group in the terminal cyclopentene ring, which is known as AFH_1, although it is not yet known whether this compound is generated by hydroxylation of AFL or the reduction of aflatoxin AFQ_1 (Guzmán de Peña, 2007; Bbosa et al., 2013; Rushing und Selim, 2018). Another product related to NADPH is aflatoxin B_2a, which is a hemiacetal form of AFB_1, it is considered a detoxification product, however

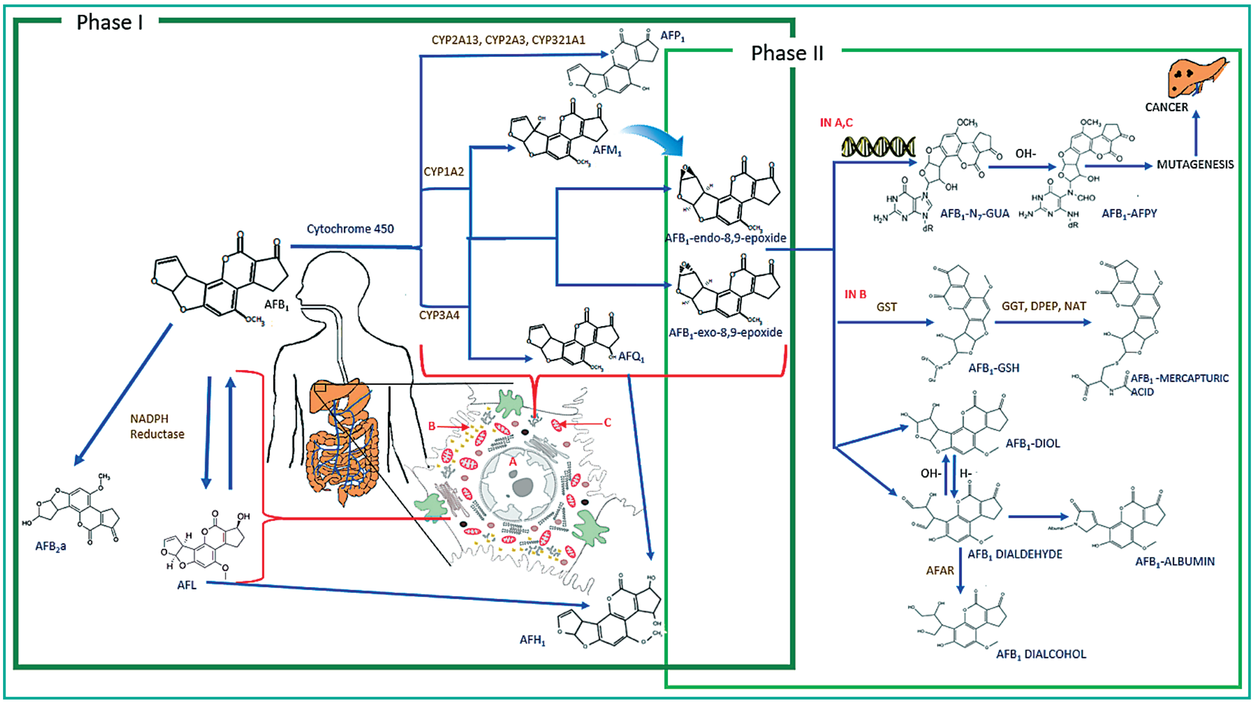

FIGURE 1: *Metabolism of aflatoxins in hepatic cells.*

it can have a strong binding to primary amines in alkaline pH, producing an adduction between phosphoethanolamine heads in phospholipids, making it a lipid-aflatoxin adduct, unique so far which can be irreversible and thus change the distribution and accumulation of AFB_1. It is important to mention that its affinity for proteins may be related to additional toxicity, because it has been confirmed that AFB_2 inhibits the activity of deoxyribonuclease, which demonstrates its ability to alter enzymatic activity in target proteins. The conversion, which this aflatoxin can reach, can be up to 50 % of AFB_1 ingested (Bbosa et al., 2013; Rushing und Selim, 2017; Rushing und Selim, 2018).

The metabolism of aflatoxin B_1 in the human body consists of two phases, the first phase occurs from the consumption of the metabolite to its conversion to aflatoxins Q_1, M_1, P_1, AFL, (which can be discarded in urine, bile or feces, aflatoxin M_1 in milk, although AFL can also be discarded in this form) and epoxides AFB_1-exo8,9 and AFB_1-endo-8,9. From the formation of these epoxides begins phase II of metabolism, however by their electrophilic nature and instability, AFB_1-exo-8,9-epoxide is more important, which has a great affinity to bind to molecules and form adducts related to carcinomas, these adducts can also be in the tissues inside the body for a long time, among them we can find (Guzmán de Peña, 2007; Bbosa et al., 2013; Marchese et al., 2018; Rushing und Selim, 2018):

1. DNA binding adducts: 8,9-dihydro-8(N^7guanyl)-9hydroxy-AFB_1 (AFB-N^7-guanina) and 8,9 dihydro-8-(N^5-formil-2,5,6-triamino-4oxo-N^5-pyrimidil)-9-hydroxylaflatoxin B_1 or AFB_1-formamidoprimidine (AFB_1-FAPY), the first adduct is directly related to liver cancer and represents 90 % of total adducts, is formed from the interaction of AFB_1-exo-8,9-epoxy with DNA; the second is consequence by the instability in the imidazole ring of AFB-N_7-guanine. Both adducts are resistant to DNA repair processes, generating malfunction and accumulation of errors in replication, such as the generated change of G to T at the third base of codon 249 of the tumor suppressor gene p53, it causes a change of amino acids of arginine to a serine in the protein P53, which can generate at the cellular level: malfunction of cycle control, synthesis and repair of ADN, differentiation, genomic plasticity and programmed death. Similarly, the AFB_1-FAPY adduct has been related to proto-oncogenes of the ras family, the point mutations that this gene has presented have been related to the proliferation and transformation of tumors (Guzmán de Peña, 2007; Bbosa et al., 2013; Marchese et al., 2018; Rushing und Selim, 2018).
2. By the catalyzation of Glutation-S transferase (GST), the epoxide is joined with glutathione (GSH). The formed adduct is a seemingly stable and nontoxic product, however, glutathione detoxifies the body‘s reactive oxygen species, so if there is a glutathione deficiency this can cause oxidative damage, leading to abnormally high levels of reactive oxygen species that may cause a decoupling in essential cellular metabolic processes. This adduct can be excreted in bile, however, it can also change in sequential metabolism in the liver and kidneys, through enzymatic reactions involving γ-glutamyltranspeptidase (GGT), dipeptidase (DPEP) and N-acetyltransferase (NAT) and can be excreted in the urine, such as mercapturic acid (aflatoxin-N-acetylcysteine) (Guzmán de Peña, 2007; Ornelas-Aguirre und Fimbre- Morales, 2015; Marchese et al., 2018; Rushing and Selim, 2018).
3. As mentioned above, AFB_1 epoxides are very unstable and these compounds can spontaneously hydrolyze before binding to some macromolecules, resulting the formation of AFB_1-dihydrodiol (AFB-2,3-dihydro-2,3-diol), it is in balance with another oxidated form, which is known as AFB_1-dialdehyde, caused by opening its ring for stability of the molecule, however, when it is in the form of aldehyde it can react by joining covalently with N-terminal side chains and lysine in cellular proteins, causing other types of adducts and other cytotoxic complexities. One of them is the hemoglobin adduct which is stable and can be detected after chronic exposure, however this affinity is in a lower proportion than that

given by albumin. AFB_1-dialdehyde can be excreted by urine as dialcohol by the action of aflatoxin aldehyde reductase (AFAR) (Marchese et al., 2018; Rushing und Selim, 2018).

In this sense, AFM_1 has also presented a slight affinity for the formation of adducts, although it is considered a product of detoxification, when aflatoxin M_1 is consumed the cytochrome P450 don't intervention and begin the production of epoxides on a smaller scale and their interaction with proteins mainly (Marchese et al., 2018). Besides what this, AFM_1 in combination with AFB_1 causes renal toxicity by activating oxidative stress by altering the expression of proline dehydrogenase and L-proline levels (Li et al., 2018).

Aflatoxicosis

The damage caused by aflatoxin is classified into two types of aflatoxicosis, acute or chronic, the first can manifest as acute hepatitis, because there is the typical yellowing of hepatitis, fever, depression, appetite and diarrhea. The doses ingested are high in a single exposure, usually. Cases reported due to this type of poisoning have been very few and rare, as in 1995, in Malaysia, where consumption in a service for children with noodles contaminated with 3 mg of aflatoxin resulted in acute liver encephalopathy; or as in 2004, in Kenya, where about 125 people died of 317, after showing symptoms, such as abdominal pain, pulmonary edema and necrosed liver, caused by the intake of contaminated maize with approximately 50 mg of AFB_1 per day. The World Health Organization (WHO) suspects that consumption of foods with concentrations equal to or greater than 1 mg/kg of aflatoxin causes aflatoxicosis, as it has estimated, based on previous studies that consumption of 20–120 µg/kg/day of AFB_1 during periods of 1 to 3 weeks produce acute toxicity (Arrúa-Alvarenga et al., 2013; Schmidt, 2013; Ornelas-Aguirre und Fiambre-Morales, 2015; Ladeira et al., 2017; Londoño-Cifuentes und Martínez-Miranda, 2017; Global Cancer, 2018; Liew und Mohd-Redzwan, 2018; Marchese et al., 2018; Martínez-Miranda et al., 2013; Nleya et al., 2018; Ojiambo et al., 2018; WHO, 2018; Spanjer, 2019). Chronic aflatoxicosis is a prolonged exposure to low doses of aflatoxins, it is the most dangerous and worrying, because it can generate carcinomas, mainly liver. The symptoms presented are vomiting, abdominal pain, and hepatitis, which are gradually presented (Schmidt, 2013).

Unfortunately, some studies claim that poisoning also affects the immune system, as specific and nonspecific immune responses of lymphocytes and macrophages are altered (Marchese et al., 2018), as the Sun Y. et al. (2018) team demonstrated, by noting that low-dose aflatoxin promotes influenza infection (SIV) and increases its severity. Another related complication, with the consumption of foods contaminated with low concentrations of aflatoxins, is the synergy observed with hepatitis B and C, due to the risk of generating liver cancer can be up to 30 times higher. Several studies have documented these associations, such as the one conducted in Guangxi, China, where, in patients with hepatitis B they found chromosomal alterations (both lost and gain), affecting any number of copies of oncogenes, tumor suppressor genes and genes associated with drug metabolism and detoxification pathways; in this relationship there is an association, with oxidative stress which helps the generation of carcinoma (Schmidt, 2013; Ramalho et al., 2018; McCullough und Lloyd, 2019). Similarly, they are cofactors that enhance other cancers (colon, lung, pancreas, and cervical-uterine) in synergy with viral cirrhosis and human papillomavirus (HPV) (Carvajal, 2013).

It is important to emphasize that the damage caused by aflatoxins can vary depending on the sex, age, and nourishment of the person, and in this case the infants are the most vulnerable. In the child population, consumption of aflatoxins has been linked to stunted growth, immune suppression, and lack of absorption of nutrients related to Kwashiorkor syndrome (protein and energy malnutrition) or Kwashiorkor marasmics. Kwashiorkor syndrome exhibits symptoms such as hypoalbuminemia, fatty liver, and immunosuppression. Most of these problems have occurred in African countries, such as 252 Sudanese children with syndromes such as marasmo, Marasmic, Kwashiorkor, and Kwashiorkor, when performing serum tests, these showed high concentrations of aflatoxin. Aflatoxin levels in food in these countries often exceed the standards or regulations to which they are subjected, due in large part to their climatic conditions (Guzmán de Peña, 2007; Martínez-Miranda et al., 2013; Ladeira et al., 2017; Rushing und Selim, 2018).

Food regulation consumption of aflatoxins

Carballo et al. (2019) adverts that intake below 1 ng/kg/day may induce cancer and for this reason consumption levels should be as low as possible. Depending on each country and seed or grain, laws or standards allow a certain parameter of these metabolites in products. In the case of cereals in general and derived products, the European Commission in Regulation 165/2010 has established a maximum aflatoxin B_1 content of 2 µg/kg and a total maximum aflatoxins content of 4 µg/kg, with the exception of maize to be subjected to a selection process or other physical treatment before human consumption, maximum aflatoxin B_1 of 5 µg/kg and maximum concentration total aflatoxins of 10 µg/kg. In dairy products (raw milk, pasteurized milk, and dairy derivatives), it is 0.05 µg/L for AFM_1. While for infant foods based on processed cereals and foods for infants and young children, the maximum established is 0.10 µg/kg for aflatoxin B_1, and for infant formula the limit is 0.025 µg/L for AFM_1 (Martínez-Miranda et al., 2013; CCA, 2017; Ismail et al., 2018; Londoño-Cifuentes und Martínez- Miranda, 2017). On the other hand, in other countries the legislation does not establish a limit between the types of food and aflatoxins, only by counting the total aflatoxins, having as a limit 20 µg/kg and 5 µg/kg for AFB_1 applied in Latin American countries by MERCOSUR and in the United States of America. As for dairy, the standard has a maximum allowed of 0.5 µg/L of AFM_1 (NOM 2002; Londoño-Cifuentes und Martínez- Miranda, 2017; Ismail et al., 2018).

Despite these laws, aflatoxins are thermoresistant and can be stable at temperatures above 300 °C; so cooking, boiling, baking, or roasting grains or seeds is not an option for the total elimination of these metabolites (Bullerman und Bianchini, 2007), in relation to this, the worldwide aflatoxin levels have been found in ready-eat foods, which exceed even laws for raw products.

Presence of aflatoxins in processed foods

The meals around of the world are different and varied with combinations of grains, seeds and meat that can be contaminated individually with aflatoxins and this can be affected the final product (Table 1). By the climatic and economic conditions, the African continent is the most vulnerable with high reports in mycotoxin contamination in processed food, studies in some countries have reported levels of aflatoxin above stablished in the regulation. In Nigeria, Ojuri et al. (2018) analyzed foods directly provided by relatives of children and young people, objects of the study, such as seeds and snacks, where they found high levels of aflatoxin B_1 in foodstuffs such as peanut butter, ogi (fermented corn puding) and baby milk. This group emphasizes that must have considering monitoring and regulation of levels of mycotoxins for final consumption foods, especially for the infant and nursing population. Foods seasoned with species especially meat are impliedly consumed in Egypt, products like kofta, sausage, luncheon, and basterma were analyzed by Shaltout et al. (2014). Who collected 100 samples (25 of each of the varieties) in different supermarkets of the governors of Kaliobia. The presence of aflatoxin B_1 was the most prevalent in los 4 types of meat, with 36, 24, 32, and 12 %, while the lowest or undetectable presence was AFG_2 with 24, 12, 16 and 0 % in the samples of kofta, sausage, luncheon and basterma, respectively. In Zambia, a method to preserve fish is drying smoking, so that Singh and Nsokolo (2020) obtained 15 samples from local markets, which belonged to 5 different species of fish (Buka, Bream, Mintesa, Catfish, Makobo) treated with this method of conservation. All samples showed total aflatoxin contamination, of which Bream contained the highest presence, while Makobo was the lowest, it is important to emphasize that the study authors mention that analyses have been made similarly on the content of aflatoxins in fish feed. In some places or farms, the quality of grains or seeds not is relevant to feed animals and this can cause AFM_1 contamination in meat and dairy products (Table 2), in Algeria, 84 samples of raw milk from different regions were collected, AFM_1 was detected in 39 samples, which were between concentrations of 95.59–557.22 ng/L, collected over one year (August 2016–July 2017), of which only 1 of them exceeded the tolerance of US food administration. The results of these samples were also divided into the geographical areas from which they were collected (Center, North 22, Northeast 23, and Northwest-39), the positive samples for the expensive regions were 30.43 %,77.27 % and 38.64 % for the Northeast, Center North and Northwest, respectively. These variations may be linked to the climatic and geographical differences of the regions (Mohammedi-Ameur et al., 2020).

As well as Africa, Asia has a high frequency in aflatoxin contamination, in Jordan, 220 samples of meat (chicken, lamb, goat, and veal), milk (bovines and/or sheep), eggs and fodder, collected from different random locations in months of different seasons, winter-spring, finding that the concentrations of aflatoxins obtained in the winter months were high compared to those of spring, this could be a consequence of the type of feeding that the animals have during these seasons. In this study, Herzallah (2009) focused not only on the presence of AFM_1, but also on the concentrations of AFB_1, AFB_2, AFG_1, AFG_2 and AFM_2, linking the presence of aflatoxins B_1 and B_2 in fodder with the concentrations of AFM_1 and AFM_2 in animals, the presence of aflatoxins in milk during spring was lower than its detection limit of 0.05 µg/kg, so this result taken as 0 % of contamination. Vietnam is another country where the urine of 1920 corn-fed fattening pigs from different regions and slaughtered was analyzed, and this research led by Hu Suk Lee (2017) found that 53.90 % of the samples are positive in AFM_1 and that the population is exposed to contamination of aflatoxins by meat intake. Chocolates are candies consumed by people of all ages in Turkey, 130 samples of 21 popular brands were analyzed, of different varieties: 15 of bitter chocolate, 23 of chocolate wafers, and 92 of milk chocolate, among which are 16 samples with pistachios, 31 with hazelnuts and 6 with peanuts. Overall, 13.3 %, 19.6 %, and 8.7 % of samples of bitter chocolate, milk, chocolate and chocolate wafers were specifically contaminated by some of the aflatoxins (B_1, B_2, G_1 and, G_2) quantified. As was expected, the most contaminated samples were milk chocolates containing any of the nuts: 33.3 %, 31.3 %, and 22.6 % corresponding to the samples of peanuts, pistachio and hazelnut respectively, where a high concentration of AFB_1 was observed in those containing pistachio (Kabak, 2019).

Rice is a cereal very consumed around the world and its preparation is very simple, it is for this reason that in Japan, due to the concern about the high consumption by its inhabitants, Sakuma et al. (2013) examined rice naturally contaminated with AFB_1 and inoculated with prepared solutions of AFB_1, AFG_1 and AFB_2-AFG_2 in acetonitrile. They found that the reduction of aflatoxins in steamed rice was only 18 %, while AFB_1 did not show a significant reduction with this method, so there is a high exposure to these metabolites.

Certainly, Europe has the legislation less permissible for the presence of this metabolite, nevertheless, some products of daily consumption have shown contamination of aflatoxins. In Greece, Athens, Villa P. and Markaki P. (2009) examined 55 breakfast cereals, both conventional and organic, collected at random from different supermarkets. The cereals were most diverse based on corn, oats, rice, and wheat, with different additives such as chocolate, dried fruits, mixed nuts, cinnamon, among others. The wheat and chocolate samples and four cereal samples with dried fruits and walnuts did not comply with European Union legislation. Sixty samples of baby and infant cereals were collected from pharmacies, supermarkets, and organic stores in Cantabria and Aragon, Spain, during 2016–2017, of which 27 were gluten-free and 33 of multiple cereals. Twelve samples (20 %) were reported with aflatoxin content, half of these samples exceeded the limits permissible by the European Union standard, and 11 had the presence of AFB_1 (Herrera et al., 2019). The gofio is a flour used to make different traditional dishes of the Canary Islands, made from wheat and / or roasted corn and has been analyzed by different working groups for being an important food and consumed by both tourists and settlers. In 2016, Luzardo et al. (2016) analyzed mycotoxins in a total of 94 packages purchased from local stores (45 corn , 23 wheat and 26 mixtures of two cereals), among which aflatoxins. In another part of this country, in Valencia, the team led by Saladino (2016) analyzed 80 commercial bread loaves bought in different local supermarkets, where it was observed that 20 % of the samples presented some type of aflatoxins, in addition, 7.5 % and 5 % of the total samples, exceeded the limits allowed by European legislation and AFB_1 was present, respectively. Samples of beverages such as tea and coffee, purchased from local supermarkets in Valencia and prepared according to manufacturing instructions or by the different methods used for consumption, were analyzed by the working groups of Pálleres (2017) and García-Moraleja (2015), respectively. Of a total of 44 tea samples (black, red, green and green tea and mint mixture), 18, 14, and 9 % of the total samples were found to contain AFG_2, AFB_2 and AFG_1, respectively. The highest mycotoxin content was in green tea with mint. The coffee samples analyzed were 169 in which they showed that 53 % of the total contained aflatoxins, none exceeding 2 µg/kg AFB_1, but 15% of the samples with total aflatoxins had a concentration greater than 5 µg/kg mostly in AFG_2.

Across the ocean in Canada, precedent local and international brands, belonging to 36 countries were collected in Canada over a 3-year period. In which 5 samples from Mexico stand out, 2 from Spain, 1 from Portugal, and 4 from India for containing AFB_1, additionally the Indian samples also showed AFB_2 (Mably et. al., 2005). In Colombia, Martínez- Miranda et al. (2018) analyzed arepas (corn-based bread), chopped bread and rice, purchased from local stores and markets in six municipalities representative of the department of Caldas, and through questionnaires made to a sector of the population, estimated the rate of consumption of these foods and characterized the margin of risk to which the adult population is exposed. Obtaining a percentage of the total of each product, where 27.1 % of the arepas analyzed are contaminated with total aflatoxins, 6.85 % of the bread samples, and 75.6 % of the rice samples, with levels exceeding European legislation. In 30 samples of Oaxaca cheese in Veracruz, Mexico, were detected aflatoxins M_1 and M_2, where the results yielded considerable levels of these mycotoxins (Ramírez-Martínez et al., 2018).

Maize is an essential grain for some Latin American's countries, its principal consumed is in the form of tortilla or product derivates of nixtamalization of this grain. The nixtamalization is a drastic method that involved heat and pH change by the addition lime (calcium oxide) (Roque-Meciel et al., 2016). In Guatemala, a study was conducted with 461 adults, to whom were measured their albumin adducts correlating them with tortilla consumption, the group led by Kroker-Lobos (2019) mentioned that tortillas are an important source of exposure to AFB_1. In Mexico, a based nixtamalized maize beverage (pozol) was analyzed in Comitán, Chiapas, 111 samples from local markets. Contamination by aflatoxins was below the rule that governs this country, however it is 4 times more permissible than European law (Méndez-Alboroles et al., 2004). In Veracruz, Wall-Martínez et al., in 2017 conducted a statistical analysis on the consumption of processed maize-based foods (especially tortillas), the analysis highlights the need to characterize the consumption of one of the staple foods in Mexico as a first step for a probabilistic risk assessment. However, nixtamalization has been considered as a method of decontamination of aflatoxins because once maize is nixtamalized, it no longer presents fluorescence, however, there are several authors who point to this process as noneffective, for its reactivation in the stomach, so if the argument is true, the concentrations ingested would be the initials of the raw maize (Torres et al., 2001; Castillo-Urueta et al., 2011; Martínez-Padrón and Hernández-Delgado, 2013; Schaarschmidt und Fauhl-Hassek, 2019).

Inactivation of aflatoxins by this treatment is related to fluorescence just as indicative, Moreno-Pedraza et al. (2015), by means of mass spectroscopy we obtained two degradation products, by subjecting the standard of AFB_1 to an acid, one of these two products resembled a molecule found by Lee et al. (2007) obtained from aflatoxin B_1 after being exposed to ammonium treatment, named aflatoxin AFD_1. Comparing their mutagenicity and toxicity, they observed that it has a minor effect compared to other aflatoxins (Lee et al., 1981; Contreras et al., 2007). The structure of aflatoxin D1 does not contain a part of coumarin (lactone), therefore it does not have fluorescence. In addition, aflatoxins can withstand high temperatures, however, heat and calcium hydroxide make a synergy that can destabilize the molecule by the pH in which it is located, not a finding in the bibliography a mechanism that explains how this process happens, the one shown in Figure 2 is proposed.

As we can see, foods undergoing some cooking or fermentation process before consumption, they have remnants of aflatoxins (Tables 1 and 2), being moderately stable (Bullerman und Bianchini, 2007), which should be alert to the actual levels contained in the grains, seeds and/ or animal products from which they come. The World Health Organization indicates that there are differences in intake in aflatoxin doses between developed and underdeveloped countries, in the first the average dietary exposure is less than 1 ng/kg body weight per day, while for other countries they exceed 100 ng/kg/day (WHO, 2018). However, the European Commission indicates that lower amounts of intake from developed countries may contribute to a high risk of liver cancer, while intake from of 10 µg/kg in a single exposure may produce some mutations (Suárez-Bonnet et. al., 2013). Thus, it is important to make an estimate of the consumption of aflatoxins that a person can ingest during a meal, in which they could be ingested one or up to five doses of the toxin, depending on the food consumed, plus the concentrations ingested in the meals of the rest of the day. Due to this reason, total diet studies are necessary, such as those presented by different working groups of countries such as Hong Kong, Lebanon, and Brazil, to obtain the approximate consumption to which its population is exposed to this mycotoxin.

Total diet studies

From June 2011 to March 2012, residents of Pirassununga, Sao Paulo, Brazil, collaborated on an investigation conducted by A.V. Jager et al. (2013), providing food from their homes 4 times every 3 months, including products derived from maize, peanuts, and milk. At the same time, they answered a feeding frequency questionnaire, to determine at what level the population is exposed. The results obtained by the group of researchers show: 42 % of the samples derived from maize were positive for total aflatoxin levels and 30 % for cheeses showed the presence AFM_1. Despite the

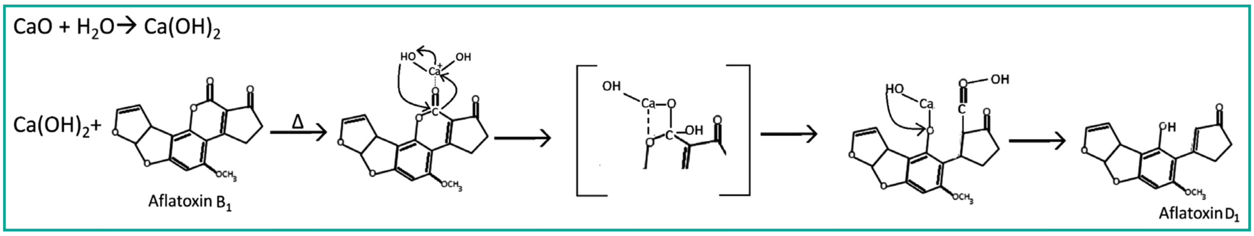

FIGURE 2: *Proposed mechanism for the conversion of aflatoxin B_1 to D_1 during the nixtamalization process.*

TABLE 1: *Aflatoxins in variety products derived of different grains and seeds.*

Country	Period of recolection	Foodstuff	% samples contaminated with total aflatoxins	Total aflatoxin content (µg/kg)(mean)	% samples contaminated with aflatoxin B1	Aflatoxin content B1 (µg/kg)(mean)	Reference
Corn derivatives							
Nigeria	January, June, 2017	Ogi	52.2	5.5	52.2	4.8	Ojuri *et al.* 2018
Nigeria	January, June, 2017	Pudding	100	3.3	92.3	2.4	Ojuri *et al.* 2018
Colombia	March- July 2017	Arepa	27.1*	3.0	20.5	5.62	Martínez-Miranda *et al.* 2018
Brazil	June 2011-March 2012	Flour	75	0.56	NM	NM	Jager *et al.*, 2013
Brazil	June 2011-March 2012	Hominy	100	1.4	NM	NM	Jager *et al.*, 2013
Mexico	November 2002-April 2003	Pozol	19	10.75	NM	NM	Mendez-Albores *et al.*, 2004
Mexico	2006-2007	Tortillas	21	194	64.6	71.65	Castillo- Urueta *et al.*, 2011
Wheat Derivatives							
Colombia	March- July 2017	Chopped bread	6.85*	0.97	1.37	0.80	Martínez-Miranda *et al.*, 2018
Spain	-	Gofio	NM	NM	26.1	0.01	Luzardo *et al.*, 2016
Spain	January- July 2015	Loaves of bread	20	3.8	5	5.65	Saladino *et al.* 2016
Lebanon	-	Bread and toast	NM	NM	100	0.258	Raad *et al.* 2014
Lebanon	-	Cakes and patizeria	NM	NM	100	0.110	Raad *et al.* 2014
Lebanon	-	Pizza y country	NM	NM	100	0.045	Raad *et al.* 2014
Peanut derivatives							
Nigeria	January, June, 2017	Peanut butter	80	9	80	7.7	Ojuri *et al.* 2018
Cereal combination							
Nigeria	January, June, 2017	Tom bran	83.33	104	80	83.4	Ojuri *et al.* 2018
Spain	-	Gofio	NM	NM	34.6	0.01	Luzardo *et al.*, 2016
Greece	2006-2007	Breakfast cereal	NM	NM	56.3	1.42	Villa & Markaki, 2009
Spain	2016-2017	Baby and infant cereals	20	NM	18.3	0.03	Herrera *et al.* 2019
Other							
Turkey	January-December 2017	Bitter chocolate	13.3	0.455	13.3	0.38	Pumpkin B. 2019
Turkey	January-December 2017	Milk chocolate	19.6	0.839	19.6	0.73	Kabak,. 2019
Turkey	January-December 2017	Chocolate wafers	8.7	0.281	8.7	0.28	Kabak, 2019
Egypt	-	Kofta	NM	NM	36	13.38	Shaltout et al., 2014
Egypt	-	Sausage	NM	NM	24	9.03	Shaltout *et al.*, 2014
Egypt	-	Luncheon	NM	NM	32	8.80	Shaltout *et al.*, 2014
Egypt	-	Basterma	NM	NM	12	4.53	Shaltout *et al.*, 2014
Zambia	-	Buka smoked dried fish	100	1.68	NM	NM	Singh & Nsokolo. 2020
Zambia	-	Dry smoked fish Besuda	100	3.81	NM	NM	Singh & Nsokolo. 2020
Zambia	-	Mintesa smoked dried fish	100	2.6	NM	NM	Singh & Nsokolo. 2020
Zambia	-	Smoked dried fish Catfish	100	3.36	NM	NM	Singh & Nsokolo. 2020
Zambia	-	Makobo smoked dried fish	100	1.56	NM	NM	Singh & Nsokolo. 2020
Jordan	Winter, 2009	Milk	16.7	2.79	16.7	2.27	Herzallah.,2009
Jordan	Spring, 2009	Local meat	6.7	3.01	6.7	2.53	Herzallah.,2009
Jordan	Winter, 2009	Local meat	13.3	6.36	13.3	3.25	Herzallah.,2009
Jordan	Spring, 2009	Imported Meat	30.0	3.77	30.0	2.85	Herzallah.,2009

frequency of onset in food, aflatoxin levels did not exceed the standard, however, this working group stresses that the population of this place is at risk by the presence of AFB_1 and AFM_1. In addition, with the data collected by the food frequency questionnaire, they obtained a rough estimate of the intake of aflatoxins per product, in which, the daily intake for peanut products was 1.56 ng/kg (body weight), while for milk, mainly intake of AFM_1 was 0.10 ng /kg/day. Motivated by the lack of information that existed on the consumption of these mycotoxins in the diet of the Lebanese population, Raad et al. (2014), conducted a daily diet study, in which they chose 47 foods which met 2 criteria for their selection, first is that the food could be identified by GEMS as possible sources of AFB_1 and AFM_1, and the second, that their consumption was greater than 1 g per day per person. The highest concentrations of AFB_1 were found in product and cereal derivatives (bread, toast, cakes, and patizeria). Based on AFB_1 levels of the foods analyzed, the daily intake estimate was estimated between 0.63–0.66 ng/kg per day, while the estimated exposure for AFM_1 is 0.22–0.31 ng/kg per day due to milk and its derivatives. They concluded that this type of work is crucial for the development and adoption of strategies in food safety management. In order to understand the estimated degree of exposure to Hong Kong's population to various toxins and nutrients, the Centre for Food Safety, the food security control authority of the Hong Kong government, conducted a total diet study. With data obtained from two non-consecutive 24-hour dietary intake questionnaires, made to 5008 adults between 20 and 84 years of both sexes validated by the USDA National Health and Nutrition Examination Survey (NHANES), 150 representative foods of 1400 consumed by the total population collected from different regions of the territory were chosen, during four sessions in March 2010 and February 2011, prepared and cooked taking care of no cross-contamination. Analysis data showed that 4 % of food is contaminated with aflatoxins, where the highest detection was for legumes, nuts, and seeds, as well as their derivatives, followed by fats and oils, sugars and confectionery and finally, cereals and their products. Levels obtained from aflatoxins were low, however, they mention that a percentage of the population has hepatitis B, which contributes to boosting liver cancer, so they conclude that aflatoxins ingested in the daily diet are responsible for approximately 8 cases of liver cancer per year (Yau et al., 2016).

In general, the concentrations of aflatoxins in food vary according to the season in which they are produced, countries in Africa and Asia where climatic conditions of drought or humidity are very present, promote the appropriate conditions for the development of aflatoxins by *A. parasiticus* and *A. flavus*, however we cannot be oblivious to the situation, due to the climate change that has been going on in recent years, as demonstrated by the Udovicki et al. (2018) and Milicevic et al. (2019) team, who, individually conduct research in Serbia, a country vulnerable to climate change. Both groups were based on collection of literature with respect to climatic conditions, aflatoxins in maize correlated with aflatoxin AFM_1 in milk, the first for a period of 12 years (2004–2016), with the exception of data from 2012 and 2014, drought and flooding respectively, while the second of 2015–2018, both groups concluded that the increase in these metabolites has been related to the climate changes that have been arising in recent years putting at risk the agronomic economy and the health of people; or as demonstrated by Bailly et al (2018), where they examined maize samples collected and stored in silios in France, during 2015, the concentrations depended on the seasons to be examined, however they confirm that monitoring on these types of crops is urgent to avoid pollution by climate change in their country.

TABLE 1: *... continued*

Jordan	Winter, 2009	Imported Meat	30.0	4.84	30.0	3.46	Herzallah.,2009
Jordan	Winter, 2009	Egg	20.0	6.15	20.0	4.5	Herzallah.,2009
Jordan	Spring, 2009	Egg	5.0	1.77	5.0	1.45	Herzallah.,2009
Jordan	Winter, 2009	Fodder	60	9.92	60	7.1	Herzallah.,2009
Jordan	Spring, 2009	Fodder	25	5.32	25	4.2	Herzallah.,2009
Drinks							
Spain	2015	Coffee	53	2.7	22	0.2	Moraleja-García et al., 2015
Spain	2017	Thé	18.18*	8.4*	NM	NM	Pallares *et al.*, 2017
Canada	1998-2002	Beer	NM	NM	26.47	0.0031	Mably *et al.* 2005

TABLE 2: *Presence of aflatoxin M_1 in derived products of animal origin.*

Country	Period of recolection	Food	% samples contaminated with total aflatoxins	Aflatoxin content M_1 (μg/kg) (mean)	Reference
Jordan	Winter, 2009	Milk	16.7	0.14	Herzallah.,2009
Jordan	Spring, 2009	Local meat	6.7	0.08	Herzallah.,2009
Jordan	Winter, 2009	Local meat	13.3	0.56	Herzallah.,2009
Jordan	Spring, 2009	Imported Meat	30.0	0.08	Herzallah.,2009
Jordan	Winter, 2009	Imported Meat	30.0	1.1	Herzallah.,2009
Jordan	Winter, 2009	Egg	20.0	0.15	Herzallah.,2009
Jordan	Spring, 2009	Egg	5.0	0.12	Herzallah.,2009
Brazil	June 2011-March 2012	Cheese	30	0.16	Jager and. Al. 2013
Brazil	June 2011-March 2012	Milk	40	0.039	Jager and. Al. 2013
Mexico	2016	Oaxaca type cheese	53.33	11.41	Ramirez-Martínez et. al.2018
Lebanon	-	Milk and milk-based drinks	100	0.15	Raad.et al., 2014
Lebanon	-	Cheese	100	0.02	Raad et al., 2014
Lebanon	-	Yogurt and yogurt products	100	0.02	Raad et al., 2014
Lebanon	-		100	0.02	Raad et al. 2014

NM= No mention

Conclusion

As final considerations, we can say that the presence of aflatoxins is a latent danger to human health, toxins can be ingested at low doses without realizing it, these doses can be accumulated for a single day or in a prolonged way through different processed foods, becoming another factor for the development of liver carcinomas, intestine, kidney, pancreas and cervix, as well as severely affecting vulnerable populations with hepatitis B or C including subjects with liver cirrhosis. In infants and adolescents, it can cause stunted growth, immune suppression, and diseases related to Kwashiorkor syndrome, based on the above, further studies are required to assess the consumption of aflatoxins in daily intake and provide data on the health risk to which the population is exposed by consumption of them. Taking into account the different seasons of the year due to climate change and their favour in increasing concentrations of aflatoxins, the fact that globally aflatoxin levels are high in already processed foods, exceeding what is allowed by legislation for raw products is worrying, so it is necessary to strengthen international regulations regarding this area.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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