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Review

Aflatoxin B1: A review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods

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ABSTRACT

Aflatoxins are a class of carcinogenic mycotoxins produced by *Aspergillus* fungi and are known to contaminate a large portion of the world's food supply. Aflatoxin B1 (AFB1) is the most potent of these compounds and has been well-characterized to lead to the development of hepatocellular carcinoma (HCC) in humans and animals. This review focuses on the metabolism of AFB1, including epoxidation and DNA adduction, as it concerns the initiation of cancer and the underlying mechanisms. The link between AFB1 consumption and HCC is also discussed including synergistic interactions with the hepatitis B virus. Toxic effects of AFB1, including growth suppression, malnutrition, and immunomodulation, are also covered. This review also describes recent reports of AFB1 occurrence in global food supplies and exposures in occupational settings. Furthermore, a summary of recent detoxification methods is included to indicate the present state of the field in developing aflatoxin control methods. This information shows that AFB1 occurs frequently in food supplies at high concentrations, particularly in maize. Regarding detoxification methods, chemical control methods were the fastest methods that still retained high detoxification efficacy. The information presented here highlights the need to implement new and/or existing detoxification methods to reduce the global burden of AFB1 toxicity.

1. Introduction

Aflatoxins are a group of secondary fungal metabolites – also known as mycotoxins – which are produced by fungi of the *Aspergillus* genus, particularly *A. flavus*. Aflatoxins were first discovered following an epidemic of "Turkey X disease" in which over 100,000 turkeys in England suddenly became ill and died over many months in the year 1960. The turkeys exhibited signs of extreme poisoning and mortality of these animals occurred within a few days or weeks. Post-mortem analysis showed that the turkeys had severe intestinal inflammation and liver necrosis. It was soon discovered that many of these turkeys were being fed groundnut meal from Brazil which, when given to poultry during feeding trials, was found to be extremely toxic (Blount, 1961). It was later discovered that the causative agent of these incidents were metabolites of *Aspergillus flavus,* which were then termed aflatoxins (*A. flavus* toxins). There are four compounds produced by *A. flavus* that belong to the aflatoxin class: aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), and aflatoxin G2 (AFG2) (Asao et al., 1963). Because these compounds significantly contaminated the food supply of these animals, there became a greater concern for food contamination in other regions of the world, especially food sources that were being consumed by humans. After evaluating published epidemiological studies that demonstrated a strong link between AFB1 consumption and cancer occurrence, the International Agency for Research on Cancer (IARC) concluded that there was enough evidence in humans to classify aflatoxins as carcinogens. AFB1 is the most carcinogenic of the aflatoxins, and it is well-documented to be a causative agent of hepatocellular carcinoma (HCC) as well as growth suppression, immune system modulation, and malnutrition (IARC, 2012).

A. flavus is ubiquitously found in soil and contaminates a wide range of the world's crops such as rice, corn, peanuts, and others. After establishing these food sources as a host, this fungus produces aflatoxins, including AFB1, which then contaminate the food supply. Fungal growth can occur on food at any point in the pre- or post-harvest stage, making it difficult to control contamination. Additionally, high temperatures and humidity favor fungal growth so countries that have these environmental conditions, namely Sub-Saharan Africa and Southeast Asia, often experience greater contamination. Furthermore, as many of these countries do not have the ability to store food in dry, temperature-controlled conditions, a large amount of AFB1

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contamination occurs during storage (Klich, 2007; Liu and Wu, 2010; Scudamore and Livese, 1998). Developed countries have access to federal regulatory bodies which set food safety standards and inspect domestic as well as imported/exported food products. Additionally, these countries have access to controlled storage conditions, which greatly reduces contamination post-harvest. These factors lead to lower overall contamination rates in developed countries. For example, the United States has reported acceptable AFB1 levels in corn (0–80 μg/kg during 1979–1983) and low daily intake of its citizens (0.34 ng/kg to 197 ng/kg depending on the year and region of the country), which is much less than other undeveloped countries (National Toxicology Program, 2016). In lesser developed countries like Kenya and India, outbreaks of AFB1 contamination in food supplies have been so severe that hundreds of people have died due to acute exposures (Azziz-Baumgartner et al., 2005; Krishnamachari et al., 1975; Lewis et al., 2005; Probst et al., 2007). To further highlight the difficulties of controlling aflatoxin contamination, it was estimated in 2004 that approximately 4.5 billion people in developing countries were at risk for chronic, uncontrolled exposure to aflatoxins (Shepherd, 2003; Williams et al., 2004).

Currently, many countries employ strict regulations to keep levels of AFB1 (and other aflatoxins) low in foods. Acceptable limits of AFB1 in foods intended for human consumption range from approximately 0-40 parts per billion (ppb) whereas levels in animal feed are allowed to be much higher, reaching upwards of 300 ppb (Dohlman, 2003; Mazumder and Sasmal, 2001). Food that does not reach regulatory limits for human consumption are either used for less profitable means (animal feed) or, if levels are too high, the food is discarded completely. This leads to large annual losses in the agricultural industry. Annual losses due to aflatoxin contamination in various countries have been estimated by several investigators. Estimated annual losses in the U.S. has ranged from $20 million – $1.68 billion USD (Mitchell et al., 2016; Robens and Cardwell, 2003; Wu et al., 2008). There are many factors that affect these variations, such as annual differences in aflatoxin levels, losses in animal productivity, insurance costs, losses in exports, and more. Large losses can be seen in Asian and African countries as well: Thailand, Indonesia, and the Philippines combined have been estimated to lose $1 billion USD annually and African exports were estimated to lose 64% of profits ($670 million USD) if European standards of aflatoxin contamination were applied (Lubulwa and Davis, 1994; Otsuki et al., 2001). Additionally, as climate change modifies average temperatures and annual rainfall, it is expected that additional regions may begin to experience issues with AFB1 contamination and countries with existing AFB1 contamination may begin to see higher levels in crops (Battilani et al., 2016; Wu et al., 2011). Therefore, solutions to AFB1 exposure must be developed before aflatoxins become an even larger global health and economic issue.

This review focuses on the metabolic transformation of AFB1 as it relates to its mechanism of carcinogenesis as well as biomarkers that are produced during this process. Additionally, human/animal toxicity, recent occurrence in food, occupational exposure, and current detoxification methods are covered.

2. Metabolism (Fig. 1)

2.1. AFBO

Mechanistically, AFB1 is metabolized in the liver by the P450 enzyme system into to the ultimate carcinogen aflatoxin B1-8,9-epoxide (AFBO), which has two isomers: *endo*-8,9-epoxide and *exo*-8,9-epoxide (Baertschi et al., 1988; K D Raney et al., 1992c). This metabolic conversion is primarily carried out in human liver by CYP3A4 and CYP1A2. At high AFB1 concentrations, CYP3A4 is the major producer of AFBO formation producing essentially only the *exo* isomer of AFBO (Ueng et al., 1995) although this seems to reverse when substrate concentration is low as CYP1A2 switches to the main producer of AFBO at lower AFB1 concentrations. Additionally, CYP1A2 was found to produce more of the *exo* isomer than CYP3A4 at these low concentrations (Gallagher et al., 1996, 1994a,b). The highly electrophilic nature of this intermediate allows it to react spontaneously biological amines in proteins and nucleic acids. In reacting with DNA, AFBO binds covalently to the N_7 position on guanine forming the adduct AFB1-N_7-guanine. The *exo* isomer has been shown to have a much higher affinity for guanine residues than the *endo* isomer, therefore AFB1-*exo*-8,9-epoxide is considered to be the major carcinogenic metabolite (Essigmann et al., 1977; Gopalakrishnan et al., 1989; Iyer et al., 1994; Johnson and Guengerich, 1997).

2.2. Hydroxylation products

AFB1 is also metabolized into a number of hydroxylation products through the P450 system. These include aflatoxin M1 (AFM1), aflatoxin Q1 (AFQ1), aflatoxin P1 (AFP1), aflatoxicol (AFL), aflatoxicol H1 (AFH1) and aflatoxin B2a (AFB2a). AFM1 is a major metabolite produced by CYP1A2 and is commonly detected in humans and animals exposed to AFB1. AFM1 is the most carcinogenic of the hydroxylated metabolites which has shown to induce tumors in rainbow trout and rats (Cullen et al., 1987; Slnnhuber et al., 1974). This is supported by the DNA binding effect of AFM1 which has been demonstrated in rat, mouse, and pig and has even been identified to form an N_7 guanine adduct similarly to AFB1 (Egner et al., 2003; Lutz et al., 1980). AFM1 is commonly found in the milk of dairy cattle and humans, leading to many potential routes of dietary exposure (Giovati et al., 2015). AFM1 is also excreted in high levels in urine following AFB1 exposure and thus has become an additional biomarker of AFB1 exposure (Ross et al., 1992).

AFQ1 is an additional hydroxylated metabolite which seems to be solely produced by CYP3A4 (Gallagher et al., 1996, 1994a,b). This metabolite was first found to be produced in monkey liver microsomal preparations that were exposed to AFB1 and it was produced at a much higher abundance than AFM1 (16–52% of substrate for AFQ1 as compared to 1–3% of substrate for AFM1), although rat microsomes produced much less AFQ1 (Masri et al., 1974). A study was conducted in which human livers from biopsies or autopsies were used to make microsomal preparations to study metabolic conversion of AFB1 to AFQ1. AFB1 was spiked into these microsomal reaction mixtures and 18 out of 22 samples were positive for AFQ1 formation. The abundance of AFQ1 ranged from 1 to 11% of the initial amount of AFB1 indicating that in humans, AFQ1 production occurs frequently and at high enough levels to detect (Yourtee et al., 1987). Furthermore, the DNA binding potential of AFQ1 was shown to be dramatically lower than that of AFBO, indicating its potential as a detoxification product in contrast to AFM1 (Kevin D. Raney et al., 1992a). In 2005, a study using 83 Chinese males monitored fecal and urinary excretion of AFM1, AFQ1, and AFB1-N_7-guanine. The study found that AFQ1 was excreted in much higher levels than AFM1 or AFB1-N_7-guanine. This effect was more pronounced in fecal samples which contained approximately 60 times more AFQ1 than AFM1. Additionally, fecal concentrations of AFM1 and AFQ1 were higher than in urine, indicating the usefulness of feces as a predictive marker for AFB1 exposure (Mykkänen et al., 2005). Despite these findings, AFQ1 is rarely used as a biomarker of AFB1 exposure even though it has been shown to be the most abundant metabolite of AFB1 in some cases.

AFP1 is produced by P450 enzymes such as CYP2A13, CYP2A3, and CYP321A1, however little is known about its production from other isoforms (Crespi et al., 1990; He et al., 2006; Niu et al., 2008). AFP1 has been found in the urine of humans who have been exposed to AFB1 as well as in individuals who have developed HCC presumably as a result of AFB1 exposure (Groopman et al., 1985; Ross et al., 1992). Toxicological studies using fertile chicken eggs showed that no significant

changes in viability or teratogenicity, indicating the role of AFP1 as a detoxification product. Additionally, AFP1 can be glucoronidated and excreted in the bile (Holeski et al., 1987).

AFL, in contrast to other AFB1 metabolites, is found in the cytosolic fractions of liver preparations and is formed by an NADPH reductase, usually in the cytosol (Lozano and Diaz, 2006; Partanen et al., 2010; Salhab and Edwards, 1976; Schoenhard et al., 1976). AFL retains its DNA binding activity, so it is not considered a detoxification product (Loveland et al., 1988). Additionally, AFL has been shown to be enzymatically reconverted back into AFB1 acting as a reservoir for AFB1, extending its toxic effects (Kumagai et al., 1983; Partanen et al., 2010; Wong et al., 1979; Wong and Hsieh, 1985). Interestingly, AFL is the sole metabolite that is able to be transferred through the human placenta and furthermore, AFL is the only metabolite that is formed from AFB1 by the placenta itself. This indicates that AFL may play a large role in developmental toxicities of AFB1 (Partanen et al., 2010). AFL has been found in human urine and breastmilk of AFB1 exposed populations (Kussak et al., 1998; Lamplugh et al., 1988; Lovelace et al., 1982). AFH1 is a metabolite that is structurally similar to AFL which contains an additional hydroxy group on the terminal cyclopentenone ring. The metabolic formation of AFH1 was found to be dependent on two enzyme systems: the microsomal hydroxylase and cytoplasmic reductase systems. It still remains unclear whether or not AFH1 is formed from a reduction of AFQ1 or a hydroxylation of AFL (Salhab and Hsieh, 1975).

AFB2a, the hemiacetal form of AFB1, was first discovered as an acid-catalyzed product of AFB1. In dilute acidic conditions, water is added across the 8,9-double bond to form the terminal hemiacetal ring (Ciegler and Peterson, 1968; Pohland et al., 1964). This nonenzymatic conversion was also found to occur in the acidic media of molds that were treated with AFB1 (Ciegler et al., 1966). When testing the biological activity of AFB2a, it was found that the toxicity was severely reduced as compared to AFB2a. Bile duct hyperplasia in ducklings and DNA binding capacity was much lower, indicating the potential of AFB2a as a detoxification product (Lillehoj and Ciegler, 1969). Although the reaction is a hydration rather than an oxidation, AFB1 has been shown to be metabolized to AFB2a in an NADPH-dependent manner in microsomal preparations of humans, rat, mice, rabbits, hamsters and chickens (Ball and Coulombe, 1991; Chipley et al., 1974; Gradelet et al., 1998; Salhab and Edwards, 1976). A unique property of AFB2a as compared to many of the other metabolites is its ability to bind to cellular proteins. Originally, this process was observed when AFB2a was incubated with amino acids and proteins at physiological pH (Ashoor and Chu, 1975). This interaction was hypothesized to be due to a Schiff base interaction, however it was later discovered that AFB2a binds to amino acids through the formation of a pyrrole ring through a Paal-Knorr synthesis mechanism. Additionally, this binding only occurs on primary amines, is favored in alkaline pHs, and this adduction can occur on phosphoethanolamine head groups on phospholipids, making it the only structurally characterized aflatoxin-lipid adduct to date (Blake R. Rushing and Selim, 2017a,b). The protein binding capability of AFB2a is thought to contribute to other potential cellular toxicities. For example, AFB2a binding has been shown to inhibit the activity of deoxyribonucleases, demonstrating the ability of AFB2a to alter enzymatic activities of target proteins (Schabort and Pitout, 1971). Interspecies differences in AFB2a can vary greatly, with AFB2a accounting for up to 50% of total AFB1 metabolism (Patterson, 1973; Patterson and Allcroft, 1970; Patterson and Roberts, 1972). AFB2a has been found in high levels in poultry eggs possibly as a result of avian metabolism, providing a potential source of dietary exposure (Tchana et al., 2010). A study that involved 161 individuals in Lagos, Nigeria found that AFB2a was the most prominent aflatoxin species in urine, showing up in 32.7% of all samples (Bean et al., 1989). These data indicate that the formation of AFB2a occurs in humans and animals, either enzymatically or nonenzymatically, and has the potential to act as a detoxification although protein binding can potentially lead to additional toxicities.

2.3. Contribution to global HCC

As one of the most potent hepatocarcinogens, AFB1 is a major contributor to the worldwide occurrence of HCC. Because human exposure to aflatoxin occurs so frequently, chronic liver damage occurs due to the ingestion of this toxin which largely remains unmonitored. Early studies in Uganda and Kenya showed that regions with high incidence of liver cancer also contained high levels of aflatoxin contamination in food products, which corresponded with AFB1's hepatocarcinogenic properties in laboratory experiments (Alpert et al., 1971; Peers and Linsell, 1973). Later studies began to find that AFB1 worked synergistically with hepatitis B virus (HBV) to drastically increase the risk of HCC development. Epidemiological studies taking place in various Asian countries, such as Shanghai and Taiwan, monitored thousands of individuals for biomarkers of AFB1 exposure (urinary AFM1 excretion or serum aflatoxin-albumin adducts) and HBV infection (hepatitis B surface antigen). After following these individuals for many years, these studies found that the odds ratio (OR) of developing HCC from AFB1 exposure or HBV infection was 1.7–6.0 and 7.3–22.8 respectively, but in combination the OR increased to 59.4–129. This indicates that the combination of AFB1 exposure and HBV infection greatly enhance HCC risk far above either factor individually, showing a synergism between AFB1 and HBV. Additionally, these studies clearly demonstrated that AFB1 exposure alone was sufficient to significantly increase the risk of cancer development. Evidence also suggests that hepatitis C virus (HCV) may also play a synergistic role with AFB1, although this hasn't been as extensively characterized as HBV (Kew, 2003; Lunn et al., 1997; Ming et al., 2002; Ross et al., 1992; Sun et al., 1999; Wang et al., 1996; Wild et al., 1993). Recently, a study in Taiwan investigated HCC risk associated with AFB1 exposure in HCV-positive and HBV-HCV-negative individuals. After 8 years of follow-up, HCV and AFB1 exposure were both found as independent risk factors for HCC development. After 20 years of follow-up, individuals positive for HCV and high AFB1 exposure had a much higher odds ratio as compared to those only positive for HCV or AFB1 exposure alone, although the interaction was not statistically significant, possibly due to a small sample size (Chu et al., 2018). Because of the high infection rates of HBV and HCV in developing countries, many individuals in these regions can be highly sensitive to the hepatocarcinogenic effects of AFB1. As a result, it is estimated that AFB1 is a causative agent in up to 28% of the world's cases of HCC (Liu and Wu, 2010). These findings have sparked awareness of the dangers of AFB1 exposure and have encouraged many countries to begin strictly monitoring aflatoxin levels in imported and exported goods.

2.4. DNA adducts lead to carcinogenesis

Once formed by the reaction of AFBO and guanine residues, the AFB1-N_7-guanine adduct undergoes one of two possible fates: 1) it forms an opened ring structure (which is favored under mild alkaline conditions) making a stable AFB1-formamidopyridine adduct (AFB1-FAPy) on the guanine residue or 2) the guanine residue can undergo depurination resulting in an apurinic (AP) site on the DNA backbone with the release of free AFB1-N_7-guanine (Groopman et al., 1981). This free AFB1-N_7-guanine is excreted in the urine and is often used as a biomarker of AFB1 exposure (Egner et al., 2006; Vidyasagar et al., 1997). Glutathione conjugation by glutathione-S-transferase (GST) of AFBO is a major route of detoxification and can occur with both *endo* and *exo* isomers (Degen and Neumann, 1978; Guengerich et al., 1998, 1996; Kevin D. Raney et al., 1992b). Conjugation to glutathione (AFB1-GSH) disrupts the ability of AFBO to bind to DNA forming an inert metabolite. Once formed, this conjugate is then converted into a mercapturic acid adduct *in vivo* through a series of enzymatic reactions involving γ-glutamyltranspeptidase (GGT), dipeptidase (DPEP), and N-acetyltransferase (NAT) and is then excreted in urine (Moss et al., 1985). In a clinical trial taking place in Qidong, People's Republic of

China, oltipraz was used as a chemopreventative agent which, at sustained low doses, protected against AFB1 toxicity by inducing phase 2 metabolism as seen by an increase in aflatoxin-mercapturic acid excretion in urine. In contrast, high doses of oltipraz protected against AFB1 toxicity by inhibiting phase 1 enzymes and had no effect on AFB1 conjugation to mercapturic acid (Wang et al., 1999). Additionally, this glutathione detoxification pathways explains why mice are more resistant to AFB1 toxicity than other animal models due to their high expression of glutathione-S-transferases (Ilic et al., 2010).

Due to the highly unstable nature of AFBO, this metabolite can spontaneously hydrolyze before binding to any macromolecules, resulting in the formation of AFB1 dihydrodiol. This diol is in equilibrium with a ring opened dialdehyde form - named AFB1 dialdehyde - which can spontaneously bind covalently to N-termini and lysine side chains on cellular proteins which is thought to be a mechanism of other AFB1 cytotoxicities (Johnson et al., 1996). AFB1 dialdehyde can be metabolized by aflatoxin aldehyde reductase (AFAR) into AFB1 dialcohol, removing its protein binding ability (Guengerich et al., 2001). The protein binding of AFB1 dialdehyde and AFBO commonly occurs on serum albumin which has a half-life of approximately twenty days making it a reliable biomarker for determining AFB1 exposure even if the time of exposure was not recent (Sabbioni et al., 1990, 1987; Wild et al., 1996, 1990) (Fig. 2). The cytotoxicity of this protein binding is believed to lead to further tissue damage creating a pro-inflammatory, pro-proliferative state which promotes carcinogenesis.

Both the AP site and the AFB1-FAPy lesions are precursors for genetic mutations and the location of these mutations determine if carcinogenesis is initiated. One of the most common mutations found in human hepatocytes exposed to AFB1 is a G→T transversion on codon 249 of the p53 gene causing a 249^{Arg} →249^{Ser} of the p53 protein (Aguilar et al., 1993; Bailey, 1996; Macé et al., 1997; Smela et al., 2002). As a tumor suppressor protein, p53 regulates many cellular functions such as cell cycle progression, DNA repair, apoptosis, and autophagy (Zilfou and Lowe, 2009). Many cancers, including HCC, have mutations of p53, which is thought to alter tumor suppressive functions, allowing the damaged cells to become cancerous (Greenblatt et al., 1994). Specifically, inducing the 249^{Ser} has been found to enhance cell growth, survival, and clonal expansion in addition to inhibiting wild type p53 activity and apoptosis (Dumenco et al., 1995; Forrester et al., 1995; Ponchel et al., 1994; Staib et al., 2003; Wang et al., 1995). In accordance with this, epidemiological studies in humans have shown that patients with HCC in high aflatoxin-risk regions exhibit this particular mutation. A study investigating five HCC patients from southern Africa - an area of high AFB1 exposure - found that four of the five patients were positive for the 249^{Ser} mutation of p53 (Bressac et al., 1991). Two studies have more recently investigated the frequency of 249^{Ser} p53 mutations in HCC patients in The Gambia – another area of high AFB1 exposure and HCC incidence. Kirk et al. showed on two separate occasions that 36% and 39.8% of HCC patients possessed this mutation in extracted DNA from plasma (Kirk et al., 2005, 2000). In agreement with these studies, Szymánska et al. identified 35% of HCC patients with this mutation in The Gambia (Szymánska et al., 2004). Stern et al. presented a meta-analysis of 49 studies that investigated 249^{Ser} p53 mutation frequency in HCC patients and correlated them based on the region's risk of aflatoxin exposure (low, moderate, and high). The authors found a significant positive correlation between 249^{Ser} p53 mutations and aflatoxin presence (Stern et al., 2001). These studies show 1) a mechanism of AFB1 forming 249^{Ser} mutations in experimental models, 2) the 249^{Ser} mutation alters p53 to promote tumor formation, and 3) humans with HCC exhibit the 249^{Ser} mutation, which is more frequent in high aflatoxin-risk regions. This gives strong evidence that AFB1 causes HCC in humans by forming the 249^{Ser} mutation in p53.

3. Additional toxicity (aflatoxicosis)

3.1. Malnutrition

AFB1 has demonstrated other toxicities apart from genotoxicity and carcinogenicity. AFB1 has been shown to cause malnutrition and growth impairment in both humans and animal models. In many African countries, children with kwashiorkor or marasmic kwashiorkor show high frequencies of AFB1 biomarkers as compared to their healthier counterparts. A study investigating 252 Sudanese children found

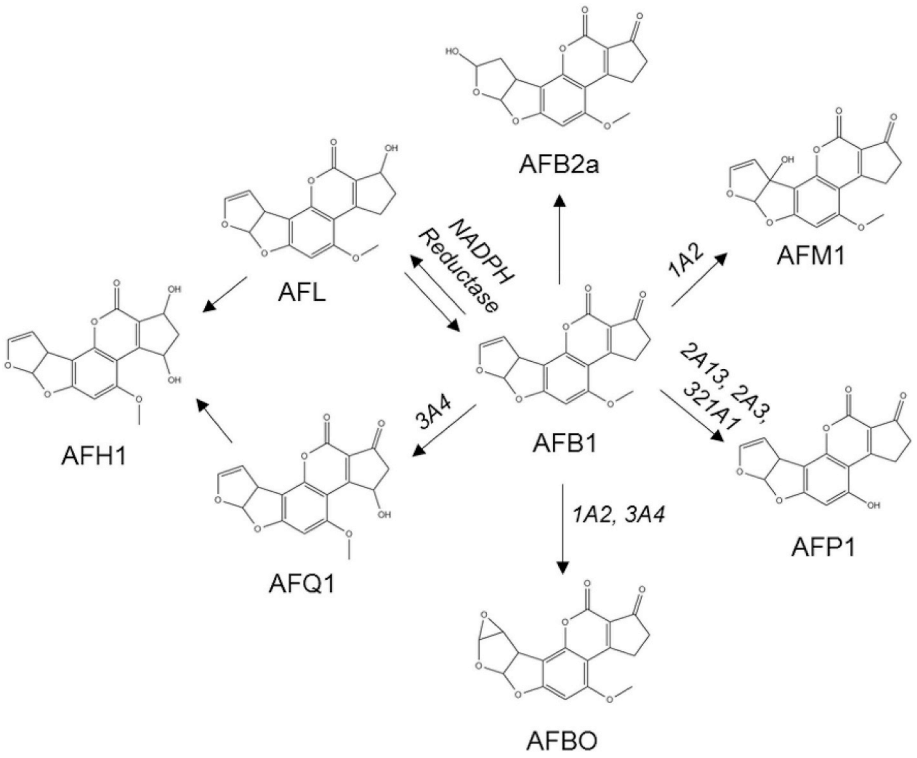

Fig. 1. P450-mediated metabolic pathway of AFB1. Metabolism of AFB1 is primarily carried out by CYP450 enzymes. CYP3A4 and CYP1A2 carry out the majority of these metabolic reactions, leading to a number of hydroxylated metabolites (AFQ1, AFP1, and AFM1). The formation of the ultimate carcinogen AFBO is also mediated by these enzymes. AFL however, is not formed by CYP450 enzymes but rather an NADPH reductase. A unique property of this metabolite is its ability to revert back into AFB1, acting as a reservoir for this toxin. Hepatic formation of AFB2a has been reported, although a specific CYP isoform has not been identified, however this metabolite is also formed spontaneously in acidic environments. Little is known about the production of AFH1, but it is likely formed from AFL or AFQ1.

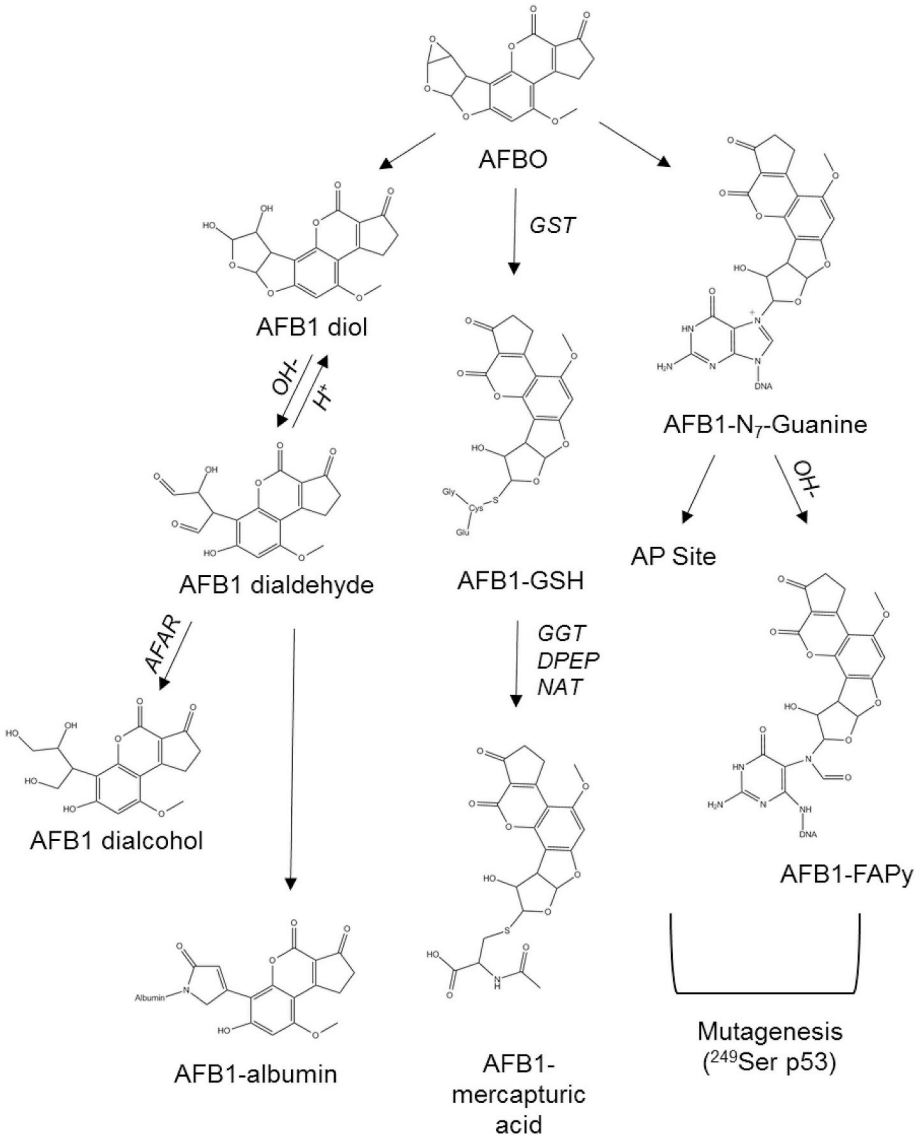

Fig. 2. Biological fate of AFBO. After being formed from AFB1, AFBO has three major fates: hydrolysis, glutathione conjugation, and DNA adduction. Hydrolysis of AFBO leads to the formation of AFB1 diol which is in equilibrium with the dialdehyde form. This dialdehyde can be reduced by AFAR or it can bind spontaneously to proteins at lysine residues. The most common product is the well-known AFB1-albumin biomarker found in serum. Glutathione conjugation leads to the formation of AFB1-GSH which is further metabolized by enzymes GGT, DPEP, and NAT to the mercapturic acid derivative which is excreted in the urine. Finally, Adduction to DNA leads to AFB1-N_7-guanine adducts. This genetic lesion can stay on the DNA backbone and spontaneously transform to the ring opened form AFB1-FAPy, or it can release from the DNA backbone forming an AP site as well as free AFB1-N_7-guanine which is excreted in the urine. Both situations lead to the formation of point mutations, the most common of which is a G→T transversion in the p53 gene causing a ^{249}Ser mutation in the p53 protein. This mutation is highly correlated with the development of HCC.

that those with marasmus, marasmic kwashiorkor, and kwashiorkor had more frequent and higher concentrations of aflatoxins in sera. Interestingly, aflatoxicol was a major metabolite found in kwashiorkor and marasmic kwashiorkor but not in the controls, indicating a possibility of altered aflatoxin metabolism in these groups (de Vries et al., 1990). Other studies have looked at smaller populations of children in Kenya, Nigeria, South Africa, and Cameroon which also found that kwashiorkor and marasmic kwashiorkor children have higher levels of AFB1 biomarkers (de Vries et al., 1990; Lamplugh and Hendrickse, 1982; Tchana et al., 2010). Additionally, Ghanaians with high AFB1-albumin have been shown to have lowered serum levels vitamins A and E (Obuseh et al., 2011; Tang et al., 2009). These data indicate that AFB1 exposure is correlated with severe malnutrition and may cause these conditions by interfering with micronutrient absorption.

Animal models and *in vitro* methods have also been used to investigate the mechanism of AFB1-induced malnutrition. Glahn et al. found that broiler chicks that were exposed to AFB1 had lowered serum concentrations of 25-hydorxy vitamin D, 1,25-dihydroxy vitamin D, and calcium possibly by impairing renal function and altering parathyroid metabolism (Glahn et al., 1991). Broiler chicks have also been shown to experience vitamin A depletion in a separate study after eating AFB1-contaminted food, which was prevented by supplementing feed with an AFB1-binding agent (Pimpukdee et al., 2004). Lowered activity of lipogenic and amino acid-metabolizing enzymes have also been shown in broiler chicks exposed to AFB1, leading to reduced lipogenesis (Bryden et al., 1979). The distribution of metal ions has been shown to be altered in rats treated intraperitoneally with AFB1. Zinc, copper, manganese, and iron levels of the testes, kidney and various brain regions were measured after exposing Wistar rats to AFB1 for 6 weeks. Results showed that zinc levels were decreased in the testis and increased in the kidney and brain, copper levels were elevated in the kidney, manganese was elevated in all three organs, and iron was decreased in all three organs (Ikegwuonu, 1984). Additionally, piglets exposed to AFB1 showed decrease zinc levels in serum further indicating the ability of AFB1 to alter metal bioavailability (Mocchegiani et al., 1998). Mechanistically, it is unclear how AFB1 alters nutrient levels. *In vitro* studies have shown the ability of AFB1 to downregulate the vitamin D receptor (VDR) and modulate the insulin-like growth factor (IGF)-2 signaling axis indicating that these may be potential mechanisms of AFB1-induced malnutrition (Costanzo et al., 2015; Ubagai et al., 2010). Furthermore, Kenyan schoolchildren that exhibited high levels of AFB1-albumin were shorter and had lower levels of IGF1 and IGFBP3 as compared to groups with lower levels of the AFB1 biomarker (Castelino et al., 2015). Additionally, AFB1 may affect nutrient absorption through intestinal toxicity. Evidence of enteropathy has been repeatedly shown in experimental models with alterations in

intestinal density and increases in fibrosis/necrosis (Yunus et al., 2011). The disruption of intestinal function by AFB1 is considered to be due to the destruction of epithelial cells and their organization due to the inhibition of protein synthesis or cytotoxicity due to DNA and protein binding. This tissue damage can alter the structure of intestinal epithelial cells, affecting the efficiency of nutrient absorption (Maresca and Fantini, 2010; Smith et al., 2012). Malnutrition in human children has been shown to be tightly correlated with enteropathies, indicating that intestinal toxicity may play a key role in malnutrition caused by AFB1 (Humphrey, 2009; Ngure et al., 2014).

3.2. Growth impairment

Growth impairment, or stunting, is a major public health issue that affects millions of children worldwide, particularly in developing countries. There are many contributing factors to this condition and much research is needed to identify causative agents and methods to mitigate their effects (Walker et al., 2016). One of the major identified risk factors of child stunting is exposure to aflatoxins. Indeed, many studies over the last few decades have shown that AFB1 exposure leads to growth impairment in developing humans and animals. In humans, a major risk factor for growth impairment is circulating levels of AFB1 or its metabolites in the mother during pregnancy. Multiple studies have shown that pregnant and nursing women have aflatoxin metabolites or biomarkers in breastmilk, serum, or cord blood, suggesting that fetuses and neonates can be exposed to aflatoxins through the mother (Abdulrazzaq et al., 2003; Ghiasain and Maghsood, 2012; Hsieh and Hsieh, 1993; Lamplugh et al., 1988; Mahdavi et al., 2010; Maxwell et al., 1989; Sadeghi et al., 2009; Wild et al., 1991). Levels of aflatoxins in pregnant women have also been linked to poor birth outcomes in humans. An early study investigating 125 pregnant Kenyan women found that 53% of the mothers were positive for aflatoxin biomarkers in the blood and 37% were positive for biomarkers in cord blood. The study also found that newborns birthed from aflatoxin-positive mothers had significantly lower birth weights. Additionally, the two stillbirths that occurred during the study only came from AFB1-positive mothers. Abdulrazzaq et al. found a strong negative correlation between AFM1 levels and birth weights which agrees with Turner et al.'s findings that AFB1-albumin in maternal blood was a predictor of poor growth of infants (Abdulrazzaq et al., 2004; Turner et al., 2007). Also, Shuaib et al. reported that mothers in the highest quartile of serum AFB1-albumin levels were highly likely to have lower birthrates than mothers with lower biomarker concentrations (Shuaib et al., 2010). After birth, continuing exposure of children to aflatoxins can further affect their development. Studies have reported significant correlations with AFB1 biomarkers in neonates and young children and impairment of their growth. Gong et al. found that 99% of 479 children in Benin and Togo were positive for AFB1-albumin with levels higher in post-weaning ages (> 3 years old). A significant negative correlation was found between AFB1-albumin levels and height/weight with stunted children exhibiting 30–40% higher AFB1-albumin levels (Gong et al., 2002). As a follow up to this, the lab re-evaluated the data for these children and found that the move to solid food was associated with a dramatic increase in AFB1-albumin levels due to a higher likelihood of eating contaminated maize (Gong et al., 2003). This indicated that weaning is a critical point in a child's exposure to aflatoxin and post-weaning diets should be carefully monitored to prevent growth impairment. This observation was repeated during a study involving 200 children in Benin, West Africa aged 16–37 months old. When dividing the children by their weaning status, it was found that the weaned population had higher AFB1-albumin levels as compared to those still receiving breast milk (the post-wean diet consisted mainly of maize-based foods). Over an eight month follow up, children who had higher AFB1-albumin levels had a significant reduction in growth with a mean reduction of 1.7 cm (Gong et al., 2004). These studies indicate that fetal and neonatal exposure to AFB1 significantly reduces birth and growth outcomes, with a particular emphasis on the post weaning stage.

Animal models have also reflected many developmental abnormalities following exposure to AFB1. In rats, these effects have been low birth weights, impaired locomotor activity, exploratory behavior, and learning ability following gestational exposure to AFB1 (Kihara et al., 2000; Supriya et al., 2016). Piglets showed reduced weight gain during AFB1 exposure and Japanese quail have shown a reduction in egg weight (Marin et al., 2002; Oliveira et al., 2002). The mechanism for this AFB1-induced growth impairment is not well understood, although a recent study has shown that newly-weaned rats exposed to AFB1 showed signs of liver injury and hepatic growth hormone (GH) resistance by reductions in insulin-like growth factor-1 (IGF-1) mRNA and GH receptor expression which was correlated with reduced body weight and tibia length (Knipstein et al., 2015). This suggests that liver damage and alterations in hepatic GH signaling may be mechanisms of AFB1-related growth suppression. The effects of AFB1 on enteropathy and malnutrition are also likely contributors to the mechanism of growth suppression. Enteropathy has been linked to stunting in children and the process may be due to an increase in inflammation due to intestinal tissue damage or by the infiltration of pathogens or immunogenic macromolecules (Campbell et al., 2003; Lin et al., 2013). The damage and disruption of intestinal function, along with impairment of nutrient absorption/utilization, are also likely key factors in the development of stunting after exposure to AFB1 (Fig. 3).

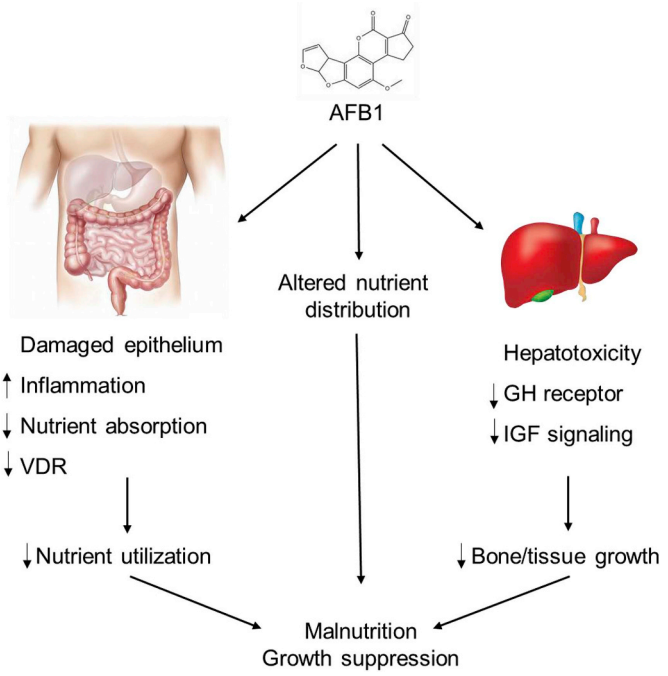

Fig. 3. Mechanism of AFB1-induced malnutrition and growth suppression. The result of stunting and/or malnutrition after exposure to AFB1 is likely due to toxic effects of the intestines and liver. Experimental evidence has shown the ability of AFB1 to damage intestinal epithelial cells, resulting in the breakdown of the intestinal structure. This leads to an influx of immune cells which may further damage the tissue and result in a reduced ability to properly absorb nutrients (vitamins A and E are most likely to be affected based on epidemiological evidence). Additionally, nutrient receptors, such as VDR, have also been shown to be decreased after AFB1 administration. Furthermore, AFB1 exposure has been shown to alter the distribution of nutrients to different organs, particularly metals. Lastly, hepatotoxicity of AFB1 has been shown to alter the GH and IGF signaling axis which leads to a decrease in bone and tissue growth. These factors combined are likely mechanisms that lead to malnutrition and growth suppression that are commonly seen after exposure to AFB1.

Table 1
Reports of AFB1 occurrence in food commodities over the last ten years.

Food Commodity	Country	Number of samples	Number positive for AFB1	% positive for AFB1	Min AFB1 Level (μg/kg)	Max AFB1 Level (μg/kg)	Reference
Rice	Sweden	99	56	56.6	0.1	46.2	Fredlund et al. (2009)
Rice	India	1200	814	67.8	0.1	308	Reddy et al. (2009)
Rice	Malaysia	13	9	69.2	0.68	3.79	Reddy et al. (2011)
Rice	Iran	256	251	98.0	0.1	6.3	Rahmani et al. (2011)
Rice	China	29	29	100.0	0.1	136.8	Sun et al. (2011)
Rice	Canada	199	99	49.7	0.05	7.1	Bansal et al. (2011)
Rice	Brazil	230	128	55.7	0.11	180.74	Almeida et al. (2012)
Rice	Ecuador	43	3	7.0	4.9	47.4	Oritz et al., 2013
Rice	Pakistan	262	250	95.4	1.07	24.65	Asghar et al. (2014)
Rice	Pakistan	1027	189	18.4	1.1	32.9	Firdous et al. (2014)
Rice	Pakistan	208	73	35.1	0.04	21.3	Iqbal et al. (2016)
Rice	Brazil	187	21	11.2	–	63.32	Katsurayama et al. (2018)
Average				**55.4**	**0.76**	**73.2**	
Nuts	Japan	21	10	47.6	0.17	2.59	Kumagai et al. (2008)
Nuts	China	17	17	100.0	0.1	0.7	Sun et al. (2011)
Nuts	Malaysia	20	13	65.0	0.66	15.33	Reddy et al. (2011)
Nuts	Burkina Faso	9	2	22.2	5.6	15.5	Warth et al. (2012)
Nuts	Mozambique	23	3	13.0	3.4	123	Warth et al. (2012)
Nuts	Thailand	25	9	36.0	0.04	4.74	Tansakul et al. (2013)
Nuts	Turkey	302	51	16.9	0.16	368	Hepsag et al. (2014)
Nuts	Pakistan	180	83	46.1	0.04	14.5	Masood et al. (2015)
Nuts	Turkey	170	11	6.5	0.09	10.6	Kabak, 2016
Nuts	Zimbabwe	208	26	12.5	0.7	175.9	Maringe et al. (2017)
Average				**36.6**	**1.1**	**73.1**	
Maize	Tunisia	17	1	5.9	0.42	–	Ghali et al. (2010)
Maize	China	108	108	100.0	1.0	50	Sun et al. (2011)
Maize	Burkina Faso	26	13	50.0	3.4	636	Warth et al. (2012)
Maize	Mozambique	13	6	46.2	16.3	363	Warth et al. (2012)
Maize	Iran	373	146	39.1	0.5	241.3	Karami-Osboo et al. (2012)
Maize	Croatia	633	241	38.1	1.1	2072	Pleadin et al. (2014)
Maize	Pakistan	100	52	52.0	2	1405.3	Firdous et al. (2014)
Maize	Tanzania	–	–	29.0	0.53	364	Kimanya et al. (2014)
Maize	Pakistan	75	73	97.3	0.5	409.3	Iram et al. (2014)
Maize	South Africa	114	15	13.2	1	133	Mngqawa et al. (2016)
Maize	Democratic Republic of Congo	50 (harvest)	16	32.0	1.5	51.23	Kamika et al. (2016)
Maize	Democratic Republic of Congo	30 (market)	30	100.0	1.75	1401.45	Kamika et al. (2016)
Maize	Zimbabwe	338	80	23.7	0.57	26.6	Murashiki et al. (2017)
Maize	Ethiopa	100	8	8.0	–	513	Getachew et al. (2017)
Maize	Serbia	360	206	57.2	1.3	88.8	Janić Hajnal et al., 2017
Average				**46.1**	**2.3**	**553.9**	
Wheat	Tunisia	46	4	8.7	0.12	18	Ghali et al. (2010)
Wheat	China	16	16	100.0	0.3	0.9	Sun et al. (2011)
Wheat	Malaysia	14	9	64.3	0.55	5.07	Reddy et al. (2011)
Wheat	China	178	11	6.2	0.03	0.12	Zhao et al. (2017)
Average				**44.8**	**0.3**	**6.0**	
Sorghum	Tunisia	49	36	73.4	0.4	25.1	Ghali et al. (2010)
Sorghum	India	1606	1173	73.0	0.01	263.98	Ratnavathi et al. (2012)
Sorghum	Sudan	60	17	28.3	0.06	12.29	Elbashir and Ali, 2014
Sorghum	Ethiopia	90	85	94.4	–	33.1	Taye et al. (2016)
Average				**67.3**	**0.2**	**83.6**	
Cereal	Tunisia	147	42	28.6	0.1	25.1	Ghali et al. (2010)
Cereal	Spain, Italy, Morocco, Tunisia	173	14	8.1	6.4	66.7	Serrano et al. (2012)
Cereal	Pakistan	237	98	41.4	0.04	6.9	Iqbal et al. (2014)
Average				**26.0**	**2.2**	**32.9**	
Dried Fruits	Tunisia	20	9	45.0	0.1	34.5	Ghali et al. (2010)
Dried Fruits	Greece	26	6	23.1	–	< 2	Kollia et al. (2014)
Dried Fruits	Pakistan	77	33	42.9	0.04	9.8	Masood et al. (2015)
Dried Fruits	Turkey	130	16	12.3	0.1	12.5	Kabak, 2016
Dried Fruits	Iran	88	50	56.8	0.3	8.4	Heshmati et al. (2017)
Average				**36.0**	**0.1**	**16.3**	
Spices	Tunisia	13	9	69.2	0.15	14.9	Ghali et al. (2010)
Spices	Malaysia	15	14	93.3	0.58	4.64	Reddy et al. (2011)
Spices	Thailand	60	40	66.7	0.1	53.62	Tansakul et al. (2013)
Spices	Italy	130	11	8.5	0.08	> 15	Prelle et al. (2014)
Spices	Malaysia	58	49	84.5	0.01	28.43	Ali et al. (2015)
Average				**64.4**	**0.2**	**25.4**	

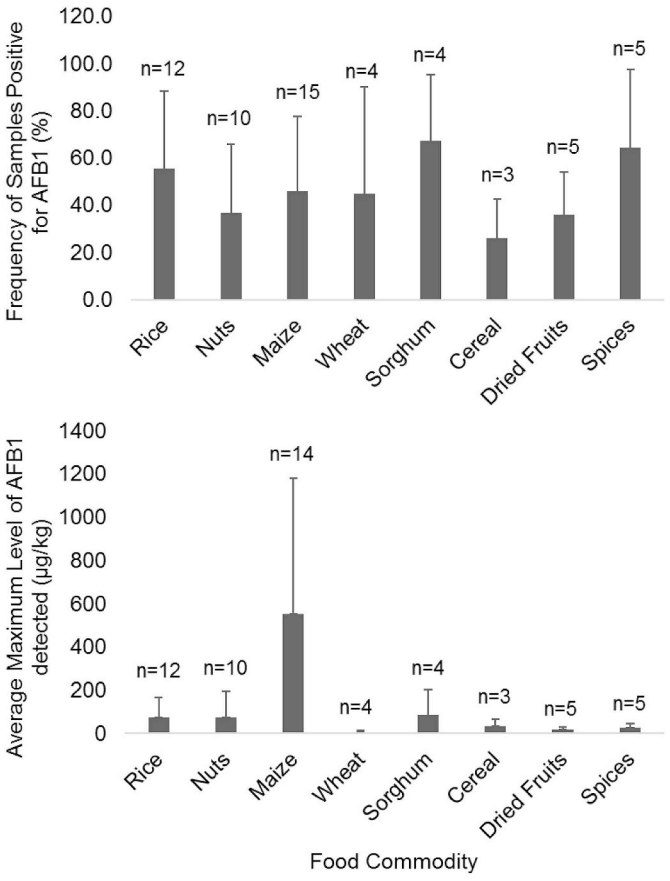

Fig. 4. Frequency and maximum concentrations of AFB1 reported across multiple studies. A review of the current literature has shown that high percentages of food samples test positive for AFB1 (a). Furthermore, average maximum concentrations found in these studies often greatly exceed the regulatory limit of ≤20 µg/kg adopted by most countries. In particular, maize has been reported to have much higher maximum levels of AFB1 as compared to other food commodities (b). Error bars are expressed as standard deviation. Sample sizes displayed above bars represent the number of studies that evaluated each commodity.

3.3. Immunomodulation

The ability of AFB1 to modulate immune function has also been established both in humans and animals. The number of infections and duration of hospitalization were compared between aflatoxin-positive kwashiorkor children and aflatoxin-negative kwashiorkor children in South Africa. This study showed that aflatoxin-positive children had longer average durations of hospitalization (31.1 vs 16.0 days) and an increase in the number of infections (observed complications were diarrheal disease, pneumonia, oral herpes, moniliasis, shock, and thrush) (Adhikari et al., 1994). Further studies linked AFB1 exposure with reduced levels or functions of immunological factors. For example, Turner et al. showed that Gambian children positive for AFB1-albumin had lower salivary IgA, which may contribute to the high infection-related mortality in this region (Turner et al., 2003). In a study investigating Ghanaians, Jiang et al. found that participants with high AFB1-albumin levels had lower percentages of $CD3^+CD69^+$ T cells and CD19 + $CD69^+$ B cell subsets. Additionally, high AFB1-albumin levels were associated with lower $CD8^+$ T cells containing perforin or both perforin and granzyme A (Jiang et al., 2005). These effects could potentially decrease host resistance to infections, also contributing to infection-related incidences. Because many regions with high AFB1 exposure also have high rates of human immunodeficiency virus (HIV) infections, some studies have investigated the immunosuppressive effect of AFB1 in HIV infected patients. Jiang et al. reported that Ghanaians who are positive for both HIV and AFB1 exposure have exhibited lower percentages of $CD4^+$ T regulatory cells, naïve $CD4^+$ T cells, and B cells as compared to HIV patients with low AFB1 exposure (Jiang et al., 2008). Additionally, Keenan et al. reported that HIV + Ghanaians with high AFB1-albumin levels had higher risks for developing tuberculosis as compared to HIV + patients with low AFB1-albumin (Keenan et al., 2011). These observations indicate that the immune functions of patients infected with HIV can be further suppressed by AFB1 exposure.

Immunomodulatory effects of AFB1 have also been demonstrated in animal models. Meissonnier et al. reported impaired lymphocyte activation and increased cytokine expression (TNF-α, IL-1β, IL-6, IL-10, and IFN-γ) in pigs vaccinated with ovalbumin after dietary AFB1 exposure (Meissonnier et al., 2008). Sahoo et al. observed a suppression of humoral immunity after observing a decrease in hemagglutination, serum protein levels, and lymphocyte infiltration in AFB1-exposed rabbits after immunizing them with sheep red blood cells (Sahoo et al., 1996). Marin et al. found that piglets exposed to a low dose of AFB1 had decreased leukocyte counts whereas, interestingly, an increase in leukocytes was observed when using a high dose, indicating a possible biphasic effect. The authors also report that a decrease in proinflammatory (IL-1β, TNF-α) and an increase in anti-inflammatory (IL-10) cytokines were seen at both the low and high AFB1 doses (Marin et al., 2002). Yunus et al. presented a review on immunomodulatory effects of AFB1 in broiler chicks in which many studies have shown a biphasic effect of AFB1 – low doses cause immunosuppression whereas higher doses may cause stimulation of the immune system (Yunus et al., 2011). The biphasic effect of AFB1 on the immune system was also shown in F344 rats. When exposed to AFB1 for a short term (1 week), rats experienced a decrease in $CD8^+$ T cells and natural killer (NK) cells, suppressed IL-4 and IFN-γ expression by T cells, and reduced TNF-α expression by NK cells. A prolonged exposure (5 weeks), rats exhibited an increase in $CD3^+$ and $CD8^+$ T cells at low AFB1 dose levels, lower IL-4 expression by $CD4^+$ and CD8a + cells, and a decrease in TNF-α expression by NK cells. This indicates that AFB1 has immunosuppressive effects during acute exposures, but chronic exposures may lead to an inflammatory response depending on the dose level (Qian et al., 2014). Overall, human and animal studies show that in general, AFB1 has the ability to reduce immune system functions, although higher doses of AFB1 have shown some stimulatory effects in some animal models.

4. Occurrence in food

Global cereal production for 2017 was forecasted to reach 2627 million metric tons with coarse grains forecasted at 1371 million metric tons. Additionally, global wheat production was projected at 754.8 million metric tons and rice was projected at 500.8 million metric tons (FAO, 2017a, 2017b). These statistics show the importance of rice, wheat, corn, cereals, and other grains in making up the global food supply. AFB1 however, is well-known to contaminate these products in addition to other highly used food commodities such as groundnuts, dried fruits, and spices. Below is a look at studies in the last ten years that detected AFB1 contamination in these commodities. A summary of these studies can be found in Table 1 and Fig. 4.

4.1. Rice

Recently, AFB1 contamination in rice has been reported in Sweden, India, Malaysia, Pakistan, Ecuador, Brazil, China, and Canada. Of the studies analyzed in the past decade for this review, rice had the third highest frequency of contamination with an average of 55.4% of samples contaminated with AFB1. In Brazil, one study analyzed 187 rice samples for aflatoxins and aflatoxin-producing strains of fungi. In these samples, 383 strains of *Aspergillus* fungi were identified with 17% of

those strains being able to produce type B aflatoxins. Approximately 14% of the rice samples showed aflatoxin contamination with AFB1 ranging from 0 to 63.32 μg/kg (Katsurayama et al., 2018). Another study in Brazil analyzed 230 rice samples that was collected from various regions during an outbreak in 2007–2009. These samples contained up to 180.74 μg/kg of AFB1 and many samples were also contaminated with other mycotoxins such as ochratoxin A, deoxynivalenol, and zearalenone (Almeida et al., 2012). In Canada, 199 rice samples were analyzed with 56 samples positive for AFB1 with concentrations up to 7.1 μg/kg (Bansal et al., 2011). Rice from China was found to have AFB1 levels from 0.1 to 136.8 μg/kg and many of these samples were co-contaminated with fumonisin B1 (Sun et al., 2011). Rice samples from Ecuador reached up to 47.4 μg/kg whereas Iran and India saw levels of up to 6.3 and 308 μg/kg respectively (Ortiz et al., 2013; Rahmani et al., 2011; Reddy et al., 2009). Three different studies analyzed rice contamination with AFB1 in Pakistan. These three separate studies found 35%, 52%, and 95.4% of the samples were contaminated with AFB1 with maximum AFB1 levels of 21.3, 32.9, and 24.54 μg/kg respectively (Asghar et al., 2014; Firdous et al., 2014; Iqbal et al., 2016). Additionally, rice samples from Sweden and Malaysia also found frequent AFB1 contamination with maximum AFB1 levels of 46.2 μg/kg and 3.79 μg/kg respectively (Fredlund et al., 2009; Reddy et al., 2011). The average maximum AFB1 concentration in rice across all of these studies was 73.2 μg/kg with an average frequency of 55.4% of samples testing positive for AFB1, making rice a considerable source of AFB1 exposure (Fig. 4a and b).

4.2. Groundnuts

Recent studies investigating AFB1 contamination in groundnuts have been reported. Peanuts are most commonly identified as contaminated groundnuts, but other varieties such as pistachios and hazelnuts have also shown contamination. A study in Japan found that ten out of twenty-one peanut butter samples contained detectable levels of AFB1, although concentrations did not exceed 2.59 μg/kg. Interestingly, unprocessed peanut samples that were also analyzed in the study did not show any aflatoxin contamination (Kumagai et al., 2008). Sun et al. investigated AFB1 occurrence in foods in three different areas in China. Peanut samples from this study showed 100% contamination of AFB1, although the concentrations were low (up to 0.7 μg/kg) (Sun et al., 2011). Malaysia has also recently shown peanut contamination with levels up to 15.33 μg/kg (Reddy et al., 2011). Another study investigated groundnut contamination in both Burkina Faso and Mozambique. Burkina Faso showed moderate levels of up to 15.5 μg/kg however Mozambique contained high AFB1 concentrations up to 123 μg/kg (Warth et al., 2012). Two separate studies taking place in 2014 and 2016 investigated groundnuts from Turkey. The former study showed contamination in 16.9% of the 302 samples tested with AFB1 ranging from 0.16 to 368 μg/kg. The latter study showed lower rates and levels of AFB1 contamination with only 6.5% of the 170 samples returning positive for AFB1 contamination with a range of only 0.09–10.6 μg/kg (Hepsag et al., 2014; Kabak, 2016). Thailand showed a low percentage of groundnut contamination (9%) and Zimbabwe, while also showing a relatively low rate of contamination (12.5%), reached high AFB1 levels of up to 175.9 μg/kg (Maringe et al., 2017; Tansakul et al., 2013). Pakistan had the highest percentage of groundnuts contaminated – 83% of 180 samples – with a range of 0.04–14.5 μg/kg (Masood et al., 2015). For the studies included in this review, groundnuts had an average frequency of 36.6% of sample positive for AFB1 contamination with an average maximum AFB1 concentration of 73.1 μg/kg (Fig. 4a and b).

4.3. Maize

Maize by far had the highest reported levels of AFB1. Of particular note are studies in Croatia, Pakistan, and the Democratic Republic of Congo, which all showed maximum AFB1 levels > 1000 μg/kg (2072, 1405.3, and 1401.45 μg/kg respectively). Regarding the study in the Democratic Republic of Congo, samples were analyzed at harvest, during transportation, and eventually at market. Frequency of AFB1 contamination increased greatly between newly harvested maize (32%) and market samples (100%) (Kamika et al., 2016). Both of the studies that collected samples from Pakistan showed high contamination. Firdous et al. reported maximum levels of 1405.3 μg/kg in Lahore, Pakistan whereas Iram et al. saw maximum levels of 409.3 μg/kg in Punjab, Pakistan (Firdous et al., 2014; Iram et al., 2014). The authors of the Croatia study noted that the collected maize samples were grown during a particularly hot and dry season which may partially explain the high levels that were observed (2072 μg/kg) (Pleadin et al., 2014). Overall, the studies investigating maize contamination saw an average frequency of 46.1% of samples positive for AFB1 and an average maximum concentration of 553.9 μg/kg (Firdous et al., 2014; Getachew et al., 2017; Ghali et al., 2010; Iram et al., 2014; Janić Hajnal et al., 2017; Kamika et al., 2016; Karami-Osboo et al., 2012; Kimanya et al., 2014; Mngqawa et al., 2016; Murashiki et al., 2017; Pleadin et al., 2014; Sun et al., 2011; Warth et al., 2012) (Fig. 4a and b).

4.4. Wheat/Sorghum/Cereals

Fewer studies have recently investigated AFB1 occurrence in wheat, sorghum, and cereals which are summarized in Table 1. Despite only appearing in a few studies, sorghum had the highest average frequency of AFB1 contamination (67.3%) and the second highest average maximum concentration of 83.6 μg/kg as compared to all other food products (Ghali et al., 2010; Reddy et al., 2011; Sun et al., 2011; Zhao et al., 2017). Although wheat showed a relatively high frequency of AFB1 contamination (44.8%) it had the lowest average maximum concentration of 6.0 μg/kg (Elbashir and Ali, 2014; Ghali et al., 2010; Ratnavathi et al., 2012; Taye et al., 2016). Conversely, cereal had the lowest average frequency (26.0%) with a moderately high average maximum AFB1 concentration at 32.9 μg/kg (Ghali et al., 2010; Iqbal et al., 2014; Serrano et al., 2012) (Fig. 4a and b).

4.5. Fruits/spices

Fruits and spices were also less recently studied but proved to be a potential source of AFB1 exposure (also shown in Table 1). Spices (including cumin, black pepper, and chili pods/powder) had the second highest average frequency of contamination (64.4%) and an average maximum AFB1 concentration of 25.4 μg/kg (Ali et al., 2015; Ghali et al., 2010; Prelle et al., 2014; Reddy et al., 2011; Tansakul et al., 2013). Dried fruits (including figs, raisins, currants, sultanas, plums, dates, and apricots) had the second lowest frequencies (36.0%) and the second lowest average maximum concentration of 16.3 μg/kg (Ghali et al., 2010; Heshmati et al., 2017; Kabak, 2016; Kollia et al., 2014; Masood et al., 2015) (Fig. 4a and b).

5. Occupational exposures

Aside from eating contaminated foods, many individuals are exposed to AFB1 through occupational exposures. Table 2 gives a summary of studies that have investigated workers who have been exposed to AFB1 in an occupational setting. For approximately thirty years, several studies have investigated the frequency of workers exposed to AFB1 in the workplace and in some studies, the number of cancer cases that developed seemed to correspond with that exposure. Occupations that have been studied are primarily those dealing with the handling or manipulation of crops as well as occupations dealing with the production of poultry or swine products. In general, it is expected that the primary route of exposure of these workers to AFB1 is respiratory although some authors note the possibility of dermal or oral exposure. AFB1 has been shown to be present in dust particles originating from

Table 2
Reports of occupational exposure to AFB1.

Country	Occupation	Number of workers	Number positive for aflatoxin	Number positive for cancer	Suspected route of exposure	Free AFB1 in serum (ng/mL)	Urinary AFM1 (ng/mL)	AFB1-albumin (pg/mg)	Reference
Netherlands	oilpress	71	–	11	respiratory	–	–	–	Hayes et al. (1984)
Sweden	grain millers	2649	–	310	–	–	–	–	Alavanja et al. (1987)
Denmark	animal feed	–	–	398	respiratory	–	–		Olsen et al. (1988)
Denmark	animal feed	45	7	–	respiratory	–	–	44–100 pg/mg	Autrup et al. (1991)
Portugal	poultry production	31	18	–	–	< 1–4.23	–	–	Viegas et al. (2012)
Nigeria	feed mill workers	28	–	–	respiratory	73.4–189.2	–	–	Oluwafemi et al. (2012)
Egypt	textile workers	58	34	–	–	–	0–2.41		Saad-Hussein et al. (2013)
Portugal	swine production	28	21	–	respiratory, oral	< 1–8.94	–	–	Viegas et al. (2013a)
Portugal	poultry and swine production	45	24	–		> 1–8.94	–		Viegas et al. (2013b)
Portugal	waste management	41	41	–	respiratory, dermal	2.5–25.9	–	–	Viegas et al. (2014)
India	food-grain workers	46	15	–	respiratory	–	–	–	Malik et al. (2014)
Egypt	wheat handlers	190	–	–	–	–	–	.06–.11	Saad-Hussein et al. (2014)
China	sugar and papermaking workers	181	102	–	–	–	–	38.51 ± 44.8	Lai et al. (2014)
Portugal	slaughterhouse	30	14	–	respiratory, dermal	0–4.03	–	–	Viegas et al. (2015)
Italy	feed production and sorting	29	23	–	respiratory	–	0–0.399	–	Ferri et al. (2017)

contaminated food/products which can then be aerosolized and inhaled by those in close proximity (Burg et al., 1982; Selim et al., 1998; Sorenson et al., 1984, 1981). In earlier studies, the exposure of workers was estimated by analyzing AFB1 levels of the food that was processed. Cancer incidence was higher in the potentially exposed workers as compared to negative control group. In general, liver cancer was the primary cancer type although significant increases in respiratory and biliary cancer was also found (Alavanja et al., 1987; Hayes et al., 1984; Olsen et al., 1988). Later studies investigated AFB1 exposure on a shorter timeframe and instead used AFB1 biomarkers to monitor exposure rather than measuring cancer outcomes. These studies used either free AFB1 in serum, urinary concentrations of AFM1, or serum AFB1-albumin levels to determine exposure. High percentages of workers positive for AFB1 were reported in these studies ranging from 15.6 to 100% of workers positive for AFB1 biomarkers. Many of these studies took place in European countries and, despite regulatory efforts to reduce AFB1 exposure, high frequencies of exposure were reported for occupations in these regions (Autrup et al., 1991; Ferri et al., 2017; Lai et al., 2014; Malik et al., 2014; Oluwafemi et al., 2012; Saad-Hussein et al., 2014, 2013; Viegas et al., 2014, 2012; S Viegas et al., 2013a; Susana Viegas et al., 2013b; Viegas et al., 2015).

6. Detoxification strategies

Because of the high prevalence of AFB1 in food, many strategies are being developed to prevent or remove contamination in order to restore the safety and edibility of food products. Control strategies are divided into pre- and post-harvest techniques. Pre-harvest strategies include the use of genetically altered crops that are resistant to *Aspergillus* infection and environmental stressors, pesticide usage, crop rotation, and timing of planting. Post-harvest strategies include physical methods such as proper drying, packaging, storage, and preservatives/pesticide usage. These strategies act as preventative measures to reduce the amount of contamination that is introduced to crops. However, these strategies are not effective at fully preventing contamination, so further post-harvest techniques are being developed to detoxify contaminated foods. These involve the use of physical processes or chemical/biological additives to be added to contaminated crops to reduce or transform AFB1. This review will focus on more recent studies investigating post-harvest techniques, a summary of which can be found in Tables 3–6.

6.1. Physical treatment: heat and irradiation

Physical means of removing AFB1 from foods are most commonly heating and irradiation using gamma (γ) rays. Aflatoxins are well known to be stable at high temperatures, so harsh heating is needed to effectively remove amounts. Recent studies have shown that temperatures of 150–200 °C can remove significant amounts of AFB1 (an average of 79% reduction), which is most effective at high humidity (Arzandeh and Jinap, 2011; Hwang and Lee, 2006; Lee et al., 2015; Park et al., 2005; Park and Kim, 2006; Raters and Matissek, 2008; Soliman, 2002; Yazdanpanah et al., 2005; Zheng et al., 2015). One of the challenges of this strategy is ensuring the integrity of product after the heating/roasting is complete. This sometimes limits the maximum temperature that can be used, which may result in only a partial removal of AFB1. However, this technique can be carried out easily, with low cost, and can be performed in 2 h or less giving it logistical advantages.

The other most commonly reported physical decontamination method is γ radiation. Studies have reported the use of γ radiation on a number of different food substrates including groundnuts, grains, and animal feed. This technique involves irradiating food products with a γ-ray source (such as ^{60}Co) until a certain amount of ionizing radiation is achieved which has ranged from 6 to 60 kGy in recent studies. This technique is moderately effective with an average percent reduction of 65% across all of the reviewed studies (Di Stefano et al., 2014a, 2014b;

Table 3
Summary of studies using physical methods to degrade AFB1.

Detoxification method	Specific Agent Used	Amount of agent	% Reduction of AFB1	Initial amount of AFB1 (ng/g)	Substrate	Treatment Time (min)	Reference
Temperature	Heat	180 °C	51.2	2.93	coffee beans	10	Soliman (2002)
	Heat	150 °C	> 95	200	pistachio	120	Yazdanpanah et al. (2005)
	Heat	160 °C	66	176–714	rice	20	Park et al. (2005)
	Heat	160 °C	83	0.54–813	rice	20	Park and Kim (2006)
	Heat	200 °C	97	100.2	wheat	30	Hwang and Lee (2006)
	Heat	180 °C	100	–	soy protein	30	Raters and Matissek (2008)
	Heat	150 °C	78.4	237	peanuts	120	Arzandeh and Jinap (2011)
	Heat	150 °C	77.6	35.8	peanuts	–	Zheng et al. (2015)
	Heat	150 °C	81.2	10	soybeans	90	Lee et al. (2015)
Irradiation	γ-radiation	25 kGy	42.7	192.1–894	chick feed	–	Herzallah et al. (2008)
	γ-radiation	10 kGy	58.6	900–9620	peanuts	–	Ghanem et al. (2008)
		10 kGy	68.8	900–9620	peeled pistachios	–	
		10 kGy	84.6	900–9620	unpeeled pistachios	–	
		10 kGy	81.1	900–9620	corn	–	
		10 kGy	87.8	900–9620	rice	–	
		10 kGy	90	900–9620	barley (feed)	–	
		10 kGy	86	900–9620	bran (feed)	–	
		10 kGy	84	900–9620	corn (feed)	–	
	γ-radiation	60 kGy	43	55	black pepper	–	Jalili et al., 2010
	γ-radiation	30 kGy	50.6	60	black and white pepper	–	Jalili et al., 2012
	γ-radiation	6 kGy	98	20	red chilis	–	Iqbal et al. (2013)
	γ-radiation	15 kGy	18.2	25	poultry feed mix	–	Di Stefano et al., 2014a,b
	γ-radiation	15 kGy	19.25	20	almonds	–	Di Stefano et al., 2014a,b
	γ-radiation	8 kGy	60.26	50.38	maize	–	Mohamed et al. (2015)
			64.68	27.49	rice	–	
			69.29	37.61	wheat	–	

Ghanem et al., 2008; Herzallah et al., 2008; Iqbal et al., 2013; Jalili et al., 2012, 2010; Mohamed et al., 2015). The logistical issues of using powerful radiation, particularly safety, may make the implementation of this technique into many developing countries difficult.

6.2. Biological treatment: organism, enzyme, extracts

Biological based interventions have also been investigated for their potential in reducing AFB1 levels in contaminated foodstuffs. One strategy is to inoculate food substrates with strains of bacteria which then reduce AFB1 presumably through metabolism or by physically binding AFB1 directly. Several genera of bacteria have been investigated such as *lactobacillus, saccharomyces, cellulosimicrobium* and others. Fungal inoculation has also been investigated as potential detoxification method as seen by Branà et al. who used *Pleurotus eryngii* to degrade AFB1. Treatment times using this approach however are very long, usually requiring several days to carry out. AFB1 degradation using these methods however is typically high, averaging approximately 86% across recent studies (Branà et al., 2017; Farzaneh et al., 2012; Hamad et al., 2017; Haskard et al., 2001; Liu et al., 2017; Oluwafemi et al., 2010).

Another approach to biological degradation of AFB1 is to use botanical extracts. These studies have used aqueous extracts of various plant species to dissolve AFB1 and determine percent degradation after incubating the toxin in this mixture for a given amount of time (24–72 h). Although this also requires long treatment times, this method has been shown to be highly effective, particularly extracts from *Adhatoda vasica Ness* and *Corymbia citriodora,* which both achieved > 95% degradation of AFB1 (Iram et al., 2016a, 2016b; 2015; Velazhahan et al., 2010; Vijayanandraj et al., 2014). Further studies need to be done to determine the efficacy of these methods when used on various food substrates. Additionally, the identification of the active components responsible for this degradation could prove useful in increasing the efficiency of this process.

Lastly, the use of purified enzymes from various biological sources has been investigated for AFB1 degradation potential. Recently, these have included laccases, manganese peroxidase, and the recently identified Bacillus aflatoxin-degrading enzyme. The efficacy of these approaches has been high, but they also have not been tested on food substrates, so the efficacy on food products is still unknown. As is the case with all the biological control methods, the time of treatment is high, taking several days to complete which may not be feasible in large scale applications (Alberts et al., 2009; Loi et al., 2016; Xu et al., 2017; Yehia, 2014). Additionally, the degradation products in many of these studies were not identified. Without characterizing the end products of the treatments, the safety of treated foods cannot be fully determined.

6.3. Chemical treatment: acidification, ammoniation, ozonation

The use of chemical additives on contaminated foods has also become a popular choice particularly if the additives themselves are already used in the food industry. Acidification of AFB1 contaminated foods has been shown to be highly effective when citric, lactic, tartaric, and hydrochloric acid are used, however other acids such as succinic, acetic, ascorbic, and formic have only been marginally successful. These methods simply involve soaking contaminated foods in acidic solutions for a given amount of time. Even when carried out at room temperature, high AFB1 degradation can be observed in 24 h or less (Lee et al., 2015; Rushing and Selim, 2016; Safara et al., 2010). Additionally, the detoxification product of AFB1 in acid has been well-characterized as AFB2a. As described earlier, AFB2a has been shown to be far less toxic than AFB1, making this method an attractive option. Another benefit is the simplicity of these methods, so the need for specialized equipment or specific skills is not required.

Conversely, ammoniation has been used to break down AFB1 in an alkaline environment. Although these studies haven't been performed

Table 4
Summary of studies using biological methods to degrade AFB1.

Detoxification method	Specific Agent Used	Amount of agent	% Reduction of AFB1	Initial amount of AFB1	Substrate	Treatment Time	Reference
Organism	*Lactobacillus rhamnosus*	2.5×10^{10} CFU/mL	71	10 ng/mL	aqueous solution		Haskard et al. (2001)
	Lactobacillus plantarum		29.9–44.5	50–500 ng/g	maize		Oluwafemi et al. (2010)
	Bacillus subtilis	-	95	2000 ng/g	pistachio	120 h	Farzaneh et al. (2012)
	Cellulosimicrobium funkei	10^8 CFU/mL	83.4	968 ng/g	cottonseed meal	144 h	Liu et al. (2017)
	Lactobacillus acidophilus	7×10^9 CFU/mL	93.12	50 ng/mL	cereal	72 h	Hamad et al. (2017)
	Bifidobacterium bifidum	7×10^9 CFU/mL					
	Saccharomyces cerevisiae	7×10^9 CFU/mL					
	Kluyveromyces lactis	7×10^9 CFU/mL					
Extract	*Pleurotus eryngii*	3 g	86	128 ng/g	maize	28 days	Branà et al. (2017)
	Trachyspermum ammi	10 g/mL	61	200 ng/mL	aqueous solution	48 h	Velazhahan et al. (2010)
	Adhatoda vasica Nees	0.33 g/mL	98.3	200 ng/mL	aqueous solution	24 h	Vijayanandraj et al. (2014)
	Corymbia citriodora	1 g/mL	95.21	100 ng/mL	aqueous solution	72 h	Iram et al. (2015)
	Ocimum basilicum	1 g/mL	90.4	100 ng/mL	aqueous solution	72 h	Iram et al. (2015)
	Trachyspermum ammi	1 g/mL	92.8	100 ng/mL	aqueous solution	72 h	Iram et al., 2016a,b
Purified enzymes	laccase from *Trametes versicolor*	1 U/mL	87.34	1400 ng/mL	PBS	72 h	Alberts et al. (2009)
	manganese peroxidase from *Pleurotus ostreatus*	1.5 U/mL	90	1 mM	aqueous solution	48 h	Yehia (2014)
	laccase-2 from *Pleurotus pulmonarius*	5 U/mL	90	1000 ng/mL	aqueous solution	72 h	Loi et al. (2016)
	Bacillus aflatoxin-degrading enzyme from *B. shackletonii*	0.4 mL of isolate	77.9	100 ng/mL	aqueous solution	72 h	Xu et al. (2017)

recently, the technique is still referenced to this day due to its efficacy. This technique involves treating contaminated foods with either gaseous or liquid ammonia (usually 1.5–2%). If carried out at room temperature, this process can take a very long time, ranging from 24 h to 15 days. The extent of degradation of this technique is high, sometimes reaching above 99% (Bagley, 1979; Galil and Naguib, 1997; Jorgensen and Price, 1981; Moerck et al., 1980; Weng et al., 1994). The degradation product due to ammoniation – aflatoxin D1 (AFD1) – is also well characterized. Formed due to a hydrolysis and decarboxylation, AFD1 has been shown to be far less mutagenic than AFB1, although a reversion back into AFB1 can occur if the extract is acidified (Grove et al., 1984; Lee and Cucullu, 1978; Schroeder et al., 1985). A disadvantage to this technique however, is the requirement for complex infrastructures to perform the ammoniation which has prevented the widespread use of this technique worldwide.

Finally, ozonation is another commonly used chemical control method. Ozonolysis at a concentration of 6–90 mg/L has been shown to be effective at degrading AFB1 especially considering the relatively short treatment times. In as little as 20 min, El-Desouky et al. observed an 86.75% reduction in AFB1 levels in wheat. Other recent studies have used treatment times of 30–180 min and have seen > 65% reductions. Longer treatment times have also been employed, with some studies going up to 96 h of treatment time. Additionally, the variety of food substrates that have been investigated with ozone is very high, indicating it can be effective on many different foodstuffs (Akbas and Ozdemir, 2006; Chen et al., 2014; de Alencar et al., 2012; Diao et al., 2013; El-Desouky et al., 2012; Inan et al., 2007; Luo et al., 2014a, 2014b; Zorlugenç et al., 2008). The breakdown products of AFB1 after ozonolysis have been identified by Diao et al. Thirteen oxidation products were identified and based on the chemical structures, the moieties responsible for mutagenicity disappeared, indicating that these products are likely less toxic, although it has not been verified using mutagenicity assays (Diao et al., 2012).

6.4. Combinations

While these methods individually have had moderate to high success in reducing AFB1 levels, the highest efficacies are seen when they are combined with one another. The combination of ammonia and heat has been shown to drastically reduce treatment times from several days to 15–120 min. This combination has been repeatedly shown to be extremely effective, with all studies showing ≥ 99% reduction of AFB1 (Galil and Naguib, 1997; Gardner et al., 1971; Park et al., 1984; Weng et al., 1994). Heating along with ozonation has also been shown to reduce treatment times while remaining effective as shown by Proctor et al. who observed a 77% reduction of AFB1 in peanuts after only 10 min when treating at 75 °C (Proctor et al., 2004). Treatment of contaminated foods with alkaline substances (other than ammonia) along with heat are another effective method. Adjustment to a pH of 10 using sodium hydroxide and incubating at 98 °C was shown to reduce AFB1 in dried figs by 97% (Karaca and Nas, 2009). Nixtamalization, the process used to make tortillas, also employs heat and alkaline treatment using calcium hydroxide. Using traditional nixtamalization methods, AFB1 has been shown to be decreased by approximately 84 and 90% in two separate studies (Elias-Orozco et al., 2002; Torres et al., 2001). The combination of acidification and heat has been very effective at degrading AFB1. The use of HCl, citric acid, and lactic acid have all been shown to have high degrading potential (85–100%) when applied at high temperatures (80–120 °C). In particular, the use of 1 M citric acid at 100 °C was shown to be able to degrade 98% of AFB1 in 20 min (Aiko et al., 2016; Aly and Hathout, 2011; Rastegar et al., 2017; Rushing and Selim, 2016). This highlights that heat and acidification is an efficacious method that can be performed in a short amount of time without the need for specialized or expensive equipment. A unique combination has recently been performed by Rushing and Selim where acidification has been used with heat and arginine. This causes AFB1 to form a stable

Table 5
Summary of studies using chemical methods to degrade AFB1.

Detoxification method	Specific Agent Used	Amount of agent	% Reduction of AFB1	Initial amount of AFB1)	Substrate	Treatment Time	Reference
Acidification	citric acid	1 N	97.22	4–30 ng/g	rice	15 min	Safara et al. (2010)
	citric acid	1 N	94.1	7.6 ng/g	soybean	18 h	Lee et al. (2015)
	lactic acid	1 N	92.7	7.4 ng/g	soybean	18 h	
	succinic acid	1 N	62	8.2 ng/g	soybean	18 h	
	tartaric acid	1 N	95.1	7.4 ng/g	soybean	18 h	
	acetic acid	1 M	12.5	200 ng/mL	aqueous solution	24 h	Rushing and Selim (2016)
	ascorbic acid	1 M	28.4	200 ng/mL	aqueous solution	24 h	
	citric acid	1 M	73.4	200 ng/mL	aqueous solution	24 h	
	formic acid	1 M	13.9	200 ng/mL	aqueous solution	24 h	
	hydrochloric acid	0.1 M	85	200 ng/mL	aqueous solution	24 h	
Ammoniation	ammonia	1.50%	99.3	750 ng/g	maize	13 days	Bagley (1979)
	ammonia	2.00%	92	200 ng/g	maize	24 h	Moerck et al. (1980)
	ammonia	2.00%	99.9	800 ng/g	cottonseed	15 days	Jorgensen and Price, 1981
	ammonia	2.00%	52.7–67.7	17–7500 ng/g	maize	60 min	Weng et al. (1994)
	ammonia	2.00%	88.02	4000 ng/g	maize	24 h	Galil and Naguib (1997)
Ozonation	ozone	9.0 mg/L	23	10 ng/g	pistachio	420 min	Akbas and Ozdemir (2006)
	ozone	66 mg/L	93	32 ng/g	red pepper	60 min	Inan et al. (2007)
	ozone	13.8 mg/L	95.21	21 ng/g	dried fig	180 min	Zorlugenç et al. (2008)
	ozone	40 ppm	86.75	10 ng/g	wheat	20 min	El-Desouky et al. (2012)
	ozone	21 mg/L	25	180 ng/g	peanuts	96 h	de Alencar et al. (2012)
	ozone	50 mg/L	89.4	189.53 ng/g	peanuts	60 h	Diao et al. (2013)
	ozone	75 mg/L	78.8	53.6 ng/g	corn flour	60 min	Luo et al., 2014a,b
	ozone	90 mg/L	88.1	83 ng/g	maize	40 min	Luo et al., 2014a,b
	ozone	6.0 mg/L	65.9	200 ng/g	peanuts	30 min	Chen et al. (2014)

pyrrole ring with the amino acid which was shown to completely non-genotoxic and unable to be absorbed across the intestinal tract. This method caused a complete conversion of AFB1 contaminated corn in 20 min. This highlights the potential for adding amino acids to acidification treatments to form stable, non-toxic forms of AFB1 (Rushing and Selim, 2017a,b). Overall, the combination of these methods has been shown to produce the best results in degrading AFB1. There are many other factors however that determine if a method will be used worldwide. These include cost effectiveness, scalability, and whether or not the technique requires complex equipment or materials to carry out. Acidification treatments seem to possess the most advantages in regard to these criteria and could even be performed by consumers due to the simplicity of the methods. Perhaps over time, these methods will see increased usage in order to provide cleaner foods worldwide.

6.5. Sorbent additives

A unique approach to solving AFB1 contamination is the addition of sorbents to food. This method is different from the degradation methods because it does not involve destroying or reducing the amount of AFB1 in the food. Instead, these sorbents act as binding agents to prevent absorption of AFB1 across the intestinal tract after ingestion in order to prevent the hepatotoxic effects of AFB1. Chlorophyllin and chlorophyll are perhaps the most well-studied of these agents as they have not only been tested in animals, but also in humans. Breinholt et al. observed that the addition of chlorophyllin to contaminated feed reduced AFB1-DNA adduct by 37% in rainbow trout which led to a 77% reduction of tumor incidence (Breinholt et al., 1995). Simonich et al. reported a 42% reduction in AFB1-DNA adducts, a 65% reduction of AFB1-albumin, and 90% reduction of urinary AFM1 in rats when adding chlorophyllin to AFB1-contaminated feed. In the same study, chlorophyll was also shown to be effective by reducing AFB1-DNA adducts, AFB1-albumin, and urinary AFM1 levels by 55, 51, and 92% respectively. Additionally, the tumor incidence in these rats was reduced by 74 and 77% after introducing chlorophyllin and chlorophyll respectively to contaminated diets (Simonich et al., 2007). Egner et al. introduced chlorophyllin into the diets of humans in high risk areas for AFB1 exposure and found that this intervention reduced AFB1-N_7-guanine levels by 55% compared to individuals who were not fed this agent (Egner et al., 2001). In a study using human volunteers, a single dose of 30 ng of AFB1 was administered on three separate occasions to four individuals. For the second and third dosing, chlorophyll and chlorophyllin were co-administered with the AFB1 dose. Results showed that chlorophyllin reduced urinary AFM1 levels by 28% while chlorophyll reduced urinary AFM1 levels by 41% (Jubert et al., 2009). These data show that the addition of binding agents to diets in high risk areas may be useful in at least partially mitigating the toxic effects of AFB1. However, the prolonged ingestion of these materials may also interfere with nutrient absorption, which would need to be addressed when administering these agents to areas of high rates of malnutrition.

Another commonly studied enterosorbent is clay. This strategy works similarly to chlorophyll and chlorophyllin in that they bind AFB1 in the digestive tract and prevent intestinal absorption of the toxin. By adding clays to animal feed, these substances have been shown to protect against AFB1 toxicities in multiple animal models by reducing AFB1 absorption and reducing AFM1 levels in milk. In particular, NovaSil (a calcium montmorillonite clay) has been shown to be particularly successful. This substance has been shown to significantly reduce the toxic effects of aflatoxin-contaminated feed and AFB1 biomarkers in a number of animal models (Phillips et al., 2008, 1988). Additionally, a long-term study was performed in which rats were fed up to 2.0% of NovaSil in their diet for 28 weeks. No overt toxicities were observed during this study, indicating the safety of using this substance (Afriyie-Gyawu et al., 2005). In a clinical trial, Ghanaians in a high-risk area for AFB1 exposure were given an oral dose of placebo, low dose, or high dose of NovaSil. Participants in the low and high dose had significantly lower urinary AFM1 and serum AFB1-albumin after a period of 3 months. Additionally, NovaSil was not shown to significantly alter liver, kidney, or hematological parameters of the study subjects and only mild, infrequent adverse effects were reported (such as nausea, diarrhea, heartburn, and dizziness) (Afriyie-Gyawu et al., 2007; Wang et al., 2008). These results indicate that the addition of

Table 6
Summary of studies using a combination of methods to degrade AFB1.

Detoxification method	Specific Agent Used	Amount of agent	% Reduction of AFB1	Initial amount of AFB1	Substrate	Treatment Time	Reference
Ammoniation + heat	ammonia + heat	48 psi ammonia +121 °C	99	519 ng/g	cottonseed meal	30 min	Gardner et al. (1971)
	ammonia + heat	4% ammonia +100 °C	99.9	4000 ng/g	cottonseed meal	30 min	Park et al. (1984)
	ammonia + heat	2.0% ammonia +121 °C	99	17–7500 ng/g	maize	120 min	Weng et al. (1994)
	ammonia + heat	2.0% ammonia +121 °C	99.9	4000 ng/g	maize	15 min	Galili and Naguib (1997)
Ozonation + heat	ozone + heat	4.2% ozone by weight at 75 °C	77	20 ng/g	peanuts	10 min	Proctor et al. (2004)
Nixtamalization	$Ca(OH)_2$ + heat	200 g $Ca(OH)_2$ + 98 °C	84.5	110 ng/g	corn	40 min cook + 14 h steep	Torres et al. (2001)
	$Ca(OH)_2$ + heat	3% $Ca(OH)_2$ + 90–96 °C	90	495 ng/g	corn	30 min cook + 24 h steep	Elias-Orozco et al. (2002)
Alkalization + heat	NaOH + heat	NaOH to pH 10 + 98 °C	97	34.5 ng/g	dried figs	60 min	Karaca and Nas (2009)
Acidification + heat	HCl + heat	5 M HCl + 110 °C	100	45.68 ng/g	maize	4 h	Aly and Hathout (2011)
	lactic acid + heat	1 M lactic acid + 80 °C	85.1	1000 ng/mL	aqueous solution	120 min	Aiko et al. (2016)
	citric acid + heat	0.1 g/mL citric acid + 120 °C	93.1	383 ng/g	pistachios	60 min	Rastegar et al. (2017)
Acidification + heat + amino acids	citric acid + phosphoric acid + heat + arginine	1 M of acids, 10 mg/mL arginine, 100 °C	100	100 ng/g	Maize	20 min	Rushing and Selim (2017)

NovaSil into the diet can be a safe and effective method to reduce AFB1 toxicity.

7. Conclusion

Evidence that has been gathered over the last several decades has shown the clear carcinogenic effect of AFB1. Also, the negative effect of AFB1 on nutritive status, growth/development, and immune system function is becoming clearer. The high frequency and levels of AFB1 recently found in food supplies of various countries, particularly in Africa and Asia, indicate that exposure of populations to this toxin still remains largely uncontrolled. Furthermore, AFB1 has become an occupational hazard for those working in the food industry, leading to some particularly high rates of exposure. Between pre- and post-harvest strategies, there are many options available for greatly reducing population exposure to this contaminant. Large scale implementations of these techniques as well as educating consumers about this issue could make a large impact on the worldwide incidence of HCC and other aflatoxin-related toxicities such as growth impairment, malnutrition, and immunosuppression.

Transparency document

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