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- Occurrence and health implications of dietary aflatoxins (AFs) in early life stages.
- High exposure of pregnant women to AFs in some African and Asian countries.
- Severe impact of AFs on infant growth, development, liver and immune system.
- Intervention strategies needed to mitigate the early life exposure to AFs in foods.

Abstract

Background: The initial stages of human life including the fetal period, infancy and early childhood are the most critical periods of human growth and development. Due to the immature immune system and rapid development phase, this is the most sensitive phase to health challenges. The exposure to xenobiotics of high toxicity, such as aflatoxins (AFs), can interfere with normal development of the body and potentially lead to severe health complications.

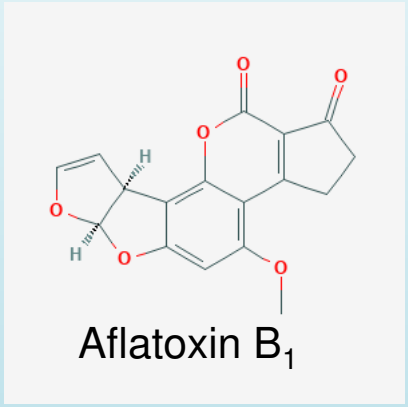
Scope and approach: This article provides a comprehensive review on the occurrence and health implications of AFs exposure in the early stages of life, including the impacts on child growth, development, immune and hepatic systems. The mechanisms involved in AFs' toxicity and control measures in infant foods are also described, along with a discussion on recent intervention strategies to mitigate the early life exposure to dietary AFs.

Key findings and conclusions: Human AFs exposure via utero and through breast milk, infant formula milk and infant foods has been linked to a number of health implications including adverse birth outcomes, impaired growth and development, suppressed immune system, and hepatic dysfunction, especially in African and Asian countries. The occurrence of AFs in infant foods in developing countries, even when reasonably strict regulations are in place, indicate that much needs to be done to ensure the proper implementation of the regulations, in order to achieve significant reductions in exposure. This carries with it many economic and cultural challenges that need to be addressed, including implementation of good agricultural practices and intervention programs aiming to supplement nutrients to reduce child malnutrition and decrease the consumption of aflatoxin-contaminated foods.

Keywords: AFB_1; AFM_1; infant foods; toxic effects; infant health; prevention; mitigation.

Graphical Abstract

Control & mitigation strategies



Severe health implications

Early Life Exposure to Dietary Aflatoxins, Health Impact and Control Perspectives: A Review

Amir Ismail[a], Iqra Naeem[a], Yun Yun Gong[b], Michael N Routledge[c,d], Saeed Akhtar[a], Muhammad Riaz[a], Leandra Naira Zambelli Ramalho[e], Carlos Augusto Fernandes de Oliveira[f]*, Zubair Ismail[a]

[a] *Institute of Food Science & Nutrition, Bahauddin Zakariya University, Multan – Pakistan*

[b] *School of Food Science and Nutrition, University of Leeds, UK*

[c] *School of Medicine, University of Leeds, UK*

[d] *School of Food and Biological Engineering, Jiangsu University, Zhenjiang, Jiangsu Province, China*

[e] *Department of Pathology and Legal Medicine, School of Medicine at Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil*

[f] *Department of Food Engineering, School of Animal Science and Food Engineering, University of São Paulo, Pirassununga, SP, Brazil*

Running title: Health impact and control of early life exposure to aflatoxins

* Corresponding author: Carlos Augusto Fernandes de Oliveira. Tel: +55 19 3565-4173; fax: +55 19 3565-4284. E-mail address: carlosaf@usp.br

Abstract

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1. Introduction

Prenatal life, infancy and early childhood are regarded as particularly susceptible periods to environmental toxicants and any health risks due to toxicant exposure during these critical periods of life could have lifelong consequences (Farzan et al., 2013). Vulnerabilities of the fetus and child to chemical hazards are mainly due to their greater rate of cellular differentiation and tissue development, as well as under-developed protective mechanisms (Papadopoulou et al., 2019). Food is the main source of exposure to many environmental hazards, and transplacental transport, breastfeeding, and complementary feeding are key routes of dietary exposure to these contaminants during gestation and early postnatal life (Papadopoulou et al., 2019). Each year, more than 0.1 million children under 5 years of age die due to foodborne illnesses, contributing around 30% of foodborne disease-related death burden worldwide (World Health Organization, 2015b). The World Health Organization (WHO) estimates that 5.3 million children under the age of 5 died in the year 2018 (World Health Organization, 2019). Fungal toxins such as aflatoxins, the secondary metabolites of some fungal species, mainly *Aspergillus flavus* and *A. parasiticus*, have the potential to interfere with growth and developmental processes in both animals and humans (Polychronaki et al., 2008). Dietary exposure to aflatoxins may pose a particular health risk in developing countries where either food regulations are lacking, or their enforcement is compromised (Akhtar et al., 2020; Ismail et al., 2020). It has been estimated that more than 5 billion people in developing countries are at the risk of aflatoxin exposure (Strosnider et al., 2006). In 2010, around 21,575 foodborne illness cases were attributable to aflatoxin exposure with about 19,455 deaths worldwide (World Health Organization, 2015a).

Chemically, aflatoxins are difuranocoumarin derivatives typically synthesized through the polyketide pathway (Kumar et al., 2017). The most prominent of the aflatoxins are aflatoxin

B_1 (AFB_1), aflatoxin B_2 (AFB_2), aflatoxin G_1 (AFG_1), and aflatoxin G_2 (AFG_2). AFB_1 is the most toxic followed by AFG_1, AFB_2, and AFG_2, respectively. The toxicity is typically explained by the epoxidation of 8,9-double bond along with the greater potency related to cyclopentenone ring of the B series as against the six-membered ring of G series (Ismail et al., 2018). Aflatoxin M_1 (AFM_1) and aflatoxin M_2 (AFM_2) are hydroxylated products of AFB_1, and AFB_2 that are excreted in the milk and/or urine of humans and animals exposed to dietary AFB_1, and AFB_2. Aflatoxins of B and G group are named on the basis of their blue or green fluorescence, respectively, under UV light, while aflatoxins of M group are named on the basis of their presence in milk and milk products. Aflatoxins are classified as group 1 carcinogens by the International Agency for Research on Cancer (IARC). Aflatoxins are also reported to impair child growth, and be immunosuppressant, teratogenic, neurotoxic, genotoxic and hepatotoxic (Gong et al., 2016). As compared to the adult population, infants and young children are at a higher risk and are around three times more likely to be affected by the toxic effects of AFs owing to their higher exposure (higher dietary intake/body weight ratio), faster rates of growth and development, and immature metabolic system (Ayelign et al., 2018; Ortiz et al., 2018).

The metabolism of aflatoxins varies greatly among adults and children (Dohnal et al., 2014). In general, AFB_1 is predominantly activated by cytochrome p450 enzymes (such as CYP3A4, 3A5, 3A7, and 1A2) in the liver and is converted into AFB_1-8,9 epoxide (AFBO) which reacts with DNA to generate the pro-mutagenic AFB_1-N^7-guanine adduct. After DNA repair, this adduct is excreted in the urine. Additionally, AFBO can also react with albumin in liver cells or, following conversion to AFB_1-dihydrodiol, with serum albumin to produce the AFB_1-albumin adduct (AF-alb), with the aflatoxin bound to lysine in albumin (Sass et al., 2015). Both AFB_1-N^7-guanine adducts and AF-alb or AFB_1-lysine have been employed as short and

94 long-term biomarkers of aflatoxin exposure in various epidemiological studies. Furthermore,
95 oxidation of AFB_1 (mainly by CYP1A2) results in the formation of a hydroxylated metabolite
96 (AFM_1) which is released with the milk and urine of animals (Di Gregorio et al., 2015) and has
97 also been validated as a biomarker of short-term exposure (Chen et al., 2018a). Other metabolic
98 products such as hydroxylated form aflatoxin P_1 (AFP_1), a demethylated form aflatoxin Q_1
99 (AFQ_1), and a reduced form aflatoxicol are less toxic and are considered as detoxification
100 products of aflatoxins metabolism (McLean and Dutton, 1995; Sánchez and Diaz, 2019).
101 Aflatoxin metabolites can also be conjugated to glutathione by the action of glutathione-s-
102 transferases (GSTs), leading to detoxification of aflatoxins (Dohnal et al., 2014).

103 A number of food commodities have been reported to contain aflatoxins well above their
104 maximum allowable limits, notably cereals, nuts, dried fruits, spices, infant formula, milk and
105 milk products (Akhtar et al., 2017; Ismail et al., 2016; Ismail et al., 2017; Ismail et al., 2018).
106 Presence of metabolic products of aflatoxin in biological fluids of infants and young children
107 such as blood (Alamu et al., 2020; Chen et al., 2018a; Chen et al., 2018b; Groopman et al., 2014;
108 Jager et al., 2016; Mahfuz et al., 2019; McMillan et al., 2018; Shirima et al., 2015), and urine
109 (Ayelign et al., 2017; Chen et al., 2018a; Ediage et al., 2013; Ezekiel et al., 2014; Jager et al.,
110 2016; Kumi et al., 2015; Polychronaki et al., 2008; Sánchez and Diaz, 2019) indicates that they
111 are continuously being exposed to aflatoxins through aflatoxin-contaminated breast milk and
112 complementary foods. This review focuses on the occurrence and health implications of
113 aflatoxin exposure in the early stages of life and the possible mechanisms involved in aflatoxins'
114 toxicity. Critical recommendations to prevent aflatoxin contamination in infant foods are also
115 described, along with a discussion on recent intervention strategies to mitigate the early life
116 exposure to dietary aflatoxins.

2. Aflatoxin exposure *in utero*

During gestation, the fetus is entirely reliant on the intrauterine environment that is regulated by maternal health, diet, and exposures to environmental chemicals, and any damage to rapidly growing cells of the fetus may result in permanent defects that could lead to health complications later in life (Carpenter and Bushkin-Bedient, 2013). Although the placenta acts as a barrier for most toxic compounds to prevent their exposure to the fetus, it is not an impassable barrier against all toxins (Partanen, 2012). After ingestion through contaminated foods, the aflatoxins are rapidly absorbed and distributed in the body compartments of pregnant women, being able to cross the placental membrane and exert harmful impacts on fetal growth and development (Partanen et al., 2009). Human fetal liver expresses CYP3A7, which can activate AFB_1 to AFBO (Li et al., 1997). Partanen et al. (2009) investigated the placental transfer and metabolism of AFB_1 in human placental perfusions (0.5 or 5μM AFB_1 for 2–4 h) *in vitro*. The results of the study provided clear evidence that human placental tissues have the capacity to transfer AFB_1 and to metabolize it into aflatoxicol (AFL), a less mutagenic form of AFB_1.

A number of studies have reported high exposure levels of pregnant women to dietary aflatoxins, especially in developing countries. Turner et al. (2007) found AF-alb in 100% of maternal blood samples (n = 119) and 48.5% of cord blood samples (n = 99) in a Gambian population, with detectable levels of AF-alb (limit of detection: 5 pg/mg), ranging between 5.0 - 260.8 and 5.0 - 89.6 pg/mg, respectively. Castelino et al. (2013) subsequently reported AF-alb levels to be higher in later pregnancy (68.7 pg/mg) as compared to early pregnancy (40.6 pg/mg) in a cohort of pregnant Gambian women. The mean value of AF-alb in pregnant women during the dry season (52.8 pg/mg) was higher than during the rainy season (29.6 pg/mg), which is

likely related to levels of AFB_1 contamination of peanuts increasing during storage. Groopman et al. (2014) quantified aflatoxin B_1-lysine adduct biomarker among a cohort of Nepalese and Bangladeshi pregnant women during the first and third trimesters of pregnancy. The ranges of the biomarkers were reported as 0.45 – 2939.30 and 1.56 – 72.8 pg aflatoxin B_1-lysine/mg albumin, respectively, indicating that the pregnant women of Nepal and Bangladesh are highly exposed to aflatoxins. Likewise, Lamplugh et al. (1988) have reported the presence of aflatoxins B_1, B_2, M_1 and M_2 in maternal blood and cord blood samples while Lei et al. (2013) have reported the presence of aflatoxin M_1 in 84% pregnant mother's urine samples (n=512) from Zhejiang province of China ranging between <LOD – 4900 ng/L. All these reports indicate that the unborn child belonging to different countries may be exposed to aflatoxins, raising the potential for risk of health implications associated with aflatoxins.

Exposure to aflatoxins *in utero* may contribute to detrimental pregnancy outcomes such as impaired fetus growth, premature delivery and pregnancy losses (Shuaib et al., 2010). Some data is available on maternal exposure to aflatoxins during pregnancy and adverse birth outcomes, specifically low-birth-weight (Abdulrazzaq et al., 2002; De Vries et al., 1989; Lauer et al., 2019; Shuaib et al., 2010), small-for-gestational-age (Andrews-Trevino et al., 2019), preterm birth (Passarelli et al., 2019), and poor growth that continued during infancy and in early childhood (Turner et al., 2007). Generally, birth weight is considered as an index of *in utero* health and nutritional status and an indicator of the child's short and long-term development. Low birth weight of newborn babies is associated with increased risk of several adverse outcomes such as preterm morbidity and mortality, child stunting, impaired immune function, reduced cognitive development and chronic illnesses in later life (Lauer et al., 2019). A significant amount of aflatoxin exposure of the fetus results in an increased rate of low

163 birthweight (Abdulrazzaq et al., 2002). In a study of 785 pregnant Ghanaian women, it was
164 reported that the women in the highest quartile of AFB_1-lysine level, i.e., > 11.34 pg/mg albumin
165 were more likely to have underweight babies as compared to women in the lowest quartile of
166 AFB_1-lysine level, i.e., ≤ 2.67 pg/mg albumin (Shuaib et al., 2010). *In utero* toxicity of aflatoxin
167 may have a direct impact on early child growth. In a study in Gambia, the results indicated a
168 significant negative association between higher AF-alb levels in maternal blood and lower
169 height-for-age Z-score (p=0.044) and weight-for-height Z-score ($p = 0.012$) values (Turner et al.,
170 2007). The authors also predicted that reducing maternal AF-alb adduct levels from 110 µg/kg to
171 10 µg/kg would bring around 0.8 kg increase in weight and 2 cm increase in height in the first
172 year of life (Turner et al., 2007). In a cohort study conducted in Uganda, maternal aflatoxin
173 exposure level was computed by measuring plasma AFB_1-lysine levels at mid-gestation stage.
174 Increased maternal AFB_1- lysine levels were significantly correlated with lower birth weight
175 ($p = 0.040$), lower weight-for-age Z-score ($p = 0.037$), smaller head circumference ($p = 0.035$),
176 and lower head circumference- for- age Z-score ($p = 0.023$) in infants at birth (Lauer et al.
177 (2019). Contrary to the above-mentioned studies, a study from Tanzania published no significant
178 association between *in utero* aflatoxin exposure measured by plasma AFB_1-lysine levels and
179 birth weight and child growth (Passarelli et al., 2019). However, in the same study, an increase in
180 natural log of AFB_1-lysine levels by a unit of pg/mg of albumin was found to be associated with
181 a small but statistically significant decline in gestational age at birth (0.47 weeks; 95% CI: −0.86
182 − 0.07). This divergence in the results from the pre-existing studies, as explained by the authors,
183 was due to the fact that the studied population was from an urban area having relatively low
184 aflatoxin exposure (median AFB_1-lysine: 1.4 pg/mg albumin), and non-anemic iron-replete
185 mothers were chosen for the study (Passarelli et al., 2019). Small-for-gestational-age (SGA) is a

term used to describe the infants having birth weight < 10^{th} percentile for their gestational age (Ng et al., 2019). Only one study by Andrews-Trevino et al. (2019) reported a significant association between maternal aflatoxin exposure and SGA indicating the role of aflatoxins in reducing the size at birth.

The potential mechanism explaining the association of *in utero* aflatoxin exposure and poor birth outcomes have not been clearly understood yet, however, Smith et al. (2017) illustrated that adverse birth outcome caused by aflatoxins might be due to downregulation of anti-inflammatory cytokines and/or up-regulation of pro-inflammatory cytokines, systemic immune activation caused by inflammation and poor barrier function of the intestine, maternal organs toxicity leading to poor placental and fetal development, and fetal organs toxicity leading to fetal inflammation and compromised fetal development. Moreover, epigenetic changes during embryonic development due to maternal exposure to aflatoxins is another proposed mechanism studied in Gambian infants (2-8 months) supporting the evidence of aflatoxin-related adverse health outcomes in the later life (Hernandez-Vargas et al., 2015). *In utero* exposure to AFB_1 was found to be associated with genome-wide DNA methylation in 71 CpG sites including growth factor genes (*FGF12* and *IGF1R*) and immune-related genes (*CCL28, TLR2*, and *TGFB1*) in the white blood cells of infants of AFB_1 exposed mothers (Hernandez-Vargas et al., 2015).

3. Occurrence of aflatoxins in breast milk, infant formula and infant foods

Breast milk is the best source of nutrients for neonates and infants during the first few months of their lives. Besides nutrients, breastmilk also contains antibodies and other protective factors that are beneficial to the baby's immune function. However, lactating mothers exposed to aflatoxin contaminated food can secrete AFM_1 and AFM_2 in their milk (Khan et al., 2018; Coppa

et l., 2020). It has been reported that around 0.3-6.2% of ingested AFB_1 is excreted as AFM_1 in maternal milk (Diaz and Sánchez, 2015; Mahdavi, Azarikia & Nikniaz, 2017; Fakhri et al., 2019). Although breast milk is the most suitable food for neonates and infants, in certain circumstances it becomes necessary to feed babies with infant formula milk (up to six months of age) and follow-on milk (6-12 months). As the child develops and growths, baby foods become the complementary food items until 2 years of age. These are soft food items prepared by the mashing of food at home or as pre-prepared baby food purchased from the market. Baby food items primarily include cereals and processed cereal products, mashed fruits, vegetables and meat products. In many developing countries, the use of processed cereals is mostly seen in richer families while the middle- and lower-income families mostly use homemade processed cereal products or home mashed fruits and vegetables. Baby foods are preferably recommended from six months of age, although in many developing countries, baby foods are introduced earlier, which increases the likelihood of childhood exposure to mycotoxins (Ojuri et al., 2019).

The presence of mycotoxins in commercial infant formula and baby food items is strictly monitored by the regulatory agencies while the quality of homemade baby food items mainly depends on the mothers/caretakers of the babies. Therefore, nations around the globe have set maximum allowable limits for aflatoxins in food stuff based on prevalence and consumption rate, and level of technological advancement, as presented in Table 1. The Codex Alimentarius Commission (CAC) has the most widely operating network but failed until now to formulate universally accepted maximum allowable limits for different types of aflatoxins in different sorts of food stuff. The possible reasons for the failure of unanimously acceptable allowable limit for aflatoxins as reported by Gong et al. (2015) are differences in food consumption, insufficient data regarding the prevalence of aflatoxins in the staple food commodities of a country and

variations in aflatoxins contamination rate of production in different countries and their economic development.

(Table 1 near here)

As indicated in Table 1, the European Union (EU) has adopted the most stringent regulations while India has adopted the most lenient regulations for aflatoxins in infant foods. Animal milk is another food commodity consumed most frequently by infants and children. The maximum allowable limit for AFM_1 in animal milk ranges between 0.05 – 0.5 µg/kg while the EU maximum allowable limit for AFM_1 in human milk is 0.025 µg/kg (European Comission, 2006; Ismail et al., 2018). Even where maximum limits for aflatoxin in food have been set, enforcement of the regulations varies depending on the economic status, infrastructure and organization of regulatory systems. In many of the countries worst affected by aflatoxin in staple crops, enforcement of regulations is particularly difficult. Further, it is concerned that nations suffering from aflatoxin risks usually have established some maximum allowable aflatoxin standards in food, but there is very little enforcement of these standards. Therefore, although regulations for aflatoxins in infant food items may not always lead to reduced aflatoxin levels, their establishment is an important step towards the goal of reduced exposure (Ismail et al., 2016; Shephard, 2008).

The worldwide prevalence of aflatoxin residues in maternal milk, infant formula and infant foods was recently reviewed by Coppa et al. (2019). However, the scientific interest on this issue has remarkably continued in the last two years, leading to new aflatoxin occurrence data in breast milk and infant formula as well as infant foods, as presented in Tables 2 and 3, respectively. Recent results corroborate previous findings on the frequent occurrence of AFM_1 in breastmilk samples at levels beyond the EU maximum tolerable limit for AFM_1 in human milk

255 (0.025 ppb), mainly in developing countries. The overall range of AFM_1 in breast milk samples
256 was <0.001 – 5.0 µg/kg. In most of the cases, a maternal diet based on cereal grains, corn,
257 groundnuts such as peanuts, and dairy products was found to be significantly associated with the
258 levels of aflatoxins in human milk.

259 (Table 2 near here)

260 Prevalence of aflatoxins in breast milk samples beyond the allowable limits is a concern
261 as the neonates/infants have an immature immune system and the exposure to toxins at this stage
262 of life may bring long-lasting impacts on the individual's life (Cherkani-Hassani et al., 2016).
263 The prevalence of aflatoxins in breastmilk samples from developing countries reflects aflatoxin
264 exposure levels that may be associated with subsistence farming, poverty, lack of education and
265 poor implementation of rules and regulations (Cherkani-Hassani et al., 2016; Fakhri et al., 2019).
266 Regarding infant formula, the overall maximum level reported for AFM_1 from across Pakistan,
267 Jordan, Lebanon and Iran was 0.214 ng/g. The presence of aflatoxins in these highly sensitive
268 food commodities demands the proper implementation of strict regulatory measures.

269 (Table 3 near here)

270 Baby food items from developing countries including Ghana, India, Nigeria, Burkina
271 Faso and Pakistan are reported to have aflatoxin levels above the maximum allowable limits.
272 Processed cereal-based foods from African countries including Nigeria, Ghana and Burkina Faso
273 were found to have alarmingly high levels of aflatoxins up to 590 µg/kg. Baby food items from
274 wealthier countries including USA, Italy, China, Spain, Portugal and Canada were found to have
275 lower levels of aflatoxins, ranging between 0.009 – 5.9 µg/kg, indicating better hygienic
276 conditions, implementation of rules and regulations and the adoption of good agricultural
277 practices in the latter countries.

278

279 **4. Health impacts of early dietary exposure to aflatoxins**

280 *4.1. Aflatoxins health effects in infancy and child growth impairment*

281 Stunting, wasting and underweight are three notable forms of undernutrition (Mawa and
282 Lawoko, 2018). Undernutrition is often associated with increased susceptibility to infectious
283 diseases and long-term cognitive impairment (Chen et al., 2018b). Globally, child undernutrition
284 is accountable for nearly 3.1 million child deaths each year i.e. around 45% of all child deaths
285 (Black et al., 2013). The global prevalence rate of stunting and wasting in 2018 was 21.9% and
286 7.3%, respectively, while higher prevalence rate was recorded from the developing countries
287 (UNICEF/WHO/ World Bank, 2019). Growth impairment, particularly stunting, is associated
288 with transitioning from breastfeeding to weaning and post-weaning foods partly owing to an
289 increase in aflatoxins exposure through consumption of aflatoxin-contaminated weaning and
290 family foods (Gong et al., 2003). Aflatoxin exposure in a cohort of Ugandan children (n=10;
291 aged 54-60 months), as evidenced from aflatoxin contaminated local foods (9.07 µg/kg) and
292 AFM_1 levels in children urine (92.71 pg/mg) (Wacoo et al., 2020), through intake of solid foods
293 from an early age could be determinant of child stunting (LAZ = -2.25 at 20-24 months' age vs
294 LAZ= -1.20 at 6-8 months' age) as observed in a cohort of Ugandan children (n=511; aged < 59
295 months) (Muhoozi et al., 2017). A number of studies from African and South Asian countries
296 have investigated the association between aflatoxin exposure (through breast milk and weaning
297 diets) and growth faltering as measured by stunting, wasting and being underweight (Chen et al.,
298 2018b; Gong et al., 2002; Gong et al., 2003; Gong et al., 2004; Magoha et al., 2014, 2016;
299 Mahdavi et al., 2010; Makori et al., 2019; McMillan et al., 2018; Mitchell et al., 2017; Shirima et
300 al., 2015; Voth-Gaeddert et al., 2018; Watson et al., 2018). Most of the studies have reported a

significant inverse association between aflatoxin exposure (as measured by plasma biomarkers or dietary exposure) and the studied growth parameters, suggesting that exposure to aflatoxins might be the underlying cause of child growth impairment. However, the evidence remains inconsistent as some studies did not find significant association between growth impairment and aflatoxins exposure during weaning, suggesting that chronic aflatoxins exposure at low levels might take longer to manifest its health implications, and there might be a threshold level of aflatoxins exposure below that child growth remains unaffected (Chen et al., 2018b; Mitchell et al., 2017; Shirima et al., 2015). Reducing exposure to dietary aflatoxins through targeted post-harvest storage interventions resulted in a considerable reduction in serum AF-alb adducts (Turner et al., 2005). In a recent study in Kenya, replacement of aflatoxin contaminated maize reduced AFB_1-lysine in serum at the end of the trial but did not improve growth (Hoffmann et al., 2018). However, at the midpoint in the study, growth improvements were observed. Another longitudinal study by the same author team even reported that low-dose aflatoxin exposure was significantly associated with increased linear growth in a population where AFB_1-lysine levels were low (Leroy et al., 2018). There is no doubt that a number of confounders, such as socioeconomic status, interact with aflatoxin in relation to child growth. Further, issues with study design, inconsistent analytical method or other co-exposure factors may also have the potential to complicate the association.

The biological mechanism involving aflatoxin-associated growth impairment is not understood. One hypothesis through which aflatoxin may cause growth impairment is the induction of environmental enteric dysfunction. This may be characterized by enterocyte damage leading to loss of intestinal integrity and ultimately systemic immune activation, while making the host more susceptible to intestinal infectious agents (Khlangwiset et al., 2011; Smith et al.,

2012; Wild et al., 2015). Aflatoxin-induced enteropathy might occur through disturbance of the gut-microbiota dependent metabolic pathways (Zhou et al., 2019). In a study of Guatemalan children (aged 8-39 months) dietary aflatoxin exposure correlated with the dysbiosis of gut microbiome and stunting, specifically for children aged > 14 months (Voth-Gaeddert et al., 2019). In another study of rural Ugandan children (n=140), the genus *Lactobacillus* in the gut microbiota revealed highest positive correlation co-efficient (0.014) with stunting (at 20-24 and 36 months of age) among all bacterial genera (total 256 taxonomic units) identified in the stool samples (Wacoo et al., 2020). Additionally, intestinal malabsorption of micronutrients is another putative pathway through which aflatoxin-induced environmental enteropathy could cause growth retardation (Smith et al., 2012). A study from Guinea reported that children (aged 10-46 months) with the highest aflatoxin exposure (mean AF-alb: 57.1 pg/mg) were 3.96 times and 1.98 times more likely to be deficient in vitamin A and zinc as compared to the children with the lowest aflatoxin exposure (Watson et al., 2016). Another mechanism through which aflatoxin may cause growth impairment is through repression of protein synthesis, which may lead to compromised hepatic metabolism (Khlangwiset et al., 2011; Smith et al., 2012; Wild et al., 2015). Castelino et al. (2015) reported that aflatoxin exposure in children (aged 6-14 years) was negatively correlated with, insulin-like growth factor 1 (IGF1) and IGF-binding protein-3 (IGFBP3) levels. Further, Path analysis indicated that approximately 16% of the impact on child height could be due to aflatoxin-related reduction in IGF levels.

4.2. Association of aflatoxin exposure and severe acute malnutrition

Severe acute malnutrition (SAM) of infants, as identified by a very low weight-for-height Z-score (below -3 SD), may exist either in the edematous form (kwashiorkor) characterized by

moderately acute wasting with edema or non-edematous form (marasmus) characterized by severe emaciation. A number of factors are thought to contribute to SAM, which along with frequent co-occurrence of various forms of malnutrition in the same child over the period of time, has been strongly associated with mortality (Bhutta et al., 2017). Aflatoxins have been considered as an underlying factor in the etiology of SAM, specifically kwashiorkor (Hendrickse et al. (1982). The possible association between aflatoxin exposure and childhood kwashiorkor has been explored by a number of studies since the 1980's (Adhikari et al., 1994; Apeagyei et al., 1986; Coulter et al., 1986; De Vries et al., 1990; De Vries et al., 1989; Hatem et al., 2005; Hendrickse et al., 1982; Househam and Hundt, 1991; McMillan et al., 2018; Onyemelukwe et al., 2012; Oyelami et al., 1997; Oyelami et al., 1998; Ramjee et al., 1992; Tchana et al., 2010). Aflatoxin and its metabolites were found more frequently in the serum of children with kwashiorkor than in healthy groups or children with other forms of SAM such as marasmus (Coulter et al., 1986; Hatem et al., 2005). McMillan et al. (2018) studied aflatoxin exposure (by measuring AFB_1-lysine adducts) in Nigerian children (aged 6-48 months) suffering from SAM and found that the concentration of AFB_1-lysine was significantly higher in children with SAM (median = 4.3 pg/mg) as compared to control group (0.8 pg/mg) ($p<0.05$). Children suffering from kwashiorkor (6.3 pg/mg) were found to have higher median AFB_1-lysine concentration as compared to children with marasmus (0.9 pg/mg). Furthermore, children with kwashiorkor who died were reported to have higher frequency of aflatoxins in the liver (Apeagyei et al., 1986) and lungs (Oyelami et al., 1997), but not in kidneys (Oyelami et al., 1998). Conversely, aflatoxins are reported less frequently in the urine of children with kwashiorkor and in significantly lower concentration compared to urinary aflatoxin levels in healthy children (Onyemelukwe et al., 2012; Ramjee et al., 1992). This suggests that there is a difference in the metabolism of aflatoxin

in children with kwashiorkor and children with other forms of SAM and control groups and also there is inefficient urinary excretion or increased exposure of aflatoxin in children with kwashiorkor as compared to other groups (Coulter et al., 1986; Onyemelukwe et al., 2012). It has also been proposed that aflatoxins act in synergy with other etiological factors to facilitate the development of kwashiorkor and liver impairments (Onyemelukwe et al., 2012). Spatial distribution of both kwashiorkor and aflatoxins presence in food, their correspondence in the induction of metabolic disturbance, immune system damage and intestinal function damage further strengthens the existence of this synergistic association (Hendrickse et al., 1982; Wild and Gong, 2009).

4.3. Aflatoxins impact on the immune system

The development of the immune system starts early *in utero* and continues during infancy and childhood (Winans et al., 2011). Imbalances in immune function, specifically in the prenatal period, has significant health consequences during early childhood that may continue throughout life (Hertz- Picciotto et al., 2008). Studies have reported that tissues with a higher turnover of protein such as immune system organs, small intestine, and liver are adversely affected by mycotoxins exposure (Jahanian et al., 2019). Based on the duration, time and dose of exposure, the effect of mycotoxins on the immune system is either suppressive or stimulatory (Jahanian, 2016; Pierron et al., 2016). There is growing evidence that aflatoxins induce biphasic response through immunostimulation in the first phase and immunosuppression in the second phase (Yunus et al., 2011), however, evidence regarding immunostimulatory effects of AFs is lacking in children. Mycotoxin induced immunosuppression may increase vulnerability to infectious diseases, reduce vaccine and therapeutic efficacy or reactivate chronic infections (Oswald et al.,

2005). Cell-mediated immunity and innate immunity are more likely to be affected by aflatoxins as compared to humoral immunity (Bondy and Pestka, 2000). Immunosuppressive effects of aflatoxins in humans have been less characterized and to date, no data is available regarding the immunomodulatory effects of aflatoxins in children under 5 years of age. One of the mechanisms by which aflatoxins cause immunosuppression is through modulation of cytokines production. Githang'a et al. (2019) studied the immunomodulatory effects of dietary aflatoxin exposure in Kenyan children (aged 1-14 years) by measuring the level of hepatitis B surface antibodies (anti-HBs). It was observed that for each unit increase in plasma aflatoxin level, anti-HBs decreased by 0.91 mIU/ml. Findings of the study suggested that higher aflatoxin exposure might play a significant role in reducing the effectiveness of vaccine induced immunization. Moreover, increased aflatoxin level was also associated with down regulation of IL-4, IL-6, and IL-8 and up regulation of TNF-alpha. Secondly, the reduction in secretory immunoglobulins levels might be another possible mechanism through which AFs imparts immunosuppressive effects. Turner et al. (2003) found that Gambian children with detectable levels of AF-alb had reduced secretory immunoglobulin A (sIgA) in their saliva. Furthermore, suppression of DNA, RNA, and protein synthesis, as well as alteration in the levels of various lymphocyte subsets (CD3+CD69+ and CD19+CD69) reviewed by Jolly et al. (2008) are other suggested mechanisms involved in aflatoxin induced suppressed immune response. The mechanisms of aflatoxin induced immune modulation remains to be determined clearly and further research is needed to establish the association between aflatoxin exposure during pregnancy and in early childhood and changes in various aspects of the immune system.

4.4. Aflatoxins impact on the liver

Chronic exposure to aflatoxins in early life might contribute significantly to the early onset of hepatic cancer (Polychronaki et al., 2008). AFB_1 is the most potent human hepatocarcinogen, accounting for around 4.6–28.2% of the total hepatocellular carcinoma (HCC) cases worldwide (Liu and Wu, 2010). Fetal exposure to carcinogens may enable carcinogenesis to begin during a critical period of tissue development (Clarke and Joshu, 2017). AFB_1-DNA adducts formed in the fetal liver are reported to produce more mutagenic effects as compared to the same amount of AFB_1-DNA adducts in the liver of adult animals, indicating the increased risk of later life genetic disorders (Chawanthayatham et al., 2014). In mice, maternal exposure to aflatoxins during gestation had been found to increase AFB_1-DNA adduct levels by increasing the metabolic activation (Sriwattanapong et al., 2017). Carcinogen exposure during childhood may contribute to cancer risk either by enhancing the duration of exposure and/or by acting during sensitive periods of development (Clarke and Joshu, 2017). The mechanism of aflatoxin-induced HCC includes DNA damage, inactivation of tumor suppressor genes, abnormality of oncogenes, inheritance alterations, and abnormal immunoreactions (Long et al., 2018). However, mutation at the codon 249 (guanine to thymine transversion) in the p53 tumor suppressor gene of hepatic cells caused by the pro-mutagenic AFB_1-DNA adducts (namely AFB_1 N7 guanine adduct and its two secondary derivatives such as AFB_1-formamidopyrimidine and an apurinic site) is the most accepted mechanism of AFB_1-induced hepatocarcinogenesis (Hamid et al., 2013; Lopez-Valdes and Medinilla-Cruz, 2017). Further, there is a strong synergistic association between AFB_1 and hepatitis B virus (HBV) infection in the etiology of HCC. Possible mechanisms are that HBV interferes with the ability of the liver cells to metabolize aflatoxin (by altering the expression AFB_1 metabolizing enzymes), increasing levels of AFB_1-DNA adducts in the liver, and increasing chances of damage to tumor suppressor genes, or chronic HBV infection

increases the necrosis and proliferation of hepatocytes which eventually leads to the induction of AFB_1-induced mutations (Kew, 2003; Tanaka et al., 2011; Turner et al., 2000). The observations that Gambian children (aged 3-4 years) with chronic and acute HBV infection had higher AF-alb adducts (44.9 pg/mg and 96.9 pg/mg, respectively) as compared to non-infected children (31.6 pg/mg) (Turner et al., 2000), and significant elevation in serum transaminases (makers of liver damage) with the increase in AF-alb adducts in children (aged 3-4 years) (Wild et al., 1993) are consistent with the above-mentioned mechanisms.

Apart from liver cancer, dietary aflatoxin exposure may also be associated with other hepatic illnesses. An early study reported that dietary aflatoxin in children (aged between 1.5 and 5 years) was associated with a varying degree of hepatic lesions such as fibrosis, the formation of fatty cysts and cirrhosis (Amla et al., 1971). Higher aflatoxin exposure in Kenyan children (aged 6-17 years) was found to be associated with childhood chronic hepatomegaly, a condition of having abnormally enlarged liver (Gong et al., 2012). Further research would be useful to explore the adverse effects of aflatoxins on various other aspects of the liver, specifically in infants and young children.

5. Control strategies for reduction of early aflatoxin exposure

Aflatoxin contamination of agricultural commodities can be prevented by using primary, secondary, or tertiary levels. Primary prevention, the most effective strategy for reducing aflatoxin production, consists of various pre-harvest practices such as the use of genetic resistant cultivars, biocontrol, and good agricultural practices. Secondary prevention involved eradication of the toxigenic fungi or suppression of their growth to avoid further aflatoxin contamination by adopting several post-harvest measures including cleaning, sorting and segregation, improved

462 drying/storage/transportation and use of chemicals such as pesticides and preservatives. Tertiary
463 prevention appertains to complete eradication of aflatoxin contaminated grains and degradation
464 or detoxification of aflatoxins to minimum safe levels to prevent the transfer of toxigenic fungi
465 and health hazardous aflatoxins highly contaminated in agricultural commodities into food
466 products intended for consumption and in the environment. It may entail agriculture extension
467 services, training programs, detoxification, good hygienic practices, and several others (Abdel-
468 Wahhab et al., 2019; Sowley et al., 2016).

469 Though nations suffering from health risks of aflatoxin exposure have minimally
470 established aflatoxins standards in food, the enforcement of these standards is often difficult. In
471 resource-poor countries where security of food is always in danger, local food traders and
472 subsistence farmers compromised on discarding the mouldy food crops and most of the time
473 people have no choice to consume mouldy food or starve (Wu and Khlangwiset. 2010). Also, the
474 risk of aflatoxin exposure may increase because of reliance on limited or restricted dietary
475 staples such as maize and groundnuts, reliance on great majority of locally grown staples, or
476 inappropriate long-lasting storage of dietary staples (Turner, 2013). Adoption of primary (pre-
477 harvest) prevention strategies is a great challenge in low and middle-income countries because of
478 their complexity and high cost. Therefore, integration of post-harvest strategies and community-
479 based approaches such as dietary modifications are more expedient in low and middle-income
480 countries.

481 Public health interventions to mitigate the risks of aflatoxin exposure have been widely
482 investigated in the literature (reviewed by Strosnider et al., 2006; Turner, 2013; Wild et al.,
483 2015). However, limited information is available about the effect of interventions on aflatoxins
484 exposure in early life stages which represents an important opportunity for interventions to

485 reduce the long-term risks of diseases, as presented in Table 4. Most of the available literature is
486 based on integrated educational community-based programs conducted in South and East
487 African regions including Kenya, Tanzania, and Zimbabwe. The agricultural interventions to
488 reduce aflatoxin exposure to high-risk population were aimed at educating households owners
489 involved in agricultural activities, about replacing high-aflatoxin contaminated maize with safe
490 maize in community food supply (i.e. local food shops) (Hoffmann et al., 2018), good
491 agricultural practices such as hand sorting (before storage and use), proper sun drying, drying
492 maize on mat/raised platforms, use of storage insecticides and de-hulling prior to milling
493 (Kamala et al., 2018), and provide them training regarding hermetic storage technology
494 (Dembezda et al., 2019). Education for agricultural interventions was mostly provided by
495 agricultural extension services accompanied by provision of technological and food-replacement
496 access to the intervention groups. The nutritional interventions to reduce aflatoxin exposure were
497 usually aimed at educating mothers/caregivers of infants about increasing diversified foods in the
498 diet, adopting optimal food preparation methods (Anitha et al., 2020) and choosing foods at low
499 risk of aflatoxin contamination for complementary food preparations (Phillips et al., 2020).

500 (Table 4 near here)

501 These intervention study by Hoffmann et al. (2018) indicated that, despite the reduction
502 in AF-alb adduct levels by 27%, no significant improvement in child LAZ was observed at
503 endline (18 months). However, child's LAZ significantly increased by 7% at midline, even
504 though there had no difference on serum AF-alb adduct levels between the two groups
505 (Hoffmann et al., 2018). The incidence of being underweight significantly reduced in the infants
506 from intervention group as compared to the infants from control group (group difference: 6.7%)
507 (Kamala et al., 2018). The average estimated daily intake of aflatoxins in the intervention group

508 significantly reduced in the intervention group as compared to control group (group difference:
509 49 ng/kg bw/day with relative difference of 78%) (Kamala et al., 2018). Also, the urinary AFM_1
510 levels was significantly higher in the group using conventional storage (geometric mean: 62.28
511 μg/L), when compared with the group using hermetic storage technology (geometric mean: 31.95
512 μg/L) (Dembezda et al., 2019). Diversified complementary foods formulated through nutritious
513 recipes resulted in higher reduction in urinary AFM_1 (64% as compared to 11% in control) and
514 increased Z-score for stunting, underweight, and wasting by 0.459, 0.493 and 0.252, respectively
515 (Anitha et al., 2020). Similarly, the consumption of low-aflatoxin pre-blended mix (prepared by
516 combination of maize and groundnuts) in the ongoing intervention study by Phillips et al. (2020)
517 reduced the prevalence of urinary AFM_1 (by 81%) in infants.

518 Though these reports are good recent examples of successful interventions targeted to
519 infant populations, their outcome also addresses several further questions. Firstly, the focus of
520 the studies was on the single stage of early life and on single class of intervention. Secondly,
521 studies lack the assessment of potential cost-effectiveness, acceptability, sustainability, and
522 suitability of nutritional and post-harvest interventions on reducing aflatoxin exposure
523 particularly in high-risk groups. Additionally, there are uncertainties regarding various factors
524 influencing the effect of agricultural and nutrition education on child linear growth i.e. child's
525 age, dietary diversity, baseline nutrient sufficiency, and follow-up period. Therefore, additional
526 studies based on clinical trials should be further developed, to completely understand the key
527 tents of aflatoxin reduction interventions.

528

529 **6. Concluding Remarks**

530 Humans can be exposed to aflatoxins during the early stages of life including *in utero*

exposure, from breast milk, through infant formula milk and through infant foods that are used up to 2 years of age. Aflatoxin exposure is especially high in many African and Asian countries. Aflatoxin exposure in the early days of life has been linked to a number of health implications including adverse birth outcomes, impaired growth and development, suppressed immune system, and hepatic dysfunction. Based on the data presented in the tables regarding the prevalence of aflatoxins in different infant food items, it is clear that the exposure to aflatoxins is unavoidable especially in the developing countries. Major factors involved in the prevalence of aflatoxins in developing countries are omnipresence of fungi responsible for the production of aflatoxins, lack of rapid low-cost aflatoxin detection tools, lack of public awareness of the risk, and lack of effective regulations of aflatoxins in the food chain. However, certain intervention strategies may help to mitigate the disease burden due to aflatoxins. Food safety recommendations tailored for pregnant and nursing mothers are important for the reduction of transplacental and lactational transfer of aflatoxins to the fetus and infants, respectively.

Protection against the risk aflatoxins pose for infants demands improved awareness among key stakeholders and the public, surveillance targeting the overall food production chain, use of fresh and hygienic food commodities and proper implementation of rules and regulations. Promoting a diversity of crops that are less likely to be contaminated with aflatoxins but fulfill the nutritional needs of complementary feeding would be valuable in ensuring the food safety and nutrition of infants and young children. Recent research highlights the importance of nutrition sensitive interventions over targeted intervention on reduction of child malnutrition. A number of programs aiming to supplement / fortify nutrients to reduce child malnutrition have failed, possibly due to the lack of control of infection and/or aflatoxins contamination in food. The success of every nutrition intervention program depends on fighting on two fronts at a same

554 time for improvement in nutritional status and reduction in aflatoxins exposure. Moreover, there
555 is an urgent need of well-designed randomized control trials to assess the impacts of aflatoxins
556 and above-mentioned adverse health outcomes in children using validated biomarkers of
557 exposure. Last but not least, it is necessary to understand and mitigate aflatoxin risk within a
558 sustainable, climate-smart agriculture food production framework whereby translational
559 interdisciplinary research is the future direction in order to achieve significant reductions in the
560 aflatoxin exposure of infants.

561

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