

REVIEW ARTICLE

Aflatoxins and growth impairment: A review

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Abstract

Aflatoxins, fungal toxins produced by *Aspergillus flavus* and *Aspergillus parasiticus* in a variety of food crops, are well known as potent human hepatocarcinogens. Relatively less highlighted in the literature is the association between aflatoxin and growth impairment in children. Foodborne aflatoxin exposure, especially through maize and groundnuts, is common in much of Africa and Asia—areas where childhood stunting and underweight are also common, due to a variety of possibly interacting factors such as enteric diseases, socioeconomic status, and suboptimal nutrition. The effects of aflatoxin on growth impairment in animals and human children are reviewed, including studies that assess aflatoxin exposure in utero and through breastfeeding. Childhood weaning diets in various regions of the world are briefly discussed. This review suggests that aflatoxin exposure and its association with growth impairment in children could contribute a significant public health burden in less developed countries.

Keywords: Aflatoxin, growth impairment, less developed countries, malnutrition, stunting, underweight

Contents

| | |
|--|-----|
| Abstract | 740 |
| I. Introduction | 740 |
| A. Aflatoxins | 740 |
| Abbreviations | 741 |
| B. Growth impairment and global burden of disease | 741 |
| II. Aflatoxin and growth impairment in animals | 742 |
| III. Aflatoxin and growth impairment in humans | 743 |
| A. Aflatoxin exposure in utero and early childhood | 743 |
| B. Past studies on aflatoxin and kwashiorkor | 748 |
| C. Aflatoxin and growth impairment in children | 748 |
| IV. Childhood weaning foods | 750 |
| V. Discussion | 751 |
| Declaration of interest | 752 |
| References | 752 |

I. Introduction

A. Aflatoxins

Much of the policy attention surrounding *aflatoxin*, a common contaminant in the global food supply, has focused on its role in inducing liver cancer in humans (EFSA, 2009; FAO, 2004; JECFA, 1998; FDA, 1994), with little or no attention devoted to the role of aflatoxin in

growth impairment. Among other reasons, it is because the weight of evidence linking aflatoxin to human growth impairment has historically been much weaker than that linking aflatoxin to human liver cancer. However, animal studies over the last several decades have demonstrated a significant association between aflatoxin and growth impairment; furthermore,

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Abbreviations

ADFI average daily feed intake
 ADG average daily gain
 AF-alb aflatoxin-albumin adducts
 ALT alanine aminotransferase
 AST aspartate aminotransferase
 DALY disability adjusted life years
 DMSO dimethylsulfoxide
 FCE feed conversion efficiency

FCR feed conversion ratio
 GDP gross domestic product
 HAZ height-for-age z-score
 HCC hepatocellular carcinoma
 HSCAS hydrated sodium calcium aluminosilicate
 IP intraperitoneal
 PPP purchasing power parity
 WAZ weight-for-age z-score
 WHZ weight-for-height z-score

especially in the last decade, epidemiological studies have emerged suggesting similar effects in human children. Validation of serum- and urine-based biomarkers of aflatoxin exposure and effect in the last two decades has greatly assisted these epidemiological studies (Groopman et al., 2008). In this paper, we review the literature associating aflatoxin with growth impairment in both animals and humans.

Aflatoxins are secondary metabolites of the fungi *Aspergillus flavus*, *Aspergillus parasiticus*, and occasionally other *Aspergillus* species. These fungal species are prevalent in food crops, particularly maize, groundnuts, oilseeds, and tree nuts, in tropical and subtropical regions worldwide. Factors that influence whether these fungi produce aflatoxin include drought stress and rainfall, adaptation ability of crop genotype for its climate, insect damage, and agricultural practices (Wu et al., 2011). These fungi can also produce aflatoxin in postharvest conditions: food storage, transportation, and processing. Maize and groundnuts are the major sources of aflatoxin exposure in humans (the number of exposed persons exceeding several billion) because of the high consumption rates of these foods worldwide and their susceptibility to *Aspergillus* infection (Strosnider et al., 2006).

Aflatoxin B₁ (AFB₁), the most toxic form of the aflatoxins, is the most potent naturally occurring chemical liver carcinogen known. For people who are chronically infected with hepatitis B virus (HBV; common in China and Africa), aflatoxin consumption synergistically increases the risk of hepatocellular carcinoma (HCC; liver cancer) compared with either exposure alone (Groopman et al., 2005). Acute aflatoxicosis, characterized by hemorrhage, acute liver damage, edema, and death, can result from extremely high doses of aflatoxin in the diet (FDA, 2004). In 2004 and 2005, hundreds of acute aflatoxicosis cases in Kenya and 125 deaths were associated with the consumption of contaminated homegrown maize (Strosnider et al., 2006). Aflatoxin exposure has also been associated with immunotoxicity in humans (Jiang et al., 2005; Jolly et al., 2008; Turner et al., 2003; Williams et al., 2004), and, as this review highlights, with stunted growth and other indicators of growth impairment in children.

B. Growth impairment and global burden of disease

Childhood growth performance is usually measured by one or more of three indicators: height for age, weight for age, and weight for height. Based on the World Health Organization (WHO) definitions, children whose heights for ages, weights for ages, and weights for heights are 2 standard errors or more below WHO growth standards ($z\text{-score} \leq -2$) are considered to be *stunted*, *underweight*, and *wasted*, respectively (WHOSIS, 2008). Wasting is an indicator of deficits in tissue and fat mass, which may be caused by acute malnutrition, whereas stunting is regarded as an indicator of chronic malnutrition. The prevalence of severe wasting decreases by 24 months of age, whereas stunting prevalence increases by age and reaches a plateau at 24–36 months (Black et al., 2008; WHO, 1986).

Stunting is a widely used indicator of chronic malnutrition in early childhood, including malnutrition during fetal development due to poor maternal nutrition. Children are considered stunting if their height-for-age $z\text{-score}$ (HAZ) is -2 or lower. Once established, stunting and its effects usually last for years. Children who are stunted often develop long-term developmental and cognitive problems, and are more vulnerable to infectious diseases (Ricci et al., 2006). In one study, Filipino children aged between 8 and 11 years who were stunted as 2-year-olds had significantly lower test scores than non-stunted children later in life, as well as delays in school enrollment, increased school absences, and repetition of school years (Mendez and Adair, 1999).

The World Health Organization (WHO, 2008) assigns each case of childhood stunting an average disability weight—a weighting factor that reflects the severity of a disease or condition—of 0.002 on a 0–1 scale. This is relatively low compared with other conditions and diseases, in part because the associated risk factors of stunting (increased susceptibility to infectious disease, cognitive impairment) are not included in the estimation of the disability weight of stunting. However, stunting may still cause a high global burden of disease because of its prevalence, as well as its associated risk factors, and hence deserves public health attention. In 2004, an estimated 182.7 million children in developing countries were considered to be stunted. Seventy percent of these

stunted children live in South and Southeast Asia and sub-Saharan Africa (WHO, 2008). Globally, 21% of deaths and disability adjusted life years (DALYs) in children aged 5 years and under are estimated to be attributed to stunting, severe wasting, and intrauterine growth restriction (Black et al., 2008). Table 1 lists the socioeconomic characteristics of selected nations worldwide, and estimated dietary aflatoxin exposure and proportion of stunted children. Though the relationship is not consistent, it appears that, in general, the proportion of childhood stunting is directly correlated with proportion of population living below the national poverty line, and inversely correlated with gross domestic product (GDP) per capita. As is the case with HCC, childhood stunting is prominent in world regions where foodborne aflatoxin exposure is high: South and East Asia, and sub-Saharan Africa.

Underweight children are significantly more at risk of death from diseases, including diarrhea, pneumonia, malaria, and measles. It has been estimated that children with a weight-for-age *z*-score (WAZ) of -1 to -2 are twice as likely to die from diarrheal diseases compared with children of normal weight, whereas children with WAZ from -2 to -3 are 5 times as likely to die. Additionally, 52% of pneumonia deaths in children aged 5 and under are associated with low body weight (Caulfield et al., 2004). Although the prevalence of underweight is expected to decrease from 26.5% in 1990 to 17.6% in 2015, this decrease would not be uniform across the world. In Asia and Latin America, childhood underweight is expected to decrease by about 50%, whereas in Africa, underweight prevalence may even increase by 2–3% compared with 1990 (de Onis et al., 2004). WHO does not assign a specific disability weight to childhood underweight; however, low birth weight is assigned a disability weight of 0.106 per case (WHO, 2008).

Wasting in children (weight-for-height *z*-score, or WHZ, is -2 or lower) is believed to be a condition related to acute malnutrition (Jacobs and Roberts, 2004; Yip and Sharp, 1993), either from insufficient food intake or infectious diseases. Immune system impairment in wasted children makes them more susceptible to infections

(Schaible and Kaufmann, 2007). As a result, wasting increases the risk of death in children with this condition (WHO, 2010a). WHO assigns a disability weight of 0.053 per wasting case. In 2004, the global prevalence of wasting in children aged 5 years and under was about 56.2 million (WHO, 2008).

This article reviews the evidence linking aflatoxin exposure to growth impairment in animals and in human children. We first review the literature on animal studies over the past 50 years in which associations were found between aflatoxin exposure and reduced feed conversion efficiency, reduced weight gain, and other measures of growth impairment in animals. Then we describe the studies that show evidence of aflatoxin exposure in children in various parts of the world, review a previously examined association between aflatoxin exposure and kwashiorkor (a disease of protein energy malnutrition), and discuss the studies that link aflatoxin exposure with stunting, underweight, and wasting in children. We describe weaning foods in various cultures worldwide, and end with a discussion of possible mechanisms by which aflatoxin may result in growth impairment in animals and humans.

II. Aflatoxin and growth impairment in animals

The adverse effects of exposure to aflatoxin on various indicators of growth performance have been demonstrated in multiple animal species over the last five decades. Reduced feed intake and subsequent weight gain reduction in animals exposed to aflatoxin have been reported in mule ducklings (Cheng et al., 2001), mice (Kocabas et al., 2003), Japanese quail (Sadana et al., 1992), Cherry Valley commercial ducks (Han et al., 2008), chickens (Bryden et al., 1979; Doerr et al., 1983; Giambrone et al., 1985; Huff, 1980; Huff et al., 1986; Pimpukdee et al., 2004; Prabakaran et al., 1999; Ram et al., 1988; Randall and Bird, 1979; Shukla and Pachauri, 1985), turkeys (Giambrone et al., 1985), pigs (Armbrecht et al., 1971; Harvey et al., 1989, 1994, 1995a, 1995b; Lindemann et al.,

Table 1. Economic, aflatoxin exposure, and health characteristics of selected nations.

| Country | % population living below national poverty line (WHO, 2010b) | GDP per capita, 2010 USD (PPP) (IME, 2010) | Aflatoxin exposure, ng/kg bw/day (Liu and Wu, 2010) | % stunted children (WHO, 2010b) |
|-------------|--|--|---|---------------------------------|
| Argentina | NA | 15 030 | 0–4 | 8 |
| China | 5 | 7240 | 17–37 | 22 |
| France | NA | 34 250 | 0.3–1.3 | NA |
| The Gambia | 58 | 1479 | 4–115 | 28 |
| India | 29 | 3176 | 4–100 | 48 |
| Kenya | 52 | 1783 | 3.5–133 | 36 |
| Nigeria | 34 | 2357 | 139–227 | 43 |
| Philippines | 37 | 3604 | 44–54 | 34 |
| Spain | NA | 29 649 | 0.3–1.3 | NA |
| Tanzania | 36 | 1484 | 0.02–50 | 44 |
| Thailand | 13 | 8479 | 53–73 | 16 |
| USA | NA | 47 702 | 0.26 | 4 |

Note. GDP = gross domestic product per capita; NA = not available; PPP = purchasing power parity.

1993; Marin et al., 2002; Panangala et al., 1986; Schell et al., 1993a, 1993b; Southern and Clawson, 1979), Nile tilapia (Chávez-Sánchez et al., 1994), and channel catfish (Jantrarotai and Lovell, 1990).

In addition, increases in feed conversion ratio (FCR)—defined here as the mass of food intake per unit weight gain by the animal—were prominent in the animals dosed with aflatoxin (Bryden et al., 1979; Edrington et al., 1994; Giambrone et al., 1985; Keyl and Booth, 1971; Lindemann et al., 1993; Panangala et al., 1986; Southern and Clawson, 1979). Aflatoxin at relatively lower doses (100–300 µg/kg) did not affect 6-month-old steer, but their weight, feed intake, and feed efficiency were adversely affected at higher doses (700–1000 µg/kg) (Keyl and Booth, 1971). Whereas channel catfish and rainbow trout were not affected by 2154 µg/kg of purified aflatoxin in feed diet in terms of growth rate, FCR, or liver lesions (Jantrarotai and Lovell, 1990), Nile tilapia showed significant reduction in weight and feed consumption when exposed to 1.8 mg/kg diet (1800 µg/kg) or higher doses of aflatoxin for 25 days (Chávez-Sánchez et al., 1994). Taken together, these studies suggest that aside from reducing feed intake and weight gain, feed conversion efficiencies across multiple animal species were also reduced by aflatoxin exposure in the diet.

Several studies observed effects of aflatoxin on growth in baby animals as a result of in utero exposure through maternal feed. The effect of aflatoxin on offspring was reported by Butler and Wigglesworth in 1966, who observed growth retardation in rat pups whose mothers were fed high doses of aflatoxin during late pregnancy (Butler and Wigglesworth, 1966). The fetuses of hamsters administered aflatoxin intraperitoneally at doses of 4 or 6 mg/kg body weight (bw) on days 8 and 9 of pregnancy experienced growth retardation, compared with controls, but there were no significant differences in malformations between the two groups (Schmidt and Panciera, 1980). Kihara et al. (2000) reported lower mean body weight, delayed physical and behavioral development in the preweaning phase, and disability of locomotor coordination and impaired avoidance performance in the postweaning periods, in rat pups whose mothers were exposed to 0.3 mg/kg/day of aflatoxin subcutaneously during pregnancy. Moreover, they found that numbers of live births were affected by aflatoxin exposure during prenatal periods (Kihara et al., 2000). Maternal exposure to AFB₁, not AFG₁, decreased body weights of piglets significantly (Mocchegiani et al., 1998). Although aflatoxin did not affect average egg production, feed conversion, and body weight, it affected feed consumption and egg weight of laying Japanese quail (Oliveira et al., 2002).

Tables 2 and 3 contain summaries of animal studies showing an association between aflatoxin exposure and growth reduction, in animals that directly consume aflatoxin (Table 2) and in utero—in baby animals whose mothers were exposed to aflatoxin during pregnancy (Table 3).

In summary, 30 animal studies are documented here (Table 2). Twenty-nine of 30 studies indicated that

animals treated with aflatoxin showed reduced weight gain or some deviant signs such as reduced feed intake or increased feed conversion ratio. Only one study reported nonsignificant effect in either body weight or feed conversion.

Table 3 lists five animal studies that show the association between in utero aflatoxin exposure and growth parameters in baby animals. All five studies reported either the reduced fetal weights/egg weights or fetal lengths of the offspring animals.

III. Aflatoxin and growth impairment in humans

A. Aflatoxin exposure in utero and in early childhood

Exposure to aflatoxin begins early in the lives of many children worldwide. Children may be exposed to aflatoxin through maternal food intake in utero, through breastfeeding, and through weaning and postweaning foods, particularly where maize and groundnuts are dietary staples. Aflatoxin exposure increases most dramatically after children are weaned from breastfeeding (Gong et al., 2003). However, even in utero exposures can have a significant effect on faltering in infant growth (Turner et al., 2007).

Detection of aflatoxins and aflatoxin-albumin adducts (AF-alb) in the cord blood of babies in various countries confirm that children are exposed to aflatoxin and/or its metabolites in utero. In a Taiwanese study, 11 of 120 placentas were found to contain aflatoxin-DNA adduct levels ranging from 0.6 to 6.3 µmol/mol DNA. In the same study, aflatoxin-DNA adducts were detected in 6 of 56 cord blood samples in the range of 1.4–2.7 µmol/mol DNA (Hsieh and Hsieh, 1993). Aflatoxin M₁ (AFM₁), a metabolite of AFB₁, was detected in 68% (113/166) and 67% (111/166) of maternal blood and cord blood samples of neonates studied in the United Arab Emirates, with mean levels of 1040 and 1880 pg/ml, respectively (Abdulrazzaq et al., 2004).

Of 282 cord blood samples from Ghana, 101 samples from Kenya, and 78 samples from Nigeria, aflatoxins were detected in 31%, 37%, and 12%, respectively (Lamplugh et al., 1988; Maxwell et al., 1989). Though the detection rate of AF-alb in maternal blood samples was not stated, the levels of AF-alb found in 755 Ghanaian mothers in a cross-sectional study were reported to range from 0.44 to 268.73 pg/mg (Shuaib et al., 2010). Detectable levels of aflatoxins were found in 22% to 82% of cord blood of Nigerian neonates (Abulu et al., 1998; Ahmed et al., 1995), and 58% of the cord blood samples from Sierra Leone (Jonsyn et al., 1995a). AF-alb was detected in 29 of 30 (97%) maternal blood samples, and 22 of 30 (70%) matched umbilical cord blood sera from Gambian neonates (Wild et al., 1991). Turner et al. (2007) found AF-alb ranging from 5 to 896 pg/mg in 48 out of 99 (48%) Gambian cord blood samples.

The studies in Kenya (Maxwell et al., 1989) and Sierra Leone (Jonsyn et al., 1995a) showed higher detection

Table 2. Animal studies of the effects of aflatoxin exposure on animal growth.

| Animal | Aflatoxin dose and duration of experiment | Results | Study |
|---|--|---|-----------------------------|
| Pigs ($n=50$) | 0 (A), 0.2 (B), 0.7 (C), 1.1 (D) mg/kg feed (16 weeks) | No significant difference in body weight between groups. Increase in FCR [4.53 (A), 4.55 (B), 4.67 (C), 4.76 (D)] ($p < .05$) | Armbrecht et al. (1971) |
| Pigs ($n=60$) | 0 (A), 1.0 (B), 2.0 (C), 4.0 (D) mg/kg feed (13 weeks) | Increase in FCR [3.14 (A), 3.82 (B), 4.13 (C), NA (D)] ($p < .001$) | Armbrecht et al. (1971) |
| Weanling pigs ($n=110$) | <2 (A), <8 (B), 51 (C), 105 (D), 233 (E) μ g/kg feed (120 days) | No significant effect on weight gain or feed conversion | Keyl and Booth (1971) |
| Weanling pigs ($n=110$) | <6 (A), 450 (B), 615 (C), 810 (D) μ g/kg feed (120 days) | Decrease in ADG at the dose of 615 and 810 μ g/kg feed [0.71 kg (A), 0.60 kg (C), 0.47 kg (D)] ($p < .05$) | Keyl and Booth (1971) |
| Young cross-bred steers ($n=50$) | 0 (A), 100 (B), 300 (C), 700 (D), 1000 (E) μ g/kg (133 days) | Decrease in ADG at 700, and 1 000 μ g/kg ($p < .01$) [1.14 kg (A), 0.86 kg (D), and 0.79 kg (E)] Increase in FCR at 700, and 1 000 μ g/kg ($p < .01$) [5.7 (A), 6.4 (D), 6.6 (E)] | Keyl and Booth (1971) |
| 30-day-old Sprague-Dawley rats ($n=24$) | 0 (A), DMSO (B), 5 mg/kg bw of AFB ₁ in DMSO (C), 7 mg/kg bw of AFB ₁ in DMSO (D) (IP single dose in 76 h) | Weight gain in 0 mg/kg bw and DMSO groups [13 g/rat (A), 15 g/rat (B)] Weight lost in 5 and 7 mg/kg bw of AFB ₁ in DMSO groups [1 g/rat (C), 8 g/rat (D)] | Doyle et al. (1977) |
| 30-day-old Sprague-Dawley rats | DMSO, 10 mg/kg bw of AFB ₁ in DMSO (IP single dose in 54 hours) | Weight gain in DMSO group [8 g/rat] Weight lost in 10 mg/kg bw of AFB ₁ in DMSO group [20 g/rat (C)] | Doyle et al. (1977) |
| Chickens ($n > 900$) | 0 (A), 0.3 (B), 1.25 (C), 2.0 (D) mg/kg (28 days) | Decrease in body weight and food intake Increase in FCR ($p < .001$) | Bryden et al. (1979) |
| Broiler chicks ($n=40-48$) | 0 (A), 5 (B) mg/kg feed aflatoxin, exercise (C), 5 mg/kg feed aflatoxin + exercise (D) (24 days) | Decrease in body weight in aflatoxin-treated group, which can be partially improved by exercise [557.6 \pm 9.3 g (A), 542.7 \pm 9.0 g (B), 366.8 \pm 7.4 g (C), 412.5 \pm 7.4 g (D)] Increase in FCR in aflatoxin treated group [1.54 (A), 1.89 (C)] | Randall and Bird (1979) |
| Layer type chicks ($n=40-48$) | 0 (A), 5 (B) mg/kg feed aflatoxin, exercise (C), 5 mg/kg feed aflatoxin + exercise (D) (39 days) | Decrease in body weight in aflatoxin treated group, which can be partially improved by exercise [469.5 \pm 9.9 g (A), 469.5 \pm 9.9 g (B), 370.8 \pm 20.2 g (C), 384.1 \pm 14.4 g (D)] Increase in FCR in aflatoxin-treated group [1.59 (A), 1.75 (C)] | Randall and Bird (1979) |
| Broiler chicks ($n=40-48$) | 0 (A), 5 (B) mg/kg feed aflatoxin, exercise (C), 5 mg/kg feed aflatoxin + exercise (D) | Decrease in body weight in aflatoxin treated group, which can be partially improved by exercise [510.5 \pm 12.5 g (A), 502.0 \pm 12.0 g (B), 414.9 \pm 19.8 g (C), 434.0 \pm 8.1 g (D)] No difference in FCR | Randall and Bird (1979) |
| Pigs ($n=32$: 8 for each of 4 groups of pigs) | 20(A), 385 (B), 750 (C), and 1480 (D) μ g/kg (control: 20 μ g/kg group) | Decrease in ADG (dose-related) [0.77 kg (A), 0.67 kg (B), 0.57 kg (C), 0.41 kg (D)]; and ADFI [2.87 kg (A), 2.53 kg (B), 2.15 kg (C), 1.61 kg (D)] ($p < .05$) Increase in FCR in the 1480 μ g/kg treated group [3.74 (A), 3.97 (D)] ($p < .05$) | Southern and Clawson (1979) |
| Broiler chickens ($n=75$) | 0 (A), 0.075 (B), 0.225 (C), and 0.675 (D) mg/kg feed (7 weeks) | Decrease in body weight in all aflatoxin-treated groups [2256 \pm 21 g (A), 2098 \pm 26 g (B), 1989 \pm 20 g (C), 2047 \pm 24 g (D)] ($p < .05$) | Doerr et al. (1983) |
| Broiler chickens ($n=75$) | 0 (A), 0.3(B), 0.9 (C), and 2.7 (D) mg/kg feed (7 weeks) | Decrease in body weight in only 2.7 mg of aflatoxin per kg feed group [2024 \pm 30 g (A), 1671 \pm 36 g (D)] ($p < .05$) | Doerr et al. (1983) |
| 1-day-old broilers ($n=70$) | 0 (A), 0.625 (B), 1.25 (C), 2.5 (D), 5.0 (E), and 10.0 (F) mg/kg feed (3 weeks) | Aflatoxin dose-related decrease in body weight at the dose 1.25 μ g/g and higher [511 \pm 32 g (A), 463 \pm 16 g (D), 386 \pm 25 g (E), 286 \pm 13 g (F)] and feed consumption [851 \pm 52 g (A), 773 \pm 50 g (D), 703 \pm 55 g (E) 734 \pm 14 g (F)] ($p < .05$) | Huff (1980) |
| 14-day-old turkeys ($n=200$) | 0 (A), 100 (B), 200 (C), 400 (D), or 800 (E) μ g/kg AFB ₁ (35 days) | Decrease in percent weight gain at the dose of 400 μ g/kg and higher [averaged 5-week percent weight gain: 48.2% (A), 33.2% (D), 19.7% (E)] Increase in FCR at the two highest doses [FCR averaged in 5 weeks: 1.81 (A), 1.89 (D), 2.28 (E)] ($p < .05$) | Giambrone et al. (1985) |
| 14-day-old broiler chickens ($n=200$) | 0 (A), 100 (B), 200 (C), 400 (D), or 800 (E) μ g/kg AFB ₁ (35 days) | No significant difference in weight gain ($p > .05$) Increase in FCR at the dose of 800 μ g/kg [FCR: 2.02 (A), 2.11 (E)] | Giambrone et al. (1985) |
| 105-day-old chicks ($n=120$) | 0 (A), 2.5 (B), 5.0 (C), and 10.0 (D) mg/kg feed (4 weeks) | Aflatoxin dose-related decrease in body weight ($p < .05$) [1.85 \pm 0.03 kg (A), 1.57 \pm 0.05 g (B), 1.51 \pm 0.04 kg (C), 1.47 \pm 0.03 g (D)] | Shukla and Pachauri (1985) |
| Male broiler chicks ($n=180$) | 0 (A), 2.5 (B) mg/kg of aflatoxin, and 2.5 mg/kg of aflatoxin + 16 mg/kg of deoxynivalinol (C) (3 weeks) | Decrease in body weight [626 \pm 11 g (A), 521 \pm 12 g (B), 488 \pm 9 g (C)], weight gain [490 \pm 10 g (A), 397 \pm 10 g (B), 365 \pm 8 g (C)], protein serum levels [2.9 \pm 0.1 g/100 ml (A), 2.0 \pm 0.1 g/100 ml (B), and 2.1 \pm 0.1 g/100 ml (C)] ($p < .05$) | Huff et al. (1986) |

Table 2. continued on next page

Table 2. Continued.

| Animal | Aflatoxin dose and duration of experiment | Results | Study |
|--|---|--|---------------------------------|
| 5–6-week-old pigs ($n=30$: 10 each in control, 300 and 500 $\mu\text{g}/\text{kg}$ groups) | 0, 300, and 500 $\mu\text{g}/\text{kg}$ of feed (10 weeks) | Decrease in weight gain in both aflatoxin-treated groups up to 2 kg in 10-week period and feed consumption in high-dose group compared with controls ($p < .01$) | Panangala et al. (1986) |
| 1-day-old broilers and layer chicks ($n=40$ each) | 0 (A), 1 (B), 4 (C) mg/kg feed (4 weeks) | Aflatoxin dose-dependent decrease in body weights ($p < .05$). Broilers: 332 ± 17.81 g (A), 254 ± 14.35 g (B), 239 ± 13.50 g (C). Layer chicks: 158 ± 3.6 g (A), 139 ± 4.41 g (B), 126 ± 5.82 g (C) | Ram et al. (1988) |
| 7-week-old pigs ($n=15$) | 0 (A), 2.0 mg aflatoxin (B), 2.0 mg ochratoxin (C), and 2.0 mg aflatoxin + 2.0 mg ochratoxin (D) /kg feed (28 days). | Decrease in body weight gain in all aflatoxin-treated groups [18.2 ± 0.9 kg (A), 13.5 ± 0.8 kg (B), 13.8 ± 1.0 kg (C), 8.8 ± 0.9 kg (D)] ($p < .05$) | Harvey et al. (1989) |
| Channel catfish ($n=450$) | 0, 100, 404, 2154, or 10,000 $\mu\text{g}/\text{kg}$ (10 weeks) | Decrease in weight gain in the 10 000 $\mu\text{g}/\text{kg}$ group by 24% compared with the control ($p < .05$) [weight gain per fish in the highest dosed group = 60 g compared with 80 g/fish in the control group] | Jantraratotai and Lovell (1990) |
| Weanling swine ($n=90$) | 0 (A), 420 (B), 840 (C) $\mu\text{g}/\text{kg}$ feed (49 days) | Decrease in ADG [0.52 kg (A), 0.46 kg (B), 0.28 kg (C)] and ADFI [1.13 kg (A), 0.95 kg (B), 0.67 kg (C)] Increase in FCR [1.72 (A), 1.92 (B), 2.70 (C)] (linear $p < .01$, and quadratic $p < .05$) | Lindemann et al. (1993) |
| Weanling swine ($n=63$) | 0 (A), 800 (B) $\mu\text{g}/\text{kg}$ feed (42 days) | Decrease in ADG [0.64 kg (A), 0.41 kg (B)] and ADFI [1.32 (A), 0.82 kg (B)] | Lindemann et al. (1993a) |
| Weanling pigs ($n=96$) | 0 (A), 922 (B) $\mu\text{g}/\text{kg}$ feed (6 weeks) | Decrease in ADG [0.505 kg (A), 0.392 kg (B)] and ADFI [1.10 kg (A), 0.88 kg (B)] ($p < .01$) | Schell et al. (1993a) |
| Weaned pigs ($n=54$) | 0 (A), 800 (B) $\mu\text{g}/\text{kg}$ feed (4 weeks) | Decrease in ADG [0.64 kg (A), 0.48 kg (B)] ($p < .05$) and ADFI [1.32 kg (A), 1.0 kg (B)] ($p > .05$) Increase in FCR [2.08 (A), 2.43 (B)] ($p < .05$) | Schell et al. (1993b) |
| Weaned pigs ($n=81$) | 0 (A), 500 (B) $\mu\text{g}/\text{kg}$ feed (5 weeks) | Decrease in ADG [0.66 kg (A), 0.46 kg (B)] and ADFI [1.41 kg (A), 0.97 kg (B)] ($p < .05$) | Schell et al. (1993b) |
| Weaned pigs ($n=63$) | 0 (A), 800 (B) $\mu\text{g}/\text{kg}$ feed (4 weeks) | Decrease in ADG [0.63 kg (A), 0.52 kg (B)] ($p < .05$) and ADFI [1.29 kg (A), 1.02 kg (B)] ($p < .01$) | Schell et al. (1993b) |
| Nile tilapia ($n=160$) | 0 (A), 0.94 (B), 1.88 (C), 0.375 (D), 0.752 (E), 1.50 (F), 3.0 (G) mg/kg diet (25 days following with basal diet for 50 days) | Decrease in ADG and ADFI, but not FCR in 1.88 mg/kg group and higher ADG: 10.87–11.30 g (A), 7.28 g (C), 7.10 g (D), 4.78 g (E), 3.25 g (F), 3.66 g (G) ($p < .01$) ADFI: 0.143–0.160 g (A), 0.115 g (C), 0.116 g (D), 0.711 g (E), 0.052 g (F), 0.048 g (G) ($p < .01$) | Chávez-Sánchez et al. (1994) |
| Lambs ($n=44$) | 0 mg aflatoxin in soybean meal (A), 0 mg aflatoxin in fish meal (B), 2.5 mg/kg diet soybean meal (C), or 2.5 mg/kg diet fish meal (D) (35 days, followed by 32-day wash out period) | Decrease in feed intake, daily gain, in aflatoxin-fed lambs ($p < .05$) during treatment period and wash out period. ADG: 0.53 kg (A), 0.24 kg (C), 0.50 kg (B), 0.05 kg (D). ADFI: 4.19 kg (A), 2.74 kg (C), 4.05 kg (B), 1.70 kg (D) Increase in FCR in aflatoxin-fed lambs ($p < .05$) FCR: 7.6 (A), 11.2 (C), 7.6 (B), –45.5 (D) | Edrington et al. (1994) |
| Growing barrows ($n=40$) | 0 (A), 3 (B) mg/kg feed ^b (28 days) | Decrease in weight gain [19.1 ± 0.73 kg (A), 10.7 ± 1.06 kg (B)] ($p < .05$) | Harvey et al. (1994) |
| Pigs ($n=27$) | 0 (A), 2.5 (B) mg aflatoxin/kg feed, 2.5 mg of aflatoxin/kg feed + 2400 IU tocopherol (C) (32 days) | Decrease in body weight [38.4 ± 3.9 kg (A), 22.0 ± 2.0 kg (B), and 23.5 ± 3.0 kg (C)] and feed consumption [138 ± 20.0 kg (A), 41 ± 4.5 kg (B), and 45 ± 2.0 kg (C)] ($p < .05$) | Harvey et al. (1995a) |
| Pigs ($n=18$) | 0 (A), 2.5 (B) mg aflatoxin/kg, 2.5 mg of aflatoxin plus 100 mg of fumonisin B ₁ /kg of feed (C) (35 days) | Decrease in body weight [49.2 kg (A), 33.2 kg (B), 23.9 kg (C)], weight gain [31.6 kg (A), 15.8 kg (B), 6.3 kg (C)], and feed consumption per pen [153.7 kg (A), 89.0 kg (B), and 42.7 kg (C)] | Harvey et al. (1995b) |
| 1-day-old broiler chicks ($n=40$) | 0 (A), 0.5 (B) mg/kg feed (32 days) | Decrease in body weight [246.32 ± 2.14 g (A), 140.79 ± 1.31 g (B)], percentage weight gain [100% (A), 57% (B)], and total feed consumption [691.0 g (A), 590.0 g (B)] ($p < .01$) | Prabaharan et al. (1999) |
| Mule ducklings ($n=320$) | 0 (A), 200 (B) $\mu\text{g}/\text{kg}$ feed (3 weeks) | Decrease in daily feed intake [37.74 ± 2.57 g (A), 31.99 ± 0.33 g (B)] and average daily weight gain [25.29 ± 1.23 g (A), 21.24 ± 1.25 g (B)] ($p < .05$). | Cheng et al. (2001) |
| 4-week-old weanling piglets ($n=36$) | 0 (A), 240 (B), 480 (C) $\mu\text{g}/\text{kg}$ feed (30 days) | Decrease in ADG [489 \pm 18 g (A), 453 \pm 12 g (B), 326 \pm 17 g (C)] ($p < .05$) | Marin et al. (2002) |
| 7-week-old Japanese quail feed (AFB ₁) ($n=256$) | 0 (A), 25 (B), 50 (C), or 100 (D) $\mu\text{g}/\text{kg}$ (168 days) | Decrease in ADFI groups exposed to 50 and 100 μg AFB ₁ /kg [28.69 ± 2.17 g (A), 27.57 ± 1.81 g (C), 27.76 ± 1.85 g (D)] ($p < .05$) No effect: Average egg production, feed use, and body weights ($p > .05$) | Oliveira et al. (2002) |

Table 2. continued on next page

Table 2. Continued.

| Animal | Aflatoxin dose and duration of experiment | Results | Study |
|--|--|---|-------------------------|
| 6-week-old male Swiss albino mice ($n=70$) | 0 μg AFB ₁ + 5% protein diet (A), 0 μg AFB ₁ + 20% protein diet (B), 0.5 μg AFB ₁ /day + 5% protein diet (C), 0.5 μg AFB ₁ /day + 20% protein diet (D) (7 weeks) | Percent weight gain increases per dose: 4% (A), 18.2% (B), 7.2% (C), and 12.2% (D). Decrease in percent weight gain ($p < 0.001$) in aflatoxin + 20% protein-fed mice (D) compared with no-aflatoxin + 20% protein-fed mice (B), but no significant difference of total protein and albumin levels between aflatoxin-treated and non-aflatoxin-treated mice ($p > 0.05$). | Kocabas et al. (2003) |
| 1-day-old broiler chicks ($n=48$) | 0 (A), 5 (B) mg/kg of AFB ₁ in feed (3 weeks) | Decrease in weight gain [866 \pm 12.7 g (A), 699 \pm 38.5 g (B)] ($p < .05$) and feed intake [1369 \pm 45.7 g (A), 957 \pm 183.5 g (B)] ($p < .05$)] No change in FCR | Pimpukdee et al. (2004) |
| Cherry Valley commercial ducks ($n=90$) | 0 (A), 20 (B), or 40 (C) $\mu\text{g}/\text{kg}$ AFB ₁ -contaminated rice (6 weeks) | Decrease in ADG in 20 and 40 $\mu\text{g}/\text{kg}$ AFB ₁ -treated groups [48.21 \pm 2.5 g (A), 42.52 \pm 2.5 g (B), and 37.44 \pm 2.7 g (C)], and feed intake in the high-dose group [142.20 \pm 4.6 g (A), 130.28 \pm 3.5 g] Increase in FCR in both aflatoxin-treated groups [2.95 \pm 0.02 (A), 3.31 \pm 0.04 (B), 3.48 \pm 0.04 (C)] ($p < .05$) | Han et al. (2008) |

Note. Letters (e.g., A, B, C, D) represent different dose groups.

^aEight of 15 pigs with 4.0 mg/kg feed suffered severe morbidity, hemorrhage, or death.

^bAflatoxin content consists of 79% AFB₁, 16% AFG₁, 4% AFB₂, and 1% AFG₂.

NA = not available, only animals referred in "aflatoxin dose and duration" were counted for sample size.

Table 3. Studies showing an association between aflatoxin exposure in utero and reduced growth in baby animals.

| Animal | Aflatoxin dose and duration of experiment | Results | Study |
|---|---|--|--------------------------------|
| Rats ($n=25$) | 0 ($n=NA$), 1 mg crystalline aflatoxin in 0.1–0.2 ml of dimethylformamide (dosed orally as single dose at day 6 [$n=6$], days 6–12 [$n=10$], and day 16 of gestation [$n=9$]) | Decrease in fetal weight ($p < .01$) in offspring rats born from mothers given aflatoxin in late pregnancy [4.75 \pm 0.059 g (untreated), 3.81 \pm 0.066 g (day 16 group)] | Butler and Wigglesworth (1966) |
| Hamster ($n=40$: 16 control, 24 tested) | 4 or 6 mg/kg of crystalline AFB ₁ by IP injection on days 8 and 9 of pregnancy | Decrease in fetal growth in offspring hamster by 0.5–0.7 cm differences in length ($p < .01$) | Schmidt and Panciera (1980) |
| 2–3 years old sows and their piglets ($n=24$) | 0 (A), 800 $\mu\text{g}/\text{kg}$ AFG ₁ (B), 800 $\mu\text{g}/\text{kg}$ AFB ₁ (C), 800 $\mu\text{g}/\text{kg}$ AFG ₁ + 800 $\mu\text{g}/\text{kg}$ AFB ₁ (D) (days 60 of pregnancy to days 28 of lactation) | Decrease in piglets' body weight in AFB ₁ -treated groups, but not in AFG ₁ -treated group: [6.51 \pm 0.42 g (A), 5.66 \pm 0.39 g (B), 5.32 \pm 0.63 g (C), 5.25 \pm 0.44 g (C)] ($p < .05$, and $< .005$ for C and D groups, respectively) | Mocchegiani et al. (1998) |
| Rat, pregnant and offspring ($n=30$, 10 of each three groups) | 0 (A), 0.3 mg/kg/day AFB ₁ dissolved in dimethylsulfoxide subcutaneously on days 11–14 (B) or 15–18 (C) of gestation | Decrease in mean birth weights in both male and female offspring treated with AFB ₁ [Male: 5.7 \pm 0.1 (A), 5.1 \pm 0.1 (B), 4.7 \pm 0.3 (C); Female: 5.4 \pm 0.1 (A), 4.9 \pm 0.1 (B), 4.7 \pm 0.3 (C)] ($p < .05$), decrease in number of live births in the group exposed to AFB ₁ on days 15–18 [15.2 \pm 0.5 (A), 12.9 \pm 0.9], delayed physical development, and delayed behavioral developments during preweaning period, impaired locomotor coordination, and deficits in avoidance performance in postweaning period | Kihara et al. (2000) |
| 7-week-old Japanese quail ($n=256$) | 0 (A), 25 (B), 50 (C), or 100 (D) $\mu\text{g}/\text{kg}$ feed (AFB ₁) (168 days) | Decrease in egg weight ($p < .05$) in groups exposed to 50 and 100 μg AFB ₁ /kg [10.67 \pm 0.24 (A), 10.53 \pm 0.21 (C), 10.51 \pm 0.21 (D)] Increase in percent shell of total egg weight ($p < .05$) in 100 μg AFB ₁ /kg fed group | Oliveira et al. (2002) |

Note. Only animals referred in "aflatoxin dose and duration" were counted for sample size.

rates of aflatoxins in maternal blood samples (53% and 75%) compared with cord blood (37% and 58%). By contrast, aflatoxins (AFB₁, AFG₁, AFG₂) were detected with much greater frequency in Thai cord blood samples (17 of 35) compared with the maternal blood samples (2 of

35), indicating transplacental transfer of aflatoxins from mothers to fetuses (Denning et al., 1990). However, low transplacental transfer of AF-alb or low efficiency of fetal metabolism to change free aflatoxins to the AF-alb form has been suggested, because of the much greater

levels (up to 10 times) of AF-alb in the venous blood of Gambian mothers compared with those in matched cord blood samples (Wild et al., 1991).

One study conducted to determine the efficacy of fetal-specific cytochrome P450 3A7 (CYP3A7) and adult-specific CYP3A4 in hamster rat found similar level of enzyme expressions to activate AFB₁ in both CYP3A lines (Hashimoto et al., 1995). An *in vitro* study was conducted in guinea pigs to compare the formation rates of aflatoxin-DNA adduct and AF-alb between adult and second trimester prenatal livers. Whereas lower expression of two aflatoxin detoxification enzymes, microsomal epoxide hydrolase and polymorphic glutathione S-transferase, and higher expression of lipooxygenase—an enzyme that can activate AFB₁ to form AFB₁-DNA adduct (Liu and Massey, 1992)—were detected in prenatal livers compared with adult livers, the formation rates of DNA adducts and protein adducts in prenatal livers and adult livers were not different (Doi et al., 2002). Recently, a human *in vitro* study showed that AFB₁ was metabolized by human placentas to aflatoxicol, a less mutagenic but equally carcinogenic metabolite of AFB₁ (Partanen et al., 2010). However, fetal metabolism can be greatly different from adult metabolism as a result of reduced hepatic blood flow and incomplete hepatic formation. Still, little is known about biotransformation of aflatoxins in fetuses, and further studies are needed.

The presence of aflatoxins, particularly AFM₁, in maternal breast milk in several regions indicates that children worldwide may be exposed to aflatoxins through breastfeeding. Though AFM₁ was found in none of the breast milk samples from French (Wild et al., 1987) and German (Somogyi and Beck, 1993) mothers, about 30% to 60% of breast milk samples from Sudanese (Coulter et al., 1984), Kenyan (Maxwell et al., 1989), Ghanaian (Lamplugh et al., 1988; Maxwell et al., 1989), and Egyptian (Polychronaki et al., 2006, 2007) mothers contained detectable levels of aflatoxins. In Sierra Leone, 99 of 113, or 88%, of breast milk samples from mothers contained detectable levels of aflatoxins (Jonsyn et al., 1995b). However, only 11% of the breast milk samples from Zimbabwean mothers (Wild et al., 1987) and 5% of breast milk samples from mothers in Cameroon (Tchana et al., 2010) were AFM₁ positive. It is worthwhile to note that the detectable AFM₁ levels are inconsistent across countries, which implies that the marker may be unreliable with linking to growth impairment. However, these studies imply that lactating mothers are exposed to aflatoxin and can transfer it to their babies through breastfeeding.

In Asia and the Middle East, AFM₁ was detected in 20 out of 91 breast milk samples of Iranian mothers, with the mean concentration of 6.96 ± 0.94 pg/ml (Mahdavi et al., 2010). About 45% of Thai mothers had detectable AFM₁ in breast milk, with a median concentration of 664 pg/ml. The AFM₁ levels in Thai mothers ranged from 39 to 1736 pg/ml (el-Nezami et al., 1995). Very high percentages of the UAE mothers—more than

90%—had detectable levels of AFM₁ in the breast milk (Abdulrazzaq et al., 2003; Saad et al., 1995). Whereas two prior studies detected aflatoxins in only 1 of 231 (0.4%) and 8 of 61 (13%) breast milk samples from Turkish mothers (Keskin et al., 2009, Turconi et al., 2004), aflatoxins were detected in all of 75 breast milk samples from the lactating Turkish mothers in a more recent study (Gurbay et al., 2010). This discrepancy may have many causes, including differences in analytical methods, differences in study populations, or issues of seasonality.

Gong et al. (2003, 2004) found that in Benin and Togo childhoods, AF-alb levels increased with age until 3 years old. This trend reflected the transitioning of children from breastfeeding to weaning and postweaning foods. Children who were completely weaned had higher levels of AF-alb than breastfed or partially breastfed children.

Because of multiple routes of exposure beginning from the fetal environment, high percentages of children in various countries have been exposed to aflatoxins, as detected in multiple studies. About 85% to 100% of children in African countries, such as Gambia, Guinea, Kenya, Benin, Togo, and Senegal, had either detectable levels of serum AF-alb or urinary aflatoxins (Gong et al., 2003, 2004; Polychronaki et al., 2008; Turner et al., 2000, 2003, 2005; Wild et al., 1990, 1993). Levels of AF-alb in children from industrial nations are typically significantly lower than those living in less developed countries. Wild et al. (1990) found AF-alb levels as high as 350 pg/mg in almost all sera of children in various African countries. By contrast, none of the French or Polish sera contained AF-alb at levels higher than 5 pg/mg albumin (Wild et al., 1990).

The seasonality of sampling has been addressed in a number of studies (Abulu et al., 1998; Hsieh and Hsieh, 1993; Jonsyn-Ellis, 2001; Lamplugh et al., 1988; Maxwell et al., 1989; Polychronaki et al., 2007; Turner et al., 2000; Wild et al., 1990). Many studies had detected aflatoxins in human body fluids more often in the wet season than the dry season. Some of them include the studies that determined aflatoxins in the cord blood samples from Kenya and Nigeria neonates (Abulu et al., 1998; Maxwell et al., 1989), AFM₁ in the breast milk of Ghanaian mothers (Lamplugh et al., 1988), and aflatoxins in the Taiwanese breast milk samples (Hsieh and Hsieh, 1993). Similarly, AFB₁, AFB₂, AFG₁, and aflatoxicol were detected more often in the urine samples of Sierra Leone children collected during the rainy season, compared with the dry season (Jonsyn-Ellis, 2001). On the other hand, in two Gambian studies, AF-alb was detected more frequently in the serum of Gambian children collected during the dry season than the wet season (Allen et al., 1992; Turner et al., 2000). Aflatoxin development in storage, after groundnuts had been harvested at the end of the wet season, was expected to be the cause of the elevated levels of AF-alb in the dry season (Turner et al., 2000; Wild et al., 2000).

B. Past studies on aflatoxin and kwashiorkor

An area of inquiry that had gained notice several decades ago concerned the possible link between aflatoxin exposure and childhood kwashiorkor, a disease of protein energy malnutrition. Both kwashiorkor and marasmus (another childhood condition common in less developed countries) are diseases of severe malnutrition. Although protein deficiency is a major etiology of either kwashiorkor or marasmus, one key difference between these two conditions is that kwashiorkor can occur even when caloric intake of the children is sufficient, whereas marasmus can be caused by deficient caloric intake. Children with marasmus are less likely to suffer from fatty liver or edema—classical manifestations of kwashiorkor. Other symptoms of kwashiorkor include light-pigmented hair and skin and anorexia (Manary et al., 1998). An individual with edema from kwashiorkor and wasting from marasmus is considered to have marasmic kwashiorkor (Collins, 2000). Whereas marasmus is sometimes perceived as an adaptive response to starvation, kwashiorkor is considered a maladaptive response to undernourishment (Manary et al., 1998; Scheinfeld and Mokashi, 2010; Shashidhar and Grigsby, 2009).

Since the 1980s, several studies have examined the possible association between aflatoxin exposure and kwashiorkor (Hendrickse et al., 1982; Lamplugh and Hendrickse, 1982; Coulter et al., 1986; De Vries et al., 1987; Oyelami et al., 1997; Hatem et al., 2005; Tchana et al., 2010). These studies found that aflatoxins or their metabolites were detected with greater frequency in the blood or urine of children with kwashiorkor than in healthy children or children with other protein malnutrition-related conditions, such as marasmus. Moreover, aflatoxins were detected more frequently (but not at statistically significant levels) in autopsies of lungs and livers, but not in kidneys, of children who died from kwashiorkor, compared with those who died from other diseases or other forms of malnutrition (Lamplugh and Hendrickse, 1982; Oyelami et al., 1997, 1998). It is worthwhile to note that only seven liver specimens were included in Lamplugh and Hendrickse (1982)—three from kwashiorkors, three from marasmic kwashiorkors, and one from marasmic children.

Other factors could explain these phenomena, however. In a study conducted in a hospital in Durban, South Africa (Ramjee et al., 1992), children with kwashiorkor were matched with controls with no symptoms of protein energy malnutrition. Aflatoxins were detected in the serum and/or urine of all children. The serum/urine ratio was significantly higher in the kwashiorkor group; the controls, however, had a higher proportion of urine aflatoxins than the kwashiorkor group. These findings may reflect impaired liver function in kwashiorkor, which could in turn lead to differences in how aflatoxin is metabolized, rather than aflatoxin is playing any direct role in causing kwashiorkor. Indeed, it has been proposed that children who suffer from kwashiorkor are at greater risk to the hazards of dietary aflatoxin (Shephard, 2008).

C. Aflatoxin and growth impairment in children

Various studies have demonstrated that aflatoxin exposure, through a variety of sources as described above (in utero, through maternal breast milk, and in weaning diets), is linked with growth impairment. Table 4 summarizes the studies that have shown an association between aflatoxin exposure and various measures of growth impairment in human children.

The studies that examined these associations were conducted primarily in the Middle East and in Africa. In a study in the United Arab Emirates, Abdulrazzaq et al. (2004) detected AFM₁ in 100% (43 of 43) of neonates born with low birth weights, but only in 55% (68 of 123) of neonates with normal birth weight. Aflatoxin levels in the cord blood and maternal blood samples were inversely associated with weight at birth ($r = -.565$, $p = .001$ and $r = -.654$, $p = .0001$) (Abdulrazzaq et al., 2004).

Two recent Iranian studies have linked AFM₁ levels in mothers' breast milk with growth impairment in babies. AFM₁ was found in 157 of 160 (98%) of breast milk samples collected from Iranian mothers living in Tehran, with concentrations ranging from 0.3 to 26.7 ng/kg. The levels of AFM₁ in breast milk were inversely correlated with length of infants at birth ($p < .01$) (Sadeghi et al., 2009). Though the mean AFM₁ levels are very low, it is likely that children born to mothers whose breast milk had these levels were exposed to aflatoxin in utero, which may affect birth length. Another study collected breast milk from mothers living in urban areas of Tabriz and its surrounding rural areas. Only 22% of breast milk samples from mothers in the rural surroundings of Tabriz contained detectable levels of AFM₁, ranging from 5.1 to 8.1 pg/ml. None of the breast milk samples from mothers living in urban areas of Tabriz were found to have AFM₁. There was a significant inverse relationship between AFM₁ levels in maternal breast milk and the height-for-age z-scores (HAZ) in infants 90–120 days old ($\beta = -.31$, $p < .015$). The children whose mothers were AFM₁ positive had lower HAZ and weight-for-age z-scores (WAZ) than children born to mothers with no detectable AFM₁ (Mahdavi et al., 2010).

In Africa, studies associating aflatoxin exposure with growth impairment in children were conducted in Kenya and several West African nations. In an early study on 125 babies in rural Kenya (De Vries et al., 1989), aflatoxins were detected in 53% of mothers' blood, and the mean birth weight of females born to mothers whose blood tested positive for aflatoxin was significantly lower (255 g) than those born to mothers with no aflatoxin detected in the blood. Additionally, the two recorded stillbirths were both to mothers who tested positive for aflatoxins.

A series of studies conducted in Togo and Benin in the early 2000s provides insightful information into the cross-sectional, longitudinal, and dose-response aspects of the association between aflatoxin exposure and childhood growth impairment (Gong et al., 2002, 2003, 2004). In a cohort of 480 children aged 9 months to 5 years in these two countries, the prevalence of stunting and

Table 4. Human studies of the effects of aflatoxin on growth impairment.

| Country/Study population | Results | Study |
|--|---|---------------------------|
| Benin/Children ages 16–37 months ($n=200$) | Significant negative correlation ($p<.0001$) between AF-alb adduct and height increase over 8-month study period A mean 1.7 cm reduction difference in growth over 8 months in the AF-alb adduct highest quartile, compared with the lowest quartile No association between AF-alb and micronutrient levels | Gong et al. (2004) |
| Benin and Togo/Children ages nine 9 months to five 5 years ($n=480$) | Negative correlation between individual AF-alb adduct and HAZ, WAZ, and WHZ ($p=.001, .005, .047$, respectively) Factors influence AF-alb adduct level: age (up to 3 years) and weaning status ($p=.0001$) Twofold higher mean AF-alb adduct levels in weaned children than those receiving a mixture of breast milk and solid foods after adjustment for age, sex, agroecological zone, and socioeconomic status | Gong et al. (2002, 2003) |
| Children ages 6 to 9 years old ($n=472$) | 93% AF-alb adduct detection rate Geometric mean level = 22.3 pg/mg; range 5–456 pg/mg Significant association between AF-alb adduct and WHZ ($p=.034$) Significant lower levels of sIgA in children with detectable AF-alb adduct compared with those with nondetectable levels (50.4 μ g/mg protein [95% CI: 48.0, 52.8] and 70.2 μ g/mg protein [95% CI: 61.1, 79.2], respectively, $p<.0001$) | Turner et al. (2003) |
| Gambia/Infants to 1-year-olds ($n=138$) | The geometric mean AF-alb adduct levels = 40.4 pg/mg (4.8–260.8), 10.1 pg/mg (5.0–189.6), and 8.7 pg/mg (5.0–30.2) in maternal, cord, and infant blood, respectively Associations between the reduction of maternal AF-alb from 110 to 10 pg/mg and 0.8 kg increase in weight and 2 cm increase in height of children within first year of life AF-alb adduct in maternal blood as a strong predictor of both weight ($p=.012$) and height ($p=.044$) gain, with lower gain in those with higher exposure | Turner et al. (2007) |
| Ghana/Pregnant women and their infants ($n=785$) | Odds ratio of having low-birth-weight babies in the highest AF-alb adduct quartile mothers = 2.09 ($p=.007$) | Shuaib et al. (2010) |
| Iran/Lactating mothers ($n=160$: 7 preterm delivery mothers, and 153 with full-term infants) | 98% (157 of 160 breast milk samples) AFM ₁ positive detection rate (average concentration: 8.2 \pm 5.1 ng/kg, range: 0.3–26.7 ng/kg) Significant association between AFM ₁ in maternal breast milk and height at birth of infants ($p<.01$) | Sadeghi et al. (2009) |
| Iran/Lactating women ($n=182$: 91 from urban areas in Tabriz and 91 from rural area) | 22% and 0% detection rates of AFM ₁ in breast milk of mothers living in rural areas, and urban areas, respectively AFM ₁ : 6.96 \pm 0.94 pg/ml Significant association between the HAZ of infants and maternal AFM ₁ ($p<.015$) Significant lower scores in HAZ and WAZ of infants born to AFM ₁ -positive mothers ($p<.05$) | (Mahdavi et al., 2010) |
| Kenya/Children ages 3–36 months ($n=242$) | Significant association between numbers of children who were wasted and were being fed flour contaminated with aflatoxin ($p=.002$) | Okoth and Ohingo (2004) |
| UAE/Pair maternal–cord blood samples from women admitted 1995–1998 ($n=166$ pairs) | 100% cord blood AFM ₁ detection rate in low birth weight neonates VS 55% detection rate in normal weight neonates Strong negative correlation between the levels of AFM ₁ in cord blood and maternal serum AFM ₁ , and birth weights ($r=-.565, p=.001$; and $r=-.654, p=.0001$) | Abdulrazzaq et al. (2004) |

Note. AF-alb = aflatoxin albumin adduct; HAZ = height-for-age z-score; WAZ = weight-for-age z-score; WHZ = weight-for-height z-score.

underweight were reported to be 33% and 29%, respectively (Gong et al., 2002, 2003). AF-alb was detected in 99% of the children, with a geometric mean level of 32.8 pg/mg (95% confidence interval [CI]: 25.3, 42.5). Clear dose-response relationships were found between mean AF-alb levels and lower HAZ and WAZ scores. Children who were stunted (HAZ ≤ -2) had 30–40% higher mean AF-alb levels compared with non-stunted children. Household socioeconomic status and maternal education were not significantly associated with AF-alb levels

in children. There was no consistent pattern between the socioeconomic status of the mothers and the adduct levels in the children (Gong et al., 2002, 2003). A subsequent 8-month longitudinal study in 200 children aged between 16 and 37 months in Benin showed a significant negative association between height velocity, but not weight, and mean AF-alb levels (Gong et al., 2004). A difference of 1.7 cm over the 8-month study period in adjusted height between the highest and lowest AF-alb quartile was observed.

Unlike Gong et al. (2002), a study in Gambia on a cohort of 472 children between 6 and 9 years old did not find that AF-alb levels were associated with HAZ or WAZ (Turner et al., 2003). It is noteworthy that the participants in the Gambian study were born during the implementation of a 5-year maternal supplementation program, in which pregnant mothers were given two groundnut biscuits daily, which provided 4250 kJ, 22 g protein, 56 g fat, 47 mg calcium, and 1.8 mg iron per day to the mothers (Moore et al., 2001). However, a subsequent study did find an association between in utero aflatoxin exposure and growth impairment. Following 138 Gambian neonates for 1 year, Turner et al. (2007) found a significant association between aflatoxin exposure in mothers during pregnancy and height and weight gain of their infants in the first year of life. They concluded that if the maternal AF-alb levels dropped from 110 to 10 pg/mg, the weights and heights of 1-year-old infants would increase by 0.8 kg and 2 cm on average, respectively (Turner et al., 2007).

In a study in the Kisumu District of Kenya (Okoth and Ohingo, 2004), weaning flours from 242 households with children aged 3–36 months were analyzed for aflatoxins. The weights and heights of the children were measured to determine prevalence of stunting, underweight, and wasting. Although only 28% of non-wasted children were from households with aflatoxin-contaminated flour, about 54% of the wasted babies were from households with detectable aflatoxin in the flour. There was a significant association between aflatoxin exposure and wasting ($p = .002$). Aflatoxins were also more frequently detected in the flour of stunted and underweight children compared with normal children. However, these differences were not statistically significant (Okoth and Ohingo, 2004).

In a recent cross-sectional study, Shuaib et al. (2010) found levels of AF-alb ranging from 0.44 to 268.73 pg/mg in maternal blood samples from 755 Ghanaian mothers. After adjusting for sociodemographic variables, it was found that the mothers in the highest quartile of AF-alb levels were at significantly higher risk of having babies with low birth weight, defined as being below 2.5 kg (odds ratio [OR] = 2.09). There were also increased odds of having preterm deliveries and stillbirths with mothers who had AF-alb in the highest quartile, though the associations between AF-alb and these risk factors were not statistically significant (Shuaib et al., 2010).

IV. Childhood weaning foods

A focus of interventions to reduce aflatoxin exposure in childhood could be on improving the quality and composition of weaning foods. In Africa and Latin America, childhood weaning foods are usually prepared from maize (NRC, 1988), which can lead to high aflatoxin exposures early in life. Several maize-based foods such as gruel, ogi (fermented maize gruel), pap (maize porridge), and eko—boiled and gelatinized ogi (Dako, 1985)—are used as weaning foods in Africa. Groundnuts can also

be commonly used as a weaning food in various African regions.

The weaning process in the West African countries starts in many cases at early ages, when the children are about 3–6 months old (Mosha and Svanberg, 1983). Up to 50% of children in Makurdi, Nigeria, consume pap as their main weaning food, followed by Cerelac, a commercial infant formula (26.5%), and pap mixed with other food (11%) (Igbedioh et al., 1995). Weaning foods in West Africa are usually made of maize, groundnuts, sorghum, millet, and guinea corn (Onofiok and Nnanyelugo, 1998). Likewise, maize is a major weaning food in some countries in East Africa. In Uganda, 89% of children are fed maize porridge regularly. About 24.5% of children aged 3 to 28 months have maize porridge 7 days a week (Kikafunda et al., 2003). Gruels prepared from maize are used as weaning foods in Kenya (Onyango et al., 1998), Tanzania (Mosha and Svanberg, 1983), and Ethiopia (Selinus, 1970). Other staple crops are also used to prepare weaning foods in these East African countries. Some of them include sorghum in Tanzania, sorghum and millet in Kenya, and barley and wheat in Ethiopia. Sorghum porridge (nasha) is a traditional weaning food in Sudan (Dicko et al., 2006).

Many children in Latin America also consume large amounts of maize in their weaning diets, which can increase aflatoxin exposure. Maize-based gruels are among several kinds of Brazilian weaning foods, which also include rice flour or cassava flour-based gruels, cassava, sugar, and diluted milk (Simmons, 1976). Maize tortillas consumed with milk, beans, bread, pasta, fruit, chicken soup, flavored gelatin, or soft drinks are commonly used as weaning foods in Mexico (Lipsky et al., 1994).

Weaning foods in Asia vary substantially from region to region. Weaning foods in China are whole eggs, vegetables and fruits, porridge (rice, maize, or wheat), and infant formula (He and Zhai, 2001; Li et al., 2003; Platt and Gin, 1938; Wang et al., 2005). Maize and even rice are contaminated with aflatoxin in many parts of China (Groopman et al., 1992; Li et al., 2001; Liu et al., 2006; Wang and Liu, 2006; Yeh et al., 1989). In 1992, maize consumption among residents of Guangxi, where HCC prevalence is among the highest in the world, was as high as 350–500 g/day (Groopman et al., 1992). In India, children may be weaned on various kinds of food: formula, porridges (maize, rice, millet, etc), commercial cereals, pulses, fruit, rice with milk and/or ghee, roti, and potatoes (Khan, 1990; Rao et al., 1959; Sinha and Kumar, 1991). Nepalese children are weaned on porridge and animal milk at ages of 2.5–6.5 months. Thai weaning foods include rice-based food, fruit juice, fruit, meat, fish, and vegetable soup (Jackson et al., 1992; Ramjee et al., 1992).

Because aflatoxin exposure in children increases markedly following weaning (Gong et al., 2003) and is associated with multiple adverse health outcomes, reducing aflatoxin levels in weaning foods is crucial

in high-risk regions of the world. Interventions could include dedicating cleaner maize and groundnuts to weaning foods, or provision of weaning foods that contain wide varieties of food crops instead of few food crops.

V. Discussion

Growth impairment in children is a pervasive public health problem in low- and middle-income countries worldwide, and is associated with a wide variety of factors such as poor nutrition, poor hygiene, socioeconomic status, local political instability, repeated infectious diseases, and environmental toxins (Black et al., 2008). Aside from adverse health effects associated with childhood growth impairment, such as cognitive impairment and increased risk of infectious diseases and death, there are also economic consequences: childhood undernutrition as indicated by stunting has been associated with lower human capital in low- and middle-income countries (Victora et al., 2008). Stunting, wasting, or underweight is associated with increased mortality risks in childhood (Black et al., 2008). Reducing risk factors for growth impairment in children aged under 5 could be a way: One of the eight goals to improve socioeconomic and human health, endorsed by the leading international organizations and world leaders in 2000, is to reduce mortality rate among children aged under 5, by two thirds in 2015 (UNDP, 2010). Reducing risk factors for growth impairment in children aged under 5 can be another way, along with other interventions, to achieve this goal.

Among the risk factors associated with growth impairment, aflatoxin emerges as playing a potentially important contributory role. The weight of evidence linking aflatoxin with growth impairment has been increasing over the last five decades of research: first primarily in animal studies, and in the last decade increasingly in epidemiological studies. When considering the Bradford Hill criteria for causality (Hill, 1965), the recent epidemiological studies have provided useful supporting evidence. When controlling for other socioeconomic and environmental factors, the strength of association between aflatoxin and stunting and underweight is strong. Moreover, the dose-response relationship between aflatoxin exposure and growth impairment is monotonically increasing (Gong et al., 2002), which is consistent with a causal effect, although other confounding factors cannot be excluded (Wild and Gong, 2010). Animal and epidemiological studies are concordant in their findings.

One critical piece of information that is currently unavailable is a mechanism by which aflatoxin causes growth impairment in humans and animals. If such a mechanism could be elucidated, then the weight of evidence linking aflatoxin with growth impairment would become even stronger. Though this exact mechanism has yet to be identified, several have been proposed. One is that immunomodulation associated with aflatoxin

exposure (Bondy and Pestka, 2000; Turner et al., 2003) can cause recurrent infections in children, which can lead to growth impairment (Gong et al., 2008). Another is that changes in intestinal integrity (possibly in part resulting from immunomodulation) could make hosts more vulnerable to intestinal foreign microbes (Gong et al., 2008). Other possible mechanisms include down-regulation of genes associated with energy production and fatty acid metabolism (Yarru et al., 2009), impairment of protein synthesis and the inability to mobilize fat (Kocabas et al., 2003), and changes in hepatic metabolism of vitamins and micronutrients (Schaeffer and Hamilton, 1991).

Given the increasingly strong evidence that aflatoxin contributes to growth impairment in children, and the knowledge that it is a common contaminant of weaning foods in many parts of the world where childhood stunting is prevalent (e.g., sub-Saharan Africa and Asia), it is important to attempt to reduce aflatoxin exposure in foods consumed by children. Multiple aflatoxin control strategies have been developed to lower aflatoxin exposure by reducing aflatoxin development in fields, during storage, or reducing aflatoxin bioavailability. We previously reviewed the cost and efficacy of various types of aflatoxin control methods (Khlanguis et al., 2010), and reported that at least two aflatoxin control interventions were cost-effective in reducing aflatoxin in maize in Nigeria and groundnuts in Guinea, respectively (Wu and Khlanguis, 2010a). However, implementing aflatoxin control interventions needs extensive involvement from multiple stakeholders, from the levels of individuals to national and international institutions. Moreover, in the parts of the world where they are most needed, aflatoxin risk-reduction interventions must be evaluated for feasibility: safety, standardizability, characteristics of delivery, requirements on government capacity, and usage characteristics, among other factors (Wu and Khlanguis, 2010b). In summary, aflatoxin appears to play a contributory role in growth impairment in both children and animals. In children, aflatoxin exposure is especially problematic in parts of the world where maize and groundnuts are dietary staples. Childhood exposure to aflatoxin can occur in utero, in mothers' breast milk, and particularly in weaning foods. Aflatoxin-associated growth impairment can, in turn, contribute to increased risk of mortality and morbidity in children worldwide. Strategies should focus on reducing aflatoxin exposure in children and mothers' diets, in ways that are cost-effective and technically feasible in parts of the world where aflatoxin risks are especially high.

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