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Mycotoxin control in low- and middle-income countries

Chidozie Amuzie, Ranajit Bandyopadhyay, Ramesh V. Bhat, Robert Black, Hester Burger, Kitty F. Cardwell, Wentzel Gelderblom, Yun Yun Gong, John D. Groopman, Martin Kimanya, et al.

To cite this version:

Chidozie Amuzie, Ranajit Bandyopadhyay, Ramesh V. Bhat, Robert Black, Hester Burger, et al.. Mycotoxin control in low- and middle-income countries. CHRISTOPHER P. WILD, J. DAVID MILLER, AND JOHN D. GROOPMAN, 978-92-832-2510-2, 54 p., 2016, 978-92-832-2510-2. hal-01604308

HAL Id: hal-01604308

https://hal.science/hal-01604308

Submitted on 5 Jun 2020

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IARC WORKING GROUP REPORTS

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EDITED BY CHRISTOPHER P. WILD,
J. DAVID MILLER, AND JOHN D. GROOPMAN

IARC WORKING GROUP
REPORT NO. 9

International Agency for Research on Cancer
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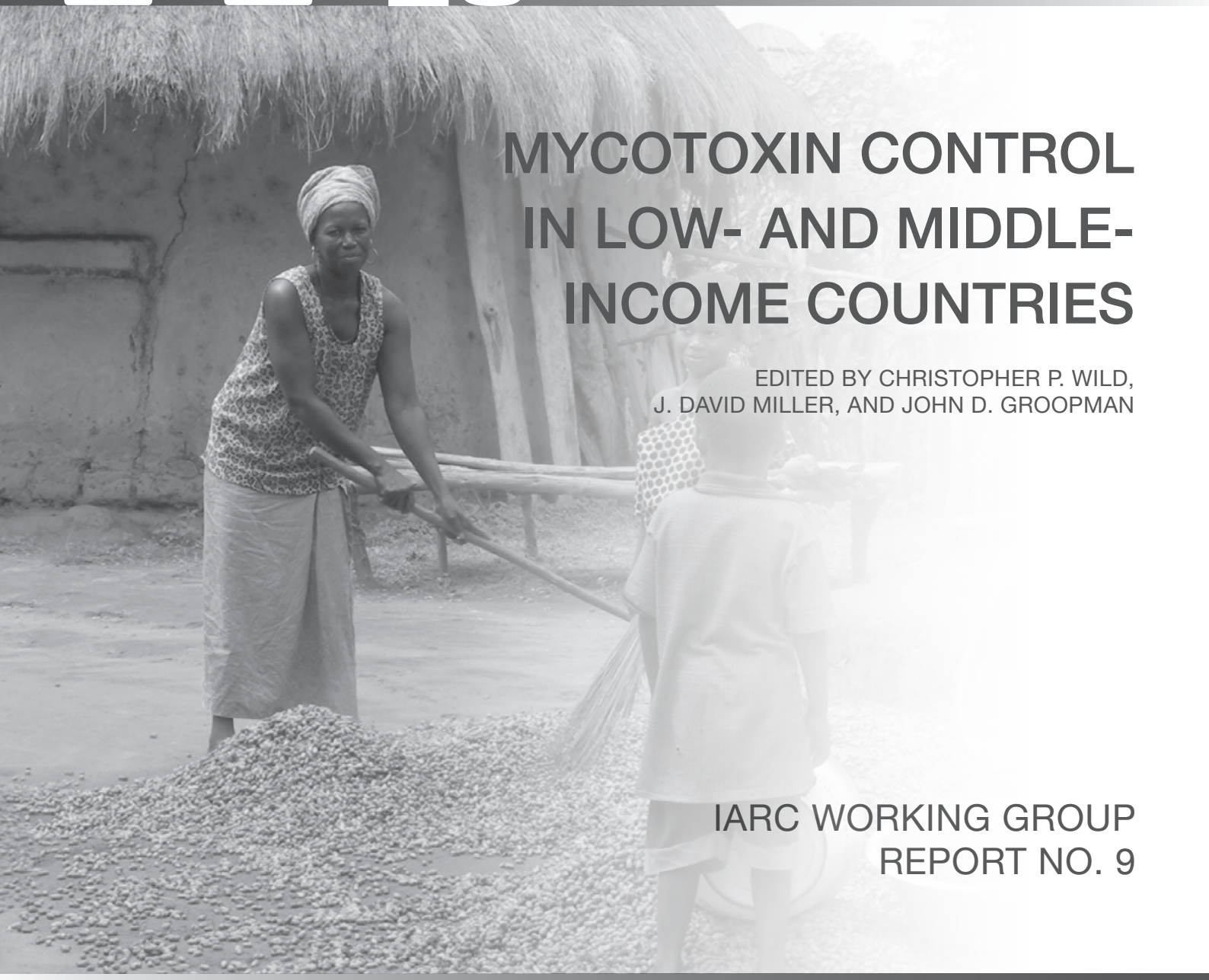
IARC WORKING GROUP REPORTS



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International Agency for Research on Cancer
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Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

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Distributed by
WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

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Cover image: Spreading groundnuts for sun-drying prior to storage in Guinea (Credit: C.P. Wild/IARC).

This book is also available in electronic format from
http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk9/index.php.

IARC Library Cataloguing in Publication Data

Mycotoxin control in low- and middle-income countries / edited by Christopher P. Wild, J. David Miller, John D. Groopman

(IARC Working Group Reports; 9)

1. Mycotoxins 2. Aflatoxins – adverse effects 3. Fumonisins – adverse effects 4. Developing Countries 5. Food Contamination – prevention and control 6. Growth Disorders – epidemiology 7. Liver Neoplasms – prevention and control
I. IARC Working Group Reports II. Series

ISBN 978-92-832-2510-2 (NLM Classification: W1)

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Acknowledgements

The production of this IARC Working Group Report was partially funded by a grant from the Bill & Melinda Gates Foundation to IARC.

Thanks go to Reetta Holmila, Rosita Accardi-Gheit, Susan Haver-Legros, and Laurence Marnat for their support at the Working Group meeting and during the preparation of this Report.

The meeting was the occasion to present the IARC Medal of Honour (2010) to Professor Gerald Wogan in person, to recognize his lifetime contribution to understanding the role of aflatoxins in human liver cancer.

Executive summary

An estimated 500 million of the poorest people in sub-Saharan Africa, Latin America, and Asia are exposed to mycotoxins at levels that substantially increase mortality and morbidity (Pitt et al., 2012). The problem is not newly recognized. Shortly after the discovery of aflatoxins, the impact on child health was brought into immediate focus. After the reporting of several deaths in children in Africa due to consumption of aflatoxin-contaminated meal, a decision was made in 1966 by the FAO/WHO/UNICEF Protein Advisory Group to set a limit of 30 ppb aflatoxin in protein supplements made from groundnuts (Anonymous, 1966). In contrast to the situation today, in 1966 throughout most of Africa the proportion of calories from maize was modest, with a greater proportion coming from sorghum, millet, and cassava.

The International Agency for Research on Cancer (IARC) of the World Health Organization convened a Working Group Meeting in Lyon from 30 June to 3 July 2014. This IARC Working Group Report provides a systematic, independent review of the scientific evidence base on the adverse health effects from aflatoxin and fumonisin exposure through consumption of contaminated maize and groundnuts. An evaluation is provided of interventions, available on an individual and a community level, to reduce human exposure and disease. Therefore, this Report provides an authoritative basis for action at an international level, enabling decision-makers to invest with confidence in effective strategies to save lives. It also provides guidance on additional critical studies needed to yield further evidence of the merit of specific intervention approaches.

The Working Group addressed current scientific knowledge in four key areas: the extent of exposures to aflatoxin and fumonisin; the effects on prenatal, infant, and child health; relevant mechanistic information; and effective intervention strategies in low-income settings. In the past, the focus has largely been on the impact of aflatoxin on cancer risk. Considering several recent studies, mainly in Africa, this Report also considers the potentially far greater burden of growth faltering after weaning (child stunting).

Stunting in children results from chronic undernutrition, leading to adverse effects on survival, health, and development, entailing a large

global population burden; in 2012, an estimated 162 million children younger than 5 years worldwide were stunted. Poor-quality diets and high rates of infection, both in pregnancy and in the first years of life, result in poor child growth, but the relative contributions to stunting are unknown. At the same time, provision of all of the established nutrition-specific interventions in the most affected regions would reduce the prevalence of stunting by only about 20% (Bhutta et al., 2013), illustrating the large knowledge gap in how to prevent stunting, including the potential impact of exposure to mycotoxins.

This Report concludes that surveillance data on exposure to aflatoxins are generally lacking outside the developed countries. However, available data from measurements of contaminated crops and through the use of exposure biomarkers in exposed populations demonstrate that mycotoxin exposures can be high throughout Africa, as well as in Latin America and parts of Asia. More recently, among maize-consuming populations in these regions, the high concurrent exposure to aflatoxins and fumonisins has been documented.

Notwithstanding the challenges, future mycotoxin monitoring programmes should be prioritized. Assessment of possible implementation within existing surveillance systems should be considered. In the short term, data from individual studies of sufficient quality should be added to the Global Environment Monitoring System (GEMS)/Food Contamination Database. Finally, a rapid screening approach aimed at the field/subsistence-farming level that is inexpensive and user-friendly and has a wide dynamic range should be developed. This could support a rapid alert system that informs responses and appropriate actions for food safety.

Aflatoxins are a cause of human liver cancer and, in high doses, have caused deaths from aflatoxicosis. More recently, significant negative effects of aflatoxin on child growth have been reported, as well as immune modulation. These observations are consistent with impaired fetal development and immune system and gut function in animal models. Taken together, the few well-documented population-based studies and the mechanistic data in relevant animal models suggest that mycotoxin exposure contributes to stunting, independent of and with other risk factors. Further longitudinal studies of mycotoxin exposure and child stunting, including studies of the underlying mechanisms, merit investment.

The Working Group assessed the question of effective interventions in low-income countries using studies where there was reliable direct or indirect evidence of improvement of health, including reduced mycotoxin biomarker levels. Using widely accepted criteria for evaluating evidence about public health interventions, some 15 interventions were placed into one of four categories: (1) sufficient evidence for implementation, (2) needs more field evaluation, (3) needs formative research, and (4) no evidence or ineffective. Recommendations on how to approach the necessary further investigation and potential scale-up were also considered.

Four of the interventions were judged to be ready for implementation. The intervention for which the strongest evidence of improvement of health exists, but which is also the most difficult to achieve, was to increase dietary diversity. Other strategies deemed ready for implementation were sorting of the crop; a package of post-harvest measures, including improved storage; and, in Latin America for maize, optimized nixtamalization. Several interventions were considered that might be used in emergency situations of extremely high contamination (e.g. chemoprotectants, agents that can be put into the diet to ameliorate the effects of aflatoxin once ingested).

As currently envisaged, the recommendations would be relevant for investment of public, nongovernmental organization, and private funds at the scale of the subsistence farmer, the smallholder, and through to a more advanced value chain.

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CHAPTER 1.

Human exposure to aflatoxins and fumonisins

Data on the prevalence of mycotoxins in staple foods are essential for all applied research into their impact on health and on effective mitigation. Country- or region-specific knowledge enables the identification of susceptible edible crops that are responsible for toxin exposure in specific populations. Prevalence data can indicate how effective maximum levels have been in influencing food safety, while acknowledging that their enforcement could have food security implications. Monitoring of prevalence also provides information on how various implemented strategies to reduce contamination or exposure levels directly affect toxin levels.

Ideally, exposure assessment, as one component of risk assessment, integrates mycotoxin levels with food consumption patterns and thus provides, via risk characterization, a clear picture of the extent to which mycotoxins compromise food safety and health, at either an individual or a population level. However, this is generally not achieved in developing countries, primarily due to a lack of country-specific data, resources, and analytical capacity.

Exposure biomarkers, such as serum aflatoxin–albumin adducts (AF–alb) or urinary fumonisin B_1 (UFB_1), offer a more integrated estimate of exposure from all sources for either aflatoxin or fumonisin, and offer potentially more reliable exposure estimates. Measurement of exposure, either by measures of food consumption combined with contamination levels or by using biomarkers of exposure, can be used to identify the main dietary contributors to exposure, detect areas with unacceptable exposures, assess health impacts of mycotoxins and their role in disease development, and determine the efficacy of intervention strategies. The recent development of multitoxin analytical methods, whether applied to food or to biological samples as biomarkers, has raised awareness of the concurrent exposure to aflatoxin and fumonisin as well as sometimes to other, unanticipated mycotoxins.

Exposure to aflatoxins

Aflatoxins are mycotoxins found in four main forms: aflatoxin B_1 (AFB_1), B_2 (AFB_2), G_1 (AFG_1), and G_2 (AFG_2). Aflatoxins occur on a wide range of crops, including the major staple cereals (e.g. maize), edible nuts and legumes, and their products. In general, AFB_1 occurs at the highest levels and is the most toxic. The main fungal producers of aflatoxins are *Aspergillus flavus*,

which produces AFB_1 and AFB_2, and *Aspergillus parasiticus*, which produces all four forms. Contamination can occur before or after harvest or both.

Aflatoxin contamination levels can vary widely, from products that meet the strict maximum levels set by the European Commission (2 µg/kg for AFB_1; 4 µg/kg for total aflatoxins [sum of AFB_1, AFB_2, AFG_1, and AFG_2] for cereals and nuts for direct human consumption) (European Commission, 2010) to products with levels that can pose a risk of acute aflatoxicosis. For example, determination of total aflatoxins in a rural market survey in four districts during an acute outbreak in Kenya, in 2004, showed a range of total aflatoxins of 1–46 400 µg/kg, with 7% of samples above 1000 µg/kg (Lewis et al., 2005). In 2003, data available from African countries were summarized by Shephard (2003). More recent data, including summaries of global occurrence in samples submitted for analysis, have been presented by Rodrigues et al. (2011) and Schatzmayr and Streit (2013). Recent African data have also been provided by Gnonlonfin et al. (2013). Examples from this literature include groundnut cake from Nigeria (range, 20–455 µg/kg); raw groundnut from Kenya (non-detectable to 7525 µg/kg) and Botswana (12–329 µg/kg); and maize from Benin (2–2500 µg/kg), Ghana (20–355 µg/kg), and Zambia (1–109 µg/kg). Other aflatoxin-contaminated food sources reported in various African countries include cassava, tiger nuts, cowpeas, sorghum, okra, and hot peppers, although due to consumption patterns, maize and groundnuts dominate in terms of level of exposure.

Aflatoxin M_1 (AFM_1) is a toxic metabolite of AFB_1 and a possible human carcinogen (IARC, 2012). This compound can be detected in the urine and milk of exposed animals, including humans. Data on the carryover of AFM_1 to breast milk are limited, but the carryover has been estimated at 0.1–0.4% (Zarba et al., 1992), and exposure of infants to AFM_1 from human breast milk has been reported in developing countries (Shephard, 2004; Turner, 2013; Magoha et al., 2014). In addition, AFM_1 from milk of livestock consuming AFB_1-contaminated feed is a further source of exposure. The 56th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) compiled data on AFM_1 levels found in commercial raw and processed dairy milk (Henry et al., 2001). However, few data were available from Africa, and those reported are unlikely to reflect typical village- or subsistence farm-level exposures. Further study is needed to better understand the consequences of AFM_1 ingestion from breast milk and/or from the milk of livestock in Africa.

Global intake estimates for aflatoxin (ng/kg body weight [bw]/day) have been reported based on estimates of typical maize and nut consumption, contamination levels, and body weight (Liu and Wu, 2010). For Africa, estimates were made for the Democratic Republic of the Congo (range, 0–27), Ethiopia (1–36), The Gambia (4–115), Kenya (4–133), Mozambique (39–180), Nigeria (139–227), South Africa (0–17), the United Republic of Tanzania (0–50), and Zimbabwe (18–43). Similarly high intakes were reported for China and countries in South-East Asia, compared with western Europe and North America at 0–1 ng/kg bw/day (Turner et al., 2012; Schleicher et al., 2013). These data indicate a much higher burden of exposure in low-income regions. However, it is important to note that these estimates are based on very limited datasets, particularly in those regions at greatest risk of high exposures.

Exposure to fumonisins

Fumonisins, which are produced mainly by *Fusarium verticillioides* (Sacc.) Nirenberg and *F. proliferatum* (Matsush.) Nirenberg, are common contaminants of maize and maize-based products. Fumonisin B_1 (FB_1) is the most abundant (generally ~70% of the total fumonisin contamination), and it normally co-occurs with lesser amounts of fumonisin B_2 (FB_2) and B_3 (FB_3). Occurrence on sorghum has also been reported (Bulder et al., 2012).

Fumonisins were evaluated by JECFA in 2001 and 2012 (Bolger et al., 2001; Bulder et al., 2012). As exposure is a product of both contamination level and consumption, certain rural communities in developing countries can exceed the provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg bw/day of fumonisin if their diet contains high amounts of maize (Burger et al., 2010).

Fumonisin intake estimates (µg/kg bw/day) in several regions of Africa were recently reviewed (Wild and Gong, 2010), including Burkina Faso (0–2); Bizana (1–19), Centane (2–36), Transkei (4), and KwaZulu-Natal (0), South Africa; and Bomet, Kenya (< 0.1). Intakes of 0.2–26 µg/kg bw/day in Tanzanian children were reported (Kimanya et al., 2014).

In Latin America, estimates of fumonisin intake in Guatemala were reported to be 3.5 µg/kg bw/day (urban) and 15.5 µg/kg bw/day (rural) (Wild and Gong, 2010), and more recently a range of 0.20–23 µg/kg bw/day was reported (Torres et al., 2014).

Biomarkers for aflatoxins and fumonisins

Food contamination and food intake can vary greatly within rural subsistence farm settings and between villages and individuals. Assessments of both of these parameters present analytical and measurement difficulties. In addition, there is interindividual variation in toxicokinetics and toxicodynamics related to toxin ingestion. For these reasons, considerable effort has been given to developing biomarkers for aflatoxins and fumonisins (Turner et al., 2012).

For AFB_1, the peripheral blood AF–alb biomarker has been validated for moderate- to long-term exposure (several months), whereas the urinary biomarkers, aflatoxin–N7-guanine and AFM_1, reflect shorter exposures. The application of these biomarkers has helped establish the link between aflatoxin exposure and the development of liver cancer (Kensler et al., 2011; IARC, 2012) and has allowed the efficacy of intervention studies to be demonstrated (Turner et al., 2005).

Validated aflatoxin biomarker data from sub-Saharan Africa show that the ranges of exposures are likely to vary greatly in many regions and within and across closely located villages and agro-ecological zones, as well as seasonally and annually (Turner et al., 2012; Turner, 2013). The biomarker data further highlight the early-life burden of exposure, including in utero and during early infancy. Exposures in West African studies involve both maize and groundnuts as the primary sources of intake of aflatoxins. Typical biomarker levels in children younger than 5 years in Benin, The Gambia, and Togo range up to 1000 pg aflatoxin–lysine/mg albumin (Turner, 2013). By comparison, levels of AF–alb reported from the recent United States National Health and Nutrition Examination Survey (NHANES) were almost all (99%) below the limit of detection (LOD), and the geometric mean of the positives was only 0.8 pg/mg (Schleicher et al., 2013).

AF–alb has also been used in various studies to assess associations between aflatoxin exposure and infant and early childhood growth faltering (Turner, 2013). Typically there is greater confidence in the long-term markers of aflatoxin exposure to assess health outcomes, as they provide an integrated measure over several months. Several putative biomarkers for fumonisin exposure have been investigated. These include sphingoid bases in plasma and urine and FB_1 in hair, nails, serum, urine, and faeces (Shephard et al., 2007); however, none of these have been validated in human studies. UFB_1 has been measured in human samples in regions with known high exposure to dietary fumonisins (Gong et al., 2008a; Xu et al., 2010; van der Westhuizen et al., 2011; Riley et al., 2012; Torres et al., 2014). In general, statistically significant relationships between UFB_1 and either estimated or measured FB_1 intakes were reported; however, the data indicate that the urinary measure was only moderately reflective of the level of intake.

Co-occurrence of aflatoxins and fumonisins

The co-occurrence of aflatoxins and fumonisins has been widely documented by both biomarker studies and food analyses. In the United Republic of Tanzania, AF–alb and UFB_1 were assessed in young children (Shirima et al., 2013). The prevalence of detection of both of the mycotoxins was high, and 82% of the children were positive for both. Also, a modest but statistically significant correlation was observed between the concentrations of these biomarkers (r = 0.375, P < 0.001) (Shirima et al., 2013). Urinary aflatoxin and fumonisins were observed less frequently in samples from two major cities, Yaoundé and Bamenda, in Cameroon (Abia et al., 2013) and from rural regions of Nigeria (Ezekiel et al., 2014), although co-exposures did occur. Differences in the sensitivities of the analytical methods between these studies limit direct comparison. A separate study from Cameroon, looking at urinary mycotoxin markers in young children, also reported aflatoxin and fumonisin exposure (Njumbe Ediage et al., 2013). These data were complemented by a survey across multiple agro-ecological zones in Cameroon, in which maize, groundnuts, and cassava were found to be contaminated with multiple mycotoxins (fumonisins were found in 74% of the maize samples and aflatoxins in 22% of the maize, 29% of the groundnuts, and 25% of the cassava samples) (Ediage et al., 2014). In a study by Probst et al. (2014), a total of 339 maize samples from 18 countries in Africa were assessed for aflatoxin and fumonisin contamination. Aflatoxins were detected (LOD, 1 µg/kg) in 47% of the samples, with 7% exceeding 20 µg/kg and 6% exceeding 100 µg/kg (the maximum level was 1409 µg/kg). Fumonisins were detected (LOD, 500 µg/kg) in 81% of the samples, with 7% exceeding 5000 µg/kg and 3% exceeding 100 000 µg/kg. Aflatoxin and fumonisin co-contamination occurred in 35% of the samples. Concentrations of co-contaminants varied by region, but for the Coast Province in Kenya, for example, 50% of samples contained high levels of both aflatoxins (mean, 97 µg/kg) and fumonisins (mean, 32 000 µg/kg) (Probst et al., 2014).

In Latin America, co-exposures to aflatoxins and fumonisins have also been documented. Maize from 22 districts in Guatemala was analysed; 36% of 572 samples tested positive for aflatoxins (mean, 63 µg/kg; range of positives, 5–2655 µg/kg), and 99% of 640 samples tested positive for fumonisins (mean, 1800 µg/kg; range of positives, 10–17 000 µg/kg) (Torres et al., 2015).

Analytical limitations

One limitation with urinary biomarker approaches is the volumes of urine required. Even though technological development of highly sensitive liquid chromatography-mass spectrometry (LC-MS) techniques will help support biomonitoring, the approach itself may be limited by instrumentation costs, restricting analysis to specialist laboratories. With the development of multitoxin analytical techniques based on LC-MS/MS, multibiomarker methods have been developed for urinary biomeasures for toxins, including FB_1 and AFM_1 (Solfrizzo et al., 2011; Warth et al., 2012), as extensions of multimycotoxin methods for food analysis. These methods have been applied in Africa to evaluate exposure (Abia et al., 2013; Shephard et al., 2013; Ezekiel et al., 2014). To date, there have been limited efforts to compare multimycotoxin methods from different laboratories. Thus, currently there is greater confidence in the data from single measures, and for increased utility these interlaboratory comparison studies are urgently needed. An additional concern is that some of the multimycotoxin methods, especially for foods, may be measuring contaminants of limited relevance to human health. This could result in additional costs (e.g. of measuring > 60 metabolites) while potentially leading to inaccurate measurements.

Key scientific gaps

The problem of mycotoxin exposure is most acute in developing countries, which lack resources and analytical capacity for analyses. Consequently, few data are reported from developing countries and those available are usually based on only a limited number of samples of uncertain quality. As a result, there is a widening gap between the quality and quantity of prevalence data generated by laboratories in developed countries compared with developing countries. There is thus a need in the developing countries to have sampling and analytical tools available that are fit for specific purposes, such as:

- A rapid screening method aimed at the field/subsistence farm level that is inexpensive and user-friendly and has a wide dynamic analytical range. This could additionally help support a rapid alert system that informs responses and appropriate actions for food safety.
- A comprehensive regional or country-wide monitoring programme, involving the establishment of a reference laboratory within a country/region. The monitoring programme should be developed within existing surveillance systems and be expanded over time. For example, many regions have national health and nutrition programmes where archived biospecimens could be requested. Future national surveys of this nature may be asked to collect larger volumes of biospecimens (e.g. to support urinary xenobiotic surveillance). De novo monitoring activities could include both food measures and biomarkers.

For a successful food monitoring programme, it is essential to have effective sampling plans in place. While it is recognized that designing effective sampling plans for mycotoxin detection in food commodities is a complex task, there is a tool available to support countries in this regard: the Food and Agriculture Organization of the United Nations (FAO) Mycotoxin Sampling Tool (http://www.fstools.org/mycotoxins/). Further, there is a World Health Organization (WHO) programme (Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme [GEMS/Food]) that collects global food contamination data and reports food consumption data. Average per capita food consumption data are reported based on the FAO Food Balance Sheet data. It is important to note that the database provides average consumption levels but will not capture the food consumption pattern at the subsistence farm level. Another database within GEMS/Food collects occurrence data for contamination levels, including aflatoxins and fumonisins in food products and crops. It would be useful to highlight the opportunity for researchers to add their studies to this database. However, acquiring data on consumption and contamination levels in subsistence farmers will remain a significant hurdle.

Among monitoring options, an approach that might be implemented is sampling at community maize milling facilities. For example, in some parts of East Africa farmers could bring maize to a local milling operation, where subsampling and aflatoxin and fumonisin analyses could be carried out using rapid test kits for field application. Relatively large data collection activities may be possible in such settings, providing an improved surveillance, although this will capture only some of the prevalence data in some regions and none in others. This also may, however, provide a target site for intervention.

Measures of individual exposures are important for epidemiological investigations of disease causation and for demonstration of efficacy of intervention. The development of a reliable source of certified standards, especially for aflatoxin biomarkers, would allow a substantial increase in biomarker-directed epidemiology research.

Therefore, the problem of insufficient data could also be addressed by the use of individual biomarkers of exposure. Aflatoxin biomarkers are well understood, but the most useful for long-term exposure studies, AF–alb, is currently measured in only a limited number of laboratories. It would be advantageous if this analysis were more generally available, especially in countries where aflatoxin exposure is known to be high. The lack of reagents such as aflatoxin–lysine and mono-adducted AF–alb is a major constraint and needs to be addressed. Enzyme-linked immunosorbent assay (ELISA) approaches are typically less expensive, but an additional issue is a lack of commercially available kits or antibodies. While LC-MS provides robust data, the analytical costs are prohibitive for most laboratories. Exposure of infants in developing countries to AFM_1 also needs to be monitored as these countries are prone to higher AFB_1 exposures.

UFB_1 has been measured by LC-MS in several world regions, and again a current concern is the cost of the analysis. While dose–response relationships were reported, the urinary measure was not as strongly predictive of the level of intake compared with relationships reported for aflatoxin biomarkers. For general biomonitoring this is not a major issue; however, this is a concern when making assessments in relation to putative health effects and assessing the efficacy of interventions. For the use of FB_1 and AFM_1, it was noted that neither of these predicts longer-term exposures, and while serum AF–alb is used for this purpose in aflatoxin biomonitoring and epidemiology, there remains a need to develop a long-term exposure biomarker for fumonisin. An additional challenge is the need for higher-throughput analytical tools, which would benefit from a cooperative activity between experts in exposure assessment and researchers with subject matter expertise in mycotoxins.

CHAPTER 2.

Child stunting in developing countries

Stunting and wasting in children are measures reflecting states of chronic and acute undernutrition that have important adverse effects on survival, health, and development. In impoverished settings, poor-quality diets and high rates of infection, both in pregnancy and in the first 2 years of life, lead to fetal growth restriction (FGR) and poor child growth. This results in an estimated 26% of the world's children younger than 5 years having stunted stature, and 8% being much too thin for their height (i.e. wasted) (UNICEF-WHO-The World Bank, 2012). Proven interventions to prevent the FGR that contributes to stunting include multiple vitamin and mineral supplements and provision of balanced energy/protein supplements to pregnant women, as well as control of maternal infections. After birth, the most effective intervention is the supply of foods with adequate nutritional quality to complement breastfeeding in the first 2 years of life.

The physical growth of children within a normative range has important implications both within that age span and into adulthood (Bhutta et al., 2013). Insufficient gains in length/height and weight from birth to age 5 years, resulting from childhood undernutrition, put the child at increased risk of morbidity and mortality from infectious diseases as well as impaired mental development, reduced learning capacity in school, and lower earning potential as an adult, among other effects (Victora et al., 2008; Adair et al., 2013; Bhutta et al., 2013). As noted, childhood undernutrition is usually defined by physical size. Measures of length/height and weight are most common, although there are others such as head circumference and mid-upper arm circumference that are commonly used in surveillance for severe acute malnutrition.

Length (recumbent, for age < 2 years) or height (standing, for age 2–4 years) or weight is compared to an international growth standard (WHO Multicentre Growth Reference Study Group, 2006), and the result is most commonly expressed as a Z-score (standard deviation score). The Z-score is the observed value for length/height or weight minus the median value of the growth standard, with this result divided by the standard deviation of the growth standard. If the Z-score for length/height-for-age is below −2, the child is considered to have inadequate linear growth or to be stunted. If the Z-score for weight-for-age is below −2, the child is said

to be underweight. The weight and length/height measures can be used together to create an indicator of wasting: a child whose Z-score for weight-for-length/height is below −2 is considered to be wasted.

Prevalence of child malnutrition

The latest UNICEF-WHO-The World Bank joint child malnutrition estimates provide global and regional prevalences for stunting and wasting based primarily on population-based, nationally representative surveys, with modelling to make regional estimates (UNICEF-WHO-The World Bank, 2012). The global prevalence of stunting in children younger than 5 years was estimated to be 26% (95% confidence interval [CI], 24–28%) for 2011, the most recent data. The number of stunted children in that year was estimated to be 165 million. The prevalence of stunting has declined from 40% in 1990, with an average annual rate of reduction of 2.1%. The prevalence of stunting varies substantially by world region (Fig. 2.1), with the highest prevalence in Africa and South-Central Asia (which includes India). The decline in the prevalence of stunting has been greater for Asia and Latin America than for Africa, which is the only region that has had an increasing number of stunted children, due to the slow declines in the prevalence and the high fertility rate (Fig. 2.2) (UNICEF-WHO-The World Bank, 2012; Bhutta et al., 2013).

In countries with an overall prevalence of stunting greater than 10%, there is a gap – in some cases very wide – between the high prevalence in the poorest 20% and the low prevalence in the least poor 20% of the population. This illustrates the relationship of stunting and other forms of undernutrition with poverty and the associated problems of food insecurity and environmental exposure to infectious agents and toxins. The global prevalence of moderate or severe wasting was estimated to be 8.0% (95% CI, 6.8–9.3%) for 2011. Again, there is regional variation in the prevalence (Fig. 2.3), with the highest prevalence in South-Central Asia (14.8%; 95% CI, 11.1–19.4%), South-East Asia (9.7%; 95% CI, 7.5–12.6%), and Africa (8.5%; 95% CI, 7.4–9.6%). The numbers of children with wasting and severe wasting were estimated to be 52 million and 19 million, respectively, for 2011. Recent estimates indicate that nearly 2 million deaths in children worldwide can be attributed to FGR and stunting, or a third of all child deaths (UNICEF-WHO-The World Bank, 2012; Bhutta et al., 2013).

Risk factors for child malnutrition

Preventable causes of FGR in utero and reduced growth of the child during the first 2 years of life include low

Fig. 2.1. Latest country prevalence estimates for stunting among children younger than 5 years. Source: Reprinted from UNICEF-WHO-The World Bank (2012), p. 9, © 2012, with the permission of the publisher.

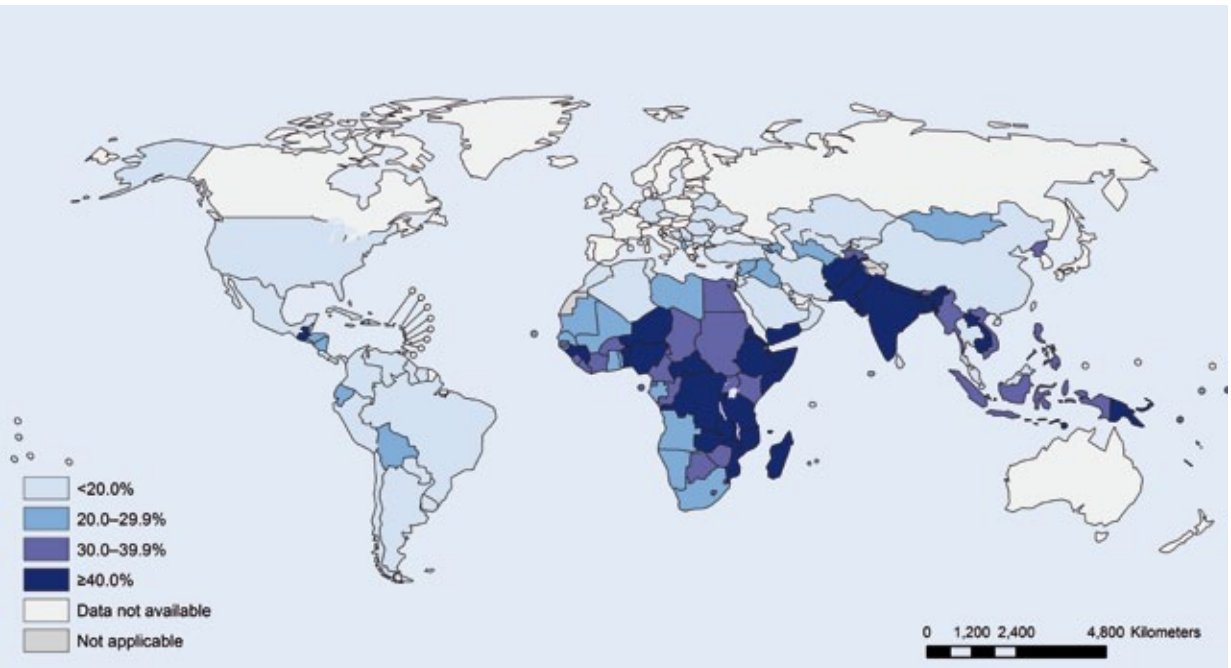


Fig. 2.2. Trends in prevalence and numbers of children with stunted growth (height-for-age Z-score < −2), by selected United Nations regions and globally, 1990–2010, and projected to 2025 on the basis of United Nations prevalence estimates. Source: Reprinted from Black et al. (2013), © 2013, with permission from Elsevier. Data from UNICEF-WHO-The World Bank (2012).

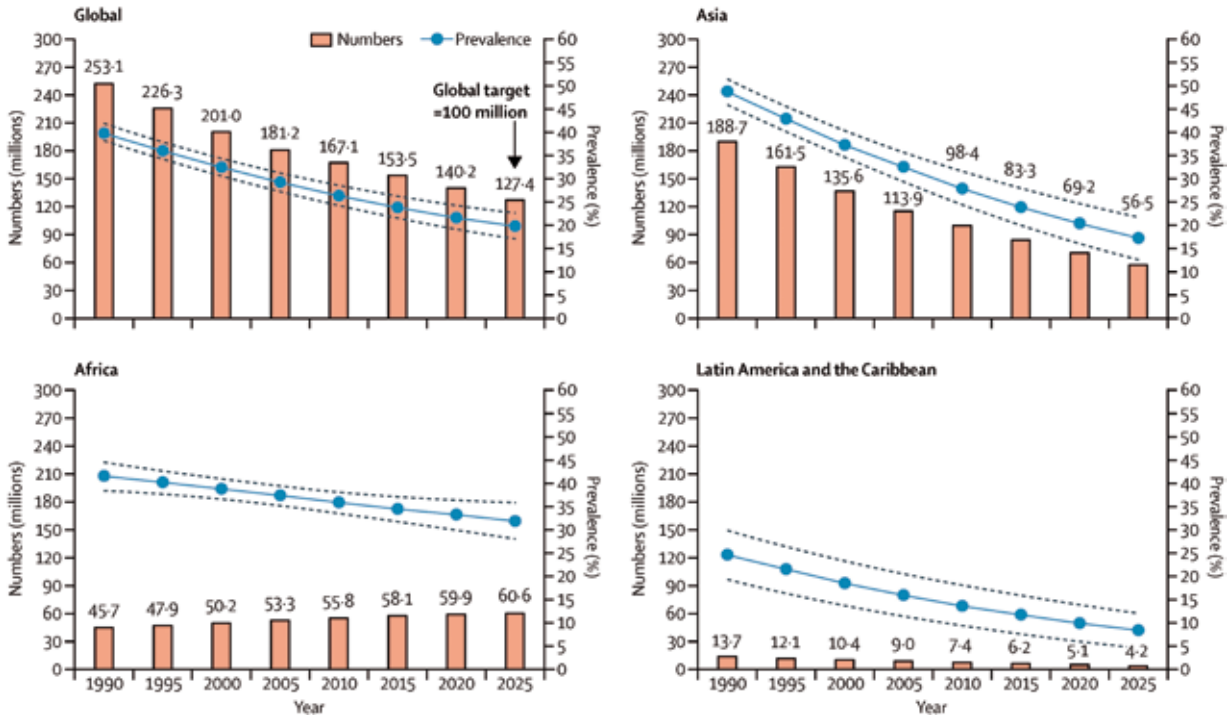
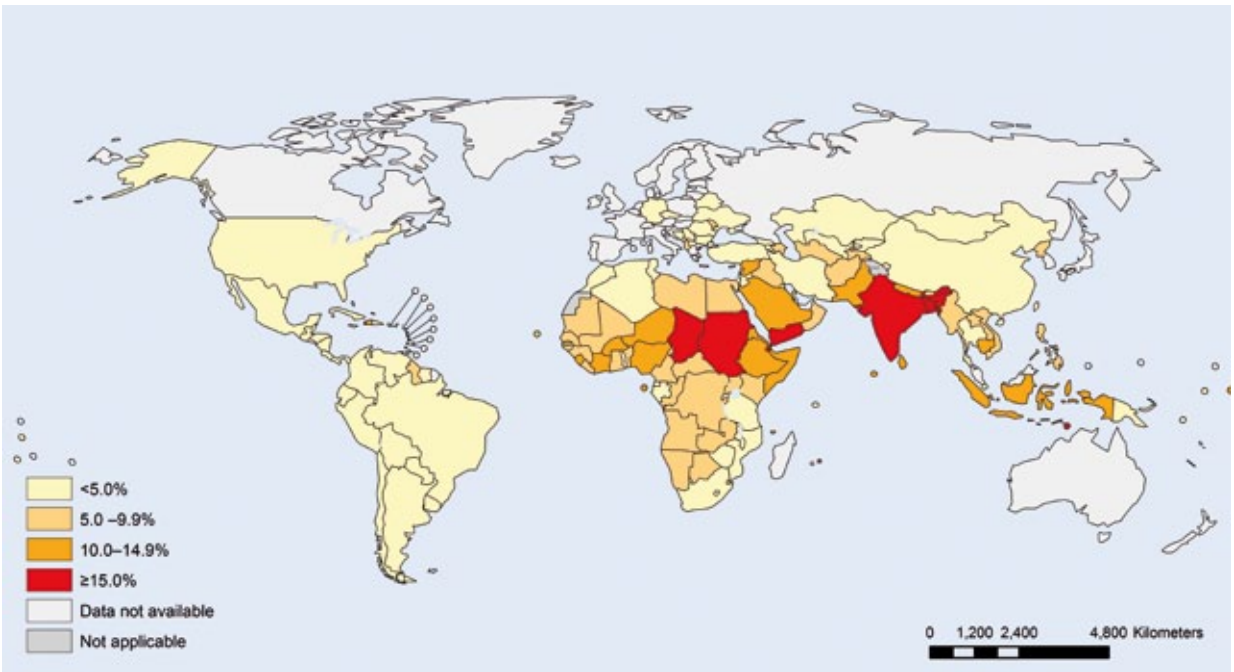


Fig. 2.3. Latest country prevalence estimates for wasting among children younger than 5 years. Source: Reprinted from UNICEF-WHO-The World Bank (2012), p. 10, © 2012, with the permission of the publisher.



body mass index, small weight gain and micronutrient deficiencies during pregnancy, and maternal infections (Bhutta et al., 2013; Christian et al., 2013). It has been estimated that 27% of all births in low- and middle-income countries have FGR, with the highest prevalence in Asia, especially South Asia (Bhutta et al., 2013; Lee et al., 2013). Nutritional status at birth is related to the risk of being stunted at age 2 years. Globally, it has been estimated that 20% of stunting can be attributed to FGR. In some countries the attributable fraction is even higher. In India, where nearly half of all births have FGR, the attributable fraction for stunting is more than a third (Christian et al., 2013).

Most of the growth faltering leading to stunting occurs between ages 3 months and 18–24 months (Victora et al., 2010), a period of vulnerability because often insufficient and poor-quality food is provided to the child. Exclusive breastfeeding is recommended for the first 6 months of life but is uncommonly practiced; globally, only about 30% of infants aged 1–5 months are exclusively breastfed (Bhutta et al., 2013). The early introduction of fluids will reduce the production and ingestion of breast milk and substitute foods of lesser nutritional quality that also have a high risk of microbial contamination. In most of the affected regions, more than 60% of children aged 6–23 months are breastfed (Bhutta et al., 2013). However, the complementary foods that are introduced too often have inadequate nutrient density, calories, protein, essential fats, and micronutrients, and may contain infectious bacteria and/or toxins. Deficiency of the micronutrient zinc has been consistently associated with stunting, and increased linear growth in infants has been demonstrated with provision of daily zinc supplements (Bhutta et al., 2013).

High rates of diarrhoea and other infectious diseases also affect this age group, even with continued breastfeeding as complementary foods are introduced. In a pooled analysis of nine community-based studies in low-income countries, the odds of stunting at age 24 months increased multiplicatively with each episode of diarrhoea or day of diarrhoea before that age. The proportion of stunting attributed to five previous episodes of diarrhoea was 25% (95% CI, 8–38%) (Checkley et al., 2008). In addition to the clinical infections, frequent exposure to contaminated food and water and the household environment results in ingestion of microbes, causing subclinical infections that damage the small intestine. It has been hypothesized that environmental enteric dysfunction (EED) or environmental enteropathy, a condition characterized by structural abnormalities of the intestinal epithelium, altered barrier integrity, mucosal inflammation, and reduced nutrient absorption, may contribute to growth faltering and stunting (Keusch et al., 2013). It has also been hypothesized that zinc deficiency may be involved in the pathogenesis of EED (Lindenmayer et al., 2014). As noted by Lunn (2000) and discussed later in this Report, there is a potential role for ingested mycotoxins to contribute to EED or to other mechanisms that lead to stunting.

Interventions against child malnutrition

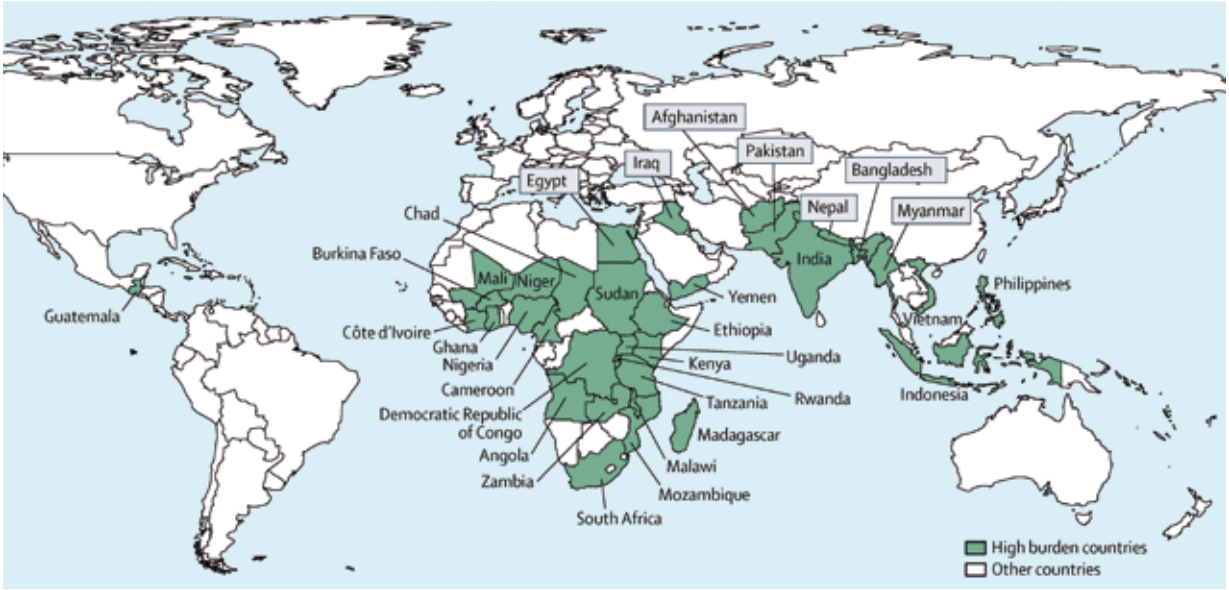
Although breastfeeding, as recommended for the first 2 years of life, is important for the babies' health and dietary intake, the major interventions to prevent stunting are related to the foods that are given in addition to breast milk from age 6–23 months (i.e. complementary diet). Education about age-appropriate quantity and quality of diets and provision of safe food supplements containing adequate micronutrients have been shown to improve growth and reduce the prevalence of stunting. Full (90% coverage) implementation of these interventions would reduce stunting by at least 20% in the 34 countries that include 90% of the world's stunted children (Fig. 2.4). These interventions would also be useful to prevent wasting (Bhutta et al., 2013). In stable non-emergency situations, wasting usually coexists with stunting after age 6–9 months. However, severe acute malnutrition (i.e. severe wasting) can occur more abruptly even in a previously well-nourished child due to food scarcity, such as in famine, natural disaster, or civil conflict. These are situations where targeted food distribution programmes are needed.

There is limited evidence that interventions in sectors other than health and nutrition may have a beneficial impact on stunting. These areas include efforts to improve agricultural productivity and improvements in water, sanitation, and hygiene, because of their potential to reduce the rates of diarrhoea and possibly the occurrence of EED (Dangour et al., 2013; Spears, 2013). Food safety interventions would be expected to positively influence nutrition and growth in young children by eliminating infectious agents that cause diarrhoea through foodborne transmission and possibly through avoidance of exposure to chemicals and mycotoxins.

Key scientific gaps and research needs

Recent publications indicate that FGR is a more important contributor to neonatal and infant mortality (Katz et al., 2013) and to stunted linear growth (Christian et al., 2013) than previously recognized.

Fig. 2.4. Countries with the highest burden of malnutrition. These 34 countries account for 90% of the global burden of malnutrition. Source: Reprinted from Bhutta et al. (2013), © 2013, with permission from Elsevier.



This makes it imperative to look more closely at the causes of FGR and possible interventions to reduce it or ameliorate its negative effects. Maternal undernutrition and infection, as well as other possible determinants of FGR, need additional study, especially to identify feasible interventions to reduce its occurrence. If programmes intend to increase the provision of balanced energy/protein supplements during pregnancy, there are questions about the composition of supplements (preferably using locally available and safe foods) and their timing in pregnancy, how best to target the food supplements to vulnerable populations and undernourished or food-insecure women, how to achieve sufficient consumption, and ultimately the cost–effectiveness of alternative ways to deliver this intervention.

In spite of the known benefits of iron and folic acid supplementation in pregnancy, the current use of this intervention is low. Supplementation with multiple micronutrients in pregnancy, instead of only iron and folic acid, would provide added benefits at modest additional cost. If multiple micronutrients are to be provided to pregnant women or to children, further product development research, linked with studies of the prevalence and extent of micronutrient deficiencies in various low-income populations, is needed. This will ensure that the composition is optimized to meet nutritional needs, reduce nutrient interactions, avoid side-effects, enhance acceptability, and reduce costs.

Most stunting of linear growth takes place in the first 2 years of life. The relative contributions to stunting of dietary insufficiency, infectious diseases or subclinical infections, and inflammation are unknown and may vary, as does the prevalence of stunting, by setting in low- and middle-income countries. There is good evidence that promotion of nutritious complementary foods or provision of food supplements improves growth and reduces the occurrence of stunting; however, the effect size relative to the height deficit is small. Zinc supplements for children in the first 2 years of life also have a statistically significant, but small, benefit in reducing stunting. The *Lancet* nutrition series estimated that the nutrition-specific interventions together, if scaled up to 90%, would reduce the prevalence of stunting by only about 20% (Bhutta et al., 2013), illustrating the large gap in our knowledge of how to prevent stunting. Additional studies of the determinants of stunted growth need to include the possible role of subclinical infections and exposure to potentially harmful agents such as mycotoxins.

The first 2 years of life are a crucial period for both development and growth, which need to be considered separately as well as jointly. Young children in impoverished households lack both the stimulation needed for cognitive and psychosocial development and the

food and environmental conditions needed to promote physical growth and prevent illness.

In conclusion, stunting and wasting are nutritional conditions that most commonly affect children in low- and middle-income countries and have serious consequences for survival, health, and development. Implementation of proven interventions to prevent their occurrence and to provide treatment must be given greater priority. Parallel efforts should address the evidence gaps through better understanding of the behavioural and biological determinants of stunting and wasting, including the possible role of mycotoxins, and the effectiveness of other nutrition-specific interventions and nutrition-sensitive approaches.

CHAPTER 3.

Effects of aflatoxins on aflatoxicosis and liver cancer

While there has been a very extensive focus on the role of aflatoxin exposure in hepatocellular carcinoma (HCC), over the years several cases of acute aflatoxicosis in humans have been reported in regions of some developing countries (Shank et al., 1971).

Acute aflatoxin poisoning

The clinical manifestations of aflatoxicosis include vomiting, abdominal pain, pulmonary oedema, fatty infiltration, and necrosis of the liver. In the 1970s, there was an outbreak of putative aflatoxin poisoning in western India when heavily moulded maize was consumed. There were at least 97 fatalities, all of which occurred in households where the contaminated maize was consumed. Histopathology of liver specimens revealed extensive bile duct proliferation, a lesion often noted in experimental animals after acute aflatoxin exposure (Krishnamachari et al., 1975; Bhat and Krishnamachari, 1977). An outbreak of acute aflatoxicosis in Kenya in 1981 was also associated with consumption of maize highly contaminated with aflatoxin (Ngindu et al., 1982). There were 20 hospital admissions, with 60% mortality. In a more recent report (Lye et al., 1995), the consumption of aflatoxin-contaminated noodles resulted in acute hepatic encephalopathy in children in Malaysia. Up to 3 mg of aflatoxin was suspected to be present in a single serving of contaminated noodles.

In April 2004, one of the largest documented aflatoxicosis outbreaks occurred in rural Kenya, resulting in 317 cases and 125 deaths. Aflatoxin-contaminated home-grown maize was the major source of the outbreak. In a survey of 65 markets and 243 maize vendors, 350 maize products were collected from the most affected districts. Of these maize products, 55% had aflatoxin levels greater than the Kenyan regulatory limit of 20 ppb, 35% had levels greater than 100 ppb, and 7% had levels greater than 1000 ppb. Makueni, the district with the most aflatoxicosis cases, had significantly higher aflatoxin levels in maize from markets than did Thika, the study district with the fewest cases (geometric mean aflatoxin, 52.91 ppb vs 7.52 ppb; $P = 0.0004$). Maize obtained from local farms in the affected area was significantly more likely to have aflatoxin levels greater than 20 ppb compared with maize bought from other regions of Kenya or other countries (odds ratio [OR], 2.71; 95% confidence interval [CI], 1.12–6.59). In addition to the

market survey for aflatoxin exposure, this outbreak in 2004 marked the first time that levels of aflatoxin–albumin adducts (AF–alb) independently confirmed the exposure in individuals (CDC, 2004; Azziz-Baumgartner et al., 2005; Lewis et al., 2005; Strosnider et al., 2006; Probst et al., 2007).

Hepatocellular carcinoma

For decades, it has been known that aflatoxin exposure causes liver cancer in humans and in several animal species. The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of aflatoxins on several occasions, starting in 1972 with Volume 1 of the IARC Monographs on the evaluation of carcinogenic risks to humans. Since that time, many studies in humans and experimental animals have provided clarifying data, and naturally occurring mixtures of aflatoxins are now classified as Group 1, carcinogenic to humans (IARC, 1993). Furthermore, as described below, concomitant exposure to aflatoxin and hepatitis B virus (HBV) is common in developing countries and greatly increases HCC risk (Wu et al., 2013). Individuals who experience both exposures have a greater risk of developing HCC than those exposed to aflatoxin alone (Wogan et al., 2012).

HCC accounts for 5.6% of all reported cancer cases and is the sixth most common cancer diagnosed worldwide (Ferlay et al., 2013). The global incidence of liver cancer varies enormously, and the burden of this nearly always fatal disease is much higher in less-developed countries of Asia and sub-Saharan Africa. Overall, there are more than 780 000 new cases of liver cancer each year and more than 745 000 deaths annually (Ferlay et al., 2013). In contrast to most cancers common in developed countries, where more than 90% of cases are diagnosed in people aged 45 years and older, in high-risk regions for liver cancer, onset begins in both men and women by age 20 years, peaking at age 40–49 years in men and age 50–59 years in women (Parkin et al., 2005; Chen et al., 2006). The earlier onset of HCC may be attributable to exposures that are both substantial and persistent across the lifespan. Sex differences in liver cancer incidence have also been described; the worldwide annual age-standardized incidence rate is 15.3 per 100 000 among men and 5.4 per 100 000 among women (Ferlay et al., 2013). These epidemiological findings are also consistent with experimental animal data for aflatoxin, in which male rats have been found to have an earlier onset of cancer compared with female rats (Wogan and Newberne, 1967).

For more than 50 years, the relationship between aflatoxin exposure and human liver cancer has been examined using ecological studies, cross-sectional surveys, case–control studies, and prospective cohort investigations in exposed populations. Early studies in the Philippines demonstrated that an oxidative metabolite of aflatoxin could be detected in urine and thus had potential to serve as an internal dose marker (Campbell et al., 1970). In later studies, Autrup et al. (1983, 1987) reported the presence of aflatoxin B_1 (AFB_1)–DNA adducts in human urine samples in Kenya. Subsequent work conducted in China and The Gambia, West Africa, areas with high incidences of HCC, examined both the dietary intake of aflatoxin and the levels of urinary aflatoxin biomarkers (Groopman et al., 1992). Urinary AFB_1–DNA adduct and aflatoxin M_1 (AFM_1) levels showed a dose-dependent relationship between aflatoxin intake and excretion. Gan et al. (1988) and Wild et al. (1992) also monitored levels of AF–alb in serum and observed a highly significant association between aflatoxin intake and adduct level.

Many published case–control studies have explored the relationship between aflatoxin exposure and HCC. In an early case–control study, Bulatao-Jayme et al. (1982) compared the dietary intake of aflatoxin in cases of HCC in the Philippines with intake in age- and sex-matched controls. They found that the mean aflatoxin exposure per day in cases of HCC was 4.5 times as high as that in the controls; however, alcohol consumption may have enhanced this effect. Van Rensburg et al. (1985) and Peers et al. (1976) used a similar design for studies in Mozambique and Swaziland, respectively. Again, the mean dietary aflatoxin intakes were positively correlated with HCC rates, and the data also suggested a dose-dependent increase in liver disease associated with increased aflatoxin intake.

In the Guangxi Zhuang Autonomous Region of China, Yeh and Shen (1986) and Yeh et al. (1989) examined the interaction between HBV infection and dietary aflatoxin exposure dichotomized for heavy and light levels of contamination. Individuals whose serum was positive for the HBV surface antigen (HBsAg) and who experienced heavy aflatoxin exposure had a 10-fold higher incidence of HCC than did people living in areas with light aflatoxin contamination. People who were HBsAg-negative and who consumed diets heavily contaminated with aflatoxin had a rate of HCC comparable to that of the HBsAg-positive people consuming diets with light aflatoxin contamination (Yeh et al., 1989). In a case–control study in Taiwan, China, two

biomarkers, AF–alb and aflatoxin–DNA adducts in liver tissue samples, were measured (Lunn et al., 1997). The proportion of subjects with a detectable level of AF–alb was higher for cases of HCC than for matched controls (OR, 1.5). A statistically significant association was found between presence of detectable AF–alb and risk of HCC among men younger than 52 years (multivariate adjusted OR, 5.3).

Another study, in Qidong, China, examined 145 men with chronic HBV infection who were followed for 10 years to determine whether exposure to aflatoxin, concomitant exposure to hepatitis C virus (HCV), or family history of HCC increased the risk of developing HCC. Eight monthly urine samples collected before the initiation of follow-up were pooled to analyse for AFM_1. AFM_1 was detected in 78 (54%) of the subjects, and the risk of HCC was increased 3.3-fold (95% CI, 1.2–8.7) in those with detectable AFM_1 (> 3.6 ng/L). The attributable risk from aflatoxin exposure, defined as the presence of detectable AFM_1, was 0.553 (95% CI, 0.087–0.94). The relative risk of fatal cirrhosis for individuals whose urine contained elevated AFM_1 was 2.8 (95% CI, 0.6–14.3). Concomitant infection with HCV increased the risk of HCC 5.8-fold (95% CI, 2.0–17), adjusted for age and AFM_1 status. This study shows that aflatoxin exposure detected by the presence of AFM_1 in urine can account for a substantial portion of HCC risk in men with chronic HBV hepatitis (Sun et al., 1999).

Two major cohort studies incorporating aflatoxin biomarkers have clearly demonstrated the etiological role of this carcinogen in HCC. The first study, comprising more than 18 000 men in Shanghai, China, examined the interaction of HBV and aflatoxin biomarkers as independent and interactive risk factors for HCC. The nested case–control data revealed a statistically significant increase in the relative risk of 3.4 for those HCC cases in whom a urinary aflatoxin biomarker (AFB_1–N7-guanine) was detected. For men whose serum was HBsAg-positive but whose urine did not indicate aflatoxin exposure, the relative risk was 7.3, but in individuals exhibiting both the urinary aflatoxin biomarker and positive HBsAg status, the relative risk was 59.4 (Ross et al., 1992; Qian et al., 1994). These results strongly support a causal relationship between the presence of carcinogen- and viral-specific biomarkers and the risk of HCC. Subsequent cohort studies in Taiwan, China, have substantially confirmed the results from the Shanghai investigation. Wang et al. (1996) examined HCC cases and controls nested within a cohort and found that in HBV-infected people there was an adjusted odds ratio of 2.8 for detectable compared with non-detectable AF–alb, and an adjusted odds ratio of 5.5 for high compared with low levels of aflatoxin metabolites in urine. In a follow-up study, there was a dose–response relationship between urinary AFM_1 levels and risk of HCC in chronic HBV carriers (Yu et al., 1997). As in the Shanghai cohort, HCC risk associated with AFB_1 exposure was most striking among HBV carriers with detectable AFB_1–N7-guanine in urine.

Furthermore, the relationship between aflatoxin exposure and development of HCC has been highlighted by molecular biological studies on the *p53* tumour suppressor gene, the gene most commonly mutated in many human cancers (Greenblatt et al., 1994). Many studies of *p53* mutations in HCC occurring in populations exposed to high levels of dietary aflatoxin have found high frequencies of G:C → T:A transversions, with clustering at codon 249 (Bressac et al., 1991; Hsu et al., 1991). In contrast, no mutations in codon 249 were found in *p53* in HCC from Japan and other areas where there was little exposure to aflatoxin (Ozturk, 1991; Aguilar et al., 1994).

Thus, studies of the prevalence of codon 249 mutations in HCC cases from populations in areas of high or low exposure to aflatoxin suggest that a G → T transversion at the third base of codon 249 is associated with aflatoxin exposure, and in vitro data would seem to support this hypothesis. Application of these specific mutations as biomarkers for early detection also offers great promise for HCC prevention (Sidransky and Hollstein, 1996). In a seminal study, Kirk et al. (2000) reported for the first time detection of *p53* codon 249 mutations in plasma of liver tumour patients residing in The Gambia; however, the mutational status of their tumours was not determined. The authors also reported the presence of this mutation in the plasma of a small number of cirrhosis patients. Given the strong relationship between cirrhosis and future development of HCC, the possibility of this mutation serving as an early detection marker needs to be explored. Jackson et al. (2001) examined 25 HCC tumours for specific *p53* mutations. Analysis of 20 additional plasma–tumour pairs showed that 11 tumours and 6 plasma samples contained the specific mutation. This group (Jackson et al., 2003) further explored the temporality of detection of this mutation in plasma before and after clinical diagnosis of HCC in the same patients. This study was facilitated by the availability of longitudinally collected plasma samples from a cohort of 1638 high-risk individuals in Qidong, China, who have been followed since 1992. The results showed that in samples

collected before liver cancer diagnosis, 21.7% (95% CI, 9.7–41.9%) of the plasma samples had detectable levels of the codon 249 mutation in *p53*, whereas this mutation was detected in 44.6% (95% CI, 21.6–70.2%) of the plasma samples collected after the diagnosis of liver cancer. This percentage of positive samples after liver cancer diagnosis compares with about 50% of all liver tumours in Qidong, suggesting a nearly 90% concordance between plasma and tumour *p53* codon 249 mutation outcome.

Finally, recent work has taken advantage of a population-based cancer registry to track primary liver cancer mortality in Qidong, China, a region of 1.1 million residents. This database indicates that a greater than 50% reduction in HCC mortality rates occurred across birth cohorts from the 1960s to the 1980s for Qidongese younger than 35 years. The prevalence of HBV infection was unchanged, since all were born before universal vaccination of newborns. Randomly selected serum samples from archived cohort collections from the 1980s to the present were analysed for aflatoxin biomarkers. Median levels of the aflatoxin biomarker AF–alb decreased from 19.3 pg/mg in 1989 to non-detectable (< 0.5 pg/mg) by 2009. A population-attributable benefit of 65% for reduced primary liver cancer mortality was estimated from a government-imposed switch of the dietary staple from maize to rice. These data reinforce the role that aflatoxin plays in high-exposure regions with populations at high risk for HCC (Chen et al., 2013).

CHAPTER 4.

Effects of aflatoxins and fumonisins on child growth

Although animal studies over the past 50 years have repeatedly shown an association between aflatoxin exposure and growth impairment in many species, the evidence has been lacking in humans.

Child growth faltering in low-income countries usually begins in utero and continues for about 2 years postnatally. Therefore, the current analysis is focused on studies of exposures to aflatoxins and/or fumonisins during pregnancy in relation to birth outcomes (e.g. low birth weight) as well as growth outcomes in early childhood. The bulk of the literature relating child growth impairment to mycotoxin exposure focuses on aflatoxin-related stunting. Khlangwiset et al. (2011) summarized the animal and epidemiological studies that showed an association between child growth impairment and aflatoxin exposure. Here, the human studies are critiqued in greater depth in relation to the results obtained and aspects of study design, such as control of important confounding factors and cofactors.

Six studies were deemed to be of high quality, with well-defined sample sizes, exposure or dose assessments, outcome measures, and appropriate multivariate analyses. These are summarized in Table 4.1 and are categorized by toxin (aflatoxin vs fumonisin) and by the timing of the exposure and outcome measurement (pre- vs postnatal).

Eight additional studies did not meet these quality criteria and are therefore not included here (De Vries et al., 1989; Abdulrazzaq et al., 2002; Turner et al., 2003; Abdulrazzaq et al., 2004; Okoth and Ohingo, 2004; Sadeghi et al., 2009; Mahdavi et al., 2010; Shouman et al., 2012).

Studies of pre- or postnatal aflatoxin exposure and postnatal growth

Two studies were published involving a total of 680 children living in four agro-ecological zones of Benin and Togo in West Africa (Gong et al., 2002, 2004). In the cross-sectional study, height-for-age and weight-for-age were lower in a dose-dependent fashion for increasing aflatoxin exposures as measured by aflatoxin–albumin adducts (AF–alb) in serum (Gong et al., 2002). Separately, in a multivariate analysis controlling for these factors as well as age and sex, it was determined that AF–alb levels in children's serum were significantly associated with weaning status: the earlier the weaning, the higher the aflatoxin exposure (Gong et al., 2003). In the longitudinal study, over

Table 4.1. Summary of evidence reviewed on the effects of aflatoxin and fumonisin on child growth

Reference	Study site; context	Study sample	Study design	Exposure measurement and characterization	Outcome measurement and reporting	Handling of covariates and confounders	Findings; inference
				AFLATOXIN STUDIES			
Postnatal exposure							
Gong et al. (2002)	Benin and Togo; rural, 16 villages selected to include high exposures; 33% stunted, 29% underweight, 6% wasted	Community-based, 479 children, 9 months to 5 years	Cross-sectional	AF–alb by ELISA; geometric mean, 32.8 pg/mg (range, 5–1064 pg/mg)	Measured height, weight, age; reported HAZ, WAZ	Age, sex, SES (undefined), agro-ecological zone, weaning status	Dose–response relationship with HAZ and WAZ; overall adjusted negative correlation with HAZ (P = 0.001) and WAZ and WHZ (P = 0.047)
Gong et al. (2004)	Benin; rural, 4 villages selected to include variable exposures; maize and groundnuts	Community-based samples, 200 children (50 per village), 16–37 months at baseline; 181 effectively analysed	Prospective, 8-month FU; samples collected at baseline, middle, and end	AF–alb by ELISA; mean exposures by village: 11.8, 31.1, 45.9, and 119.3 pg/mg	Measured height, weight, age; reported absolute change in height and weight	Age, sex, baseline height, weaning status, mother's SES, village	Height increment by AF–alb quartile, with adjustment, P < 0.001 by trend test; 8-months height increment regressed average AF–alb over 3 time points; no Z-scores reported; weight increment not associated with AF–alb
Shirima et al. (2015)	Three districts in northern and central United Republic of Tanzania; documented co-exposure with fumonisin; high maize and groundnuts	Community-based sample, 166 children recruited at age 6–14 months; 44% stunted and < 3% wasted at baseline	Prospective, 12-month FU; samples collected at baseline, 6 months, and 12 months	AF–alb by ELISA; geometric mean, 4.7, 12.9, and 23.5 pg/mg at baseline, 6 months, and 12 months, respectively (fumonisin also assessed; see below)	Measured height, weight, age; reported absolute change in height and weight	Sex, age, baseline length, village, breastfeeding, maternal education, SES, protein and energy intakes	AF–alb not associated with growth
Pre- or postnatal exposure and postnatal growth							
Turner et al. (2007)	The Gambia; rural	Pregnancy cohort; 138 singleton infants followed for 14 months; 107 analysed	Prospective, 14-month FU; samples collected twice during pregnancy (4.5 months, 8 months) and cord blood and infant at age 16 wk; monthly postnatal FU	AF–alb by ELISA; median values (% detectable): pregnancy average, 38.9 pg/mg (100%); cord blood, 2.5 pg/mg (48.5%); infant at 16 wk, 2.5 pg/mg (11.0%)	Measured birth weight, length, postnatal height, weight, age; reported WAZ and HAZ in mixed longitudinal model using GEE	Sex, age, placental weight, maternal weight, gestation duration, season	Pregnancy AF–alb associated with rate of HAZ and WAZ decline (P < 0.001); effects on WHZ not reported

Table 4.1. Summary of evidence reviewed on the effects of aflatoxin and fumonisin on child growth (continued)

Reference	Study site; context	Study sample	Study design	Exposure measurement and characterization	Outcome measurement and reporting	Handling of covariates and confounders	Findings; inference
				AFLATOXIN STUDIES (continued)			
Prenatal exposure and birth outcomes							
Turner et al. (2007)	The Gambia; rural	Mean birth weight, 2.9 kg					Pregnancy AF–alb not associated with birth weight or length
Shuaib et al. (2010)	Kumasi, Ghana	785 women presenting for delivery, singleton uncomplicated pregnancy; 20.3% LBW, 19.1% preterm, 13.6% SGA	Cross-sectional between mother and baby at birth	AF–alb by HPLC; mean, 10.9 pg/mg	Preterm birth (< 37 wk GA; method unclear); SGA (< 10th percentile of a reference; reference unclear); stillbirth (> 20 wk GA); LBW (< 2.5 kg)	Baby's sex, number of children, maternal education, maternal income, malaria exposure, anaemia, helminths, *Strongyloides stercoralis*	Rates of all outcomes except preterm highest in Q4 of AFB_1, but only LBW significant, Q4 vs Q1 AOR, 2.09 (95% CI, 1.19–3.68); NS for SGA or stillbirth
				FUMONISIN STUDIES			
Postnatal exposure							
Kimanya et al. (2010)	Rural northern United Republic of Tanzania; high maize and groundnuts	Community-based sample, 215 infants aged 6 months at baseline; stunting prevalence at baseline not reported, but LAZ appears to be < −1	Prospective, 6-month FU; samples collected at baseline and 6 months	Dietary fumonisin intake estimated when infants were aged 6–8 months by maize intake from two consecutive 24-hour recalls and HPLC analysis of FB_1, FB_2, and FB_3 in maize samples collected from the home on the days of the recall; 26 infants had intakes > 2 µg/kg bw/day (JECFA PMTDI)	Measured weight, height, age, sex; only absolute height and weight at 12 months were analysed as outcome	Total energy and protein intakes from complementary foods, village, sex, WHZ at baseline	Primary analysis was by high vs low intake of fumonisin (cut-off, 2 µg/kg bw/day); high-intake children were already significantly shorter at baseline; at age 12 months, high-intake infants were on average 1.3 cm shorter and 328 g lighter than low-intake infants
Shirima et al. (2015)	Three districts in northern and central United Republic of Tanzania; documented co-exposure with aflatoxin; high maize and groundnuts	Community-based sample, 166 children recruited at age 6–14 months; 44% stunted and < 3% wasted at baseline	Prospective, 12-month FU, samples collected at baseline, 6 months, and 12 months	Free UFB_1 in urine samples collected on 2 days was measured by HPLC-MS after solid-phase extraction	Measured height, weight, age; reported absolute change in height and weight	Sex, age, baseline length, village, breastfeeding, maternal education, SES, protein and energy intakes	UFB_1 levels at baseline and 6 months were associated with LAZ at 6 months and 12 months, respectively; mean UFB_1 levels from all 3 time points were strongly inversely related to LAZ at 12 months; UFB_1 quartiles were inversely related to LAZ in a linear dose–response manner

AF–alb, aflatoxin–albumin adducts; AFB_1, aflatoxin B_1; AOR, adjusted odds ratio; bw, body weight; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; FB_1, fumonisin B_1; FU, follow-up; GA, gestational age; GEE, generalized estimating equations; HAZ, height-for-age Z-score; HPLC-MS, high-performance liquid chromatography-mass spectrometry; JECFA, Joint WHO/FAO Expert Committee on Food Additives; LAZ, length-for-age Z-score; LBW, low birth weight; NS, not significant; PMTDI, provisional maximum tolerable dietary intake; Q1–Q4, quartile 1–quartile 4; SES, socioeconomic status; SGA, small for gestational age; UFB_1, urinary fumonisin B_1; WAZ, weight-for-age Z-score; WHZ, weight-for-height Z-score; wk, week or weeks.

a period of 8 months children with the highest aflatoxin exposures had the smallest gains in height (Gong et al., 2004). These results were also adjusted for weaning status, agro-ecological zone, and socioeconomic status. The important contribution of this body of work is that in both a cross-sectional and a longitudinal study, higher aflatoxin exposures were shown to be correlated with children's height-for-age and also growth trajectories over a critical period of child development.

A study in The Gambia found a significant association between in utero aflatoxin exposure and growth faltering in infants (Turner et al., 2007). This longitudinal study of 138 pregnant women and their infants followed the infants for 1 year and controlled for season, sex, placental weight, maternal weight, and gestation time, with AF–alb measured by enzyme-linked immunosorbent assay (ELISA). AF–alb in maternal blood serum was a strong predictor of length/height gain and weight gain in the first year of life. It was predicted that if the maternal AF–alb levels dropped from 110 pg/mg to 10 pg/mg, the weights and heights of infants at age 1 year would increase by 0.8 kg and 2 cm, respectively (Turner et al., 2007).

In the United Republic of Tanzania, Shirima et al. (2015) studied a cohort of 166 infants aged 6–14 months at enrolment and followed them for 12 months. AF–alb was measured by ELISA at baseline and 6 and 12 months later. Anthropometric measurements were also taken at each time point. Aflatoxin levels in this study were lower than in the West African studies, rising from a geometric mean of 4.7 pg/mg at baseline to 23.5 pg/mg at the end of the study. The authors found no significant association between aflatoxin dose and stunting in this population.

No study has found an association between aflatoxin exposure and wasting, although wasting was not common in these populations.

Establishing causality of the association between aflatoxin exposure and growth faltering, as reported for studies in Benin and Togo, is uncertain due to the general difficulty of separating the effects of aflatoxin level from possible poor quality of the child's diet. However, in the longitudinal study there was no association between AF–alb and micronutrient levels, suggesting that aflatoxin exposure was not accompanied by a general micronutrient deficiency (Gong et al., 2004). Furthermore, the infant diet in The Gambia includes groundnuts, as opposed to maize in Benin and Togo, and yet results were broadly consistent across these populations. The lack of an association between aflatoxin exposure and growth impairment in the Tanzanian study suggests that there may be a threshold effect. Generalizing the evidence from these four studies is difficult because of their limited geographical distribution (three sites in West Africa) and insufficient information on the links between aflatoxin level, dietary and other cofactors, and growth outcomes.

Studies of maternal aflatoxin exposure and birth outcomes

Shuaib et al. (2010) studied mothers' AF–alb levels at delivery and birth outcomes (preterm birth, small-for-gestational-age, low birth weight, and stillbirth) in Kumasi, Ghana. In this study, AF–alb was measured using high-performance liquid chromatography (HPLC) in the blood of 785 mothers immediately after they had given birth. After adjusting for sociodemographic variables (age, education, socioeconomic status, residence, and type of toilet facilities), 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 (adjusted odds ratio, 2.09; 95% confidence interval, 1.19–3.68). None of the other birth outcomes were associated with aflatoxin measure.

For the postnatal growth outcome in the Turner et al. (2007) study in The Gambia described above, birth weight and length were measured but were not associated with maternal AF–alb concentrations in mid and late pregnancy.

The validity of the findings from these studies on aflatoxin and low birth weight is uncertain because they have small sample sizes for adverse birth outcomes, and thus may not be sufficiently powered to detect important outcomes. Furthermore, it is difficult in observational studies to separate the effects of aflatoxin dose from possible poor nutritional quality of the maternal diet (i.e. monotonous maize diet with little dietary diversity).

Studies of postnatal fumonisin exposure and infant growth

Two recent studies from the United Republic of Tanzania suggest that fumonisin exposure may also be associated with stunting in children. Kimanya et al. (2010) estimated fumonisin exposure in 215 infants by measuring fumonisin in maize flour and estimating the daily fumonisin intake of the infants based on mothers' dietary recall. In this prospective cohort study, infants were enrolled at age 6 months and followed until age 12 months. Exposure was categorized as high or low using the Joint WHO/FAO Expert Committee on Food Additives (JECFA) provisional maximum tolerable dietary intake (PMTDI) of 2 μg/kg body weight/day as the cut-off.

Even at baseline, the 26 infants in the high-exposure category were shorter than those with low exposure. By age 12 months, the highly exposed infants were significantly shorter (by 1.3 cm) and lighter (by 328 g) on average than the 105 infants with low exposure, after controlling for total energy and protein intake, sex, and village.

In the same study in the United Republic of Tanzania described above for aflatoxin exposure, Shirima et al. (2015) found that levels of urinary fumonisin B_1 (UFB_1) at recruitment were negatively associated with length-for-age Z-scores (LAZ) at both 6 months and 12 months after recruitment. Mean levels of UFB_1 from all three sampling times showed an inverse association with LAZ and length velocity at 12 months after recruitment. UFB_1 levels (averaged from two urine samples) at baseline and 6 months were associated with LAZ at 6 months and 12 months, respectively. Mean UFB_1 levels from all three time points were strongly inversely related to LAZ at 12 months.

These initial studies of fumonisin and infant growth are small and offer only limited evidence but do strongly suggest the need for further research on this relationship. The Shirima et al. (2015) study also demonstrates the co-occurrence of aflatoxin and fumonisin in maize-based diets and emphasizes the need for multiple mycotoxin assessments to make clear inferences about causal factors.

Uniting aflatoxin and fumonisin in a single framework is critical because dietary co-exposure is common in Africa and parts of Latin America (see Chapter 1). Smith et al. (2012) suggested possible mechanisms by which foodborne mycotoxin exposure, singly or in combination, may contribute to impaired growth by compromising gut health. Gut enteropathy has been associated with chronic immune stimulation, which is inversely correlated with growth during infancy (Campbell et al., 2003). Increased intestinal permeability may allow translocation of microbial products, which can stimulate a systemic inflammatory response. Smith et al. (2012) described two main pathways by which environmental enteropathy may cause growth retardation: malabsorption of nutrients in the small intestine and systemic immune activation, resulting in suppression of the insulin-like growth factor 1 (IGF-1) axis, which is strongly associated with stunting in African infants (Prendergast et al., 2014). In older children (6–17 years), there is evidence that aflatoxin modulates IGF-1 (Castelino et al., 2015).

Scientific gaps and future research needs

Taken together, the studies described above suggest that mycotoxin exposure contributes to child growth impairment independent of, and together with, other risk factors that may cause stunting.

Among the multiple potential causes of growth faltering in young children globally, dietary mycotoxin exposure emerges as a potentially important factor. The weight of evidence linking aflatoxin with growth impairment has increased over the past five decades of research – first, primarily in animal studies and, in the past decade, in the epidemiological studies reviewed above.

One critical knowledge gap is the mechanism or mechanisms by which mycotoxins may cause child growth impairment. Nor, indeed, is it known whether all mycotoxins use the same mechanism of toxicity that leads to growth impairment (and this should not be assumed). As such mechanisms are elucidated, the weight of evidence linking mycotoxins with growth impairment would become stronger. Several possible mechanisms have been proposed; certainly, one or more may be relevant to the role of mycotoxins in growth impairment.

Immune system dysfunction mediated by mycotoxin exposure (Bondy and Pestka, 2000; Turner et al., 2003) could increase risk of infections in children, which can lead to growth impairment from energy losses (e.g. diarrhoea or vomiting) and/or energy expended on recovery from illness. Also, aflatoxin/fumonisin-mediated changes in intestinal integrity could make hosts more vulnerable to intestinal pathogens (Gong et al., 2008b; Smith et al., 2012).

The IGF-1 axis may represent a common causal pathway in mycotoxin effects on hepatocellular carcinoma as well as growth retardation. Deregulation of the IGF axis has been identified in the development of hepatocellular carcinoma. An increased expression of IGF-2 and the IGF-1 receptor (IGF-1R) and associated binding proteins with degrading receptors have emerged as crucial events in malignant transformation and tumour growth, in altering cell proliferation, and in deactivation of apoptotic pathways. Aflatoxin B_1 (AFB_1) was shown to induce phosphorylation of IGF-1R and activation of the signalling cascade involving Akt (also known as protein kinase B) and Erk1/2 (extracellular signal-regulated protein kinases) in hepatoma cell lines (Ma et al., 2012). AFB_1 was also found to downregulate insulin receptor substrate 1 (IRS-1) while upregulating IRS-2 through preventing proteasomal degradation. Of interest is that the *p53* mutant *p53*-mt249 increases IGF-2 transcription, suggesting that *p53* mutation may be a link between AFB_1 and IGF-2.

Given the widespread global prevalence of aflatoxin and fumonisin exposures and the large associations observed with stunting in the seminal studies from West and East Africa, additional prospective studies are needed in a wider variety of contexts. If the associations reviewed in this chapter are established, then the global burden of disease associated with mycotoxin exposure may be far greater than that based on mycotoxin links to cancer. Future prospective studies must be designed with adequate sample size to elucidate thresholds in dose–response and rigorously control for other known causes of growth faltering, such as low nutrient intake and diarrhoea prevalence. Studies of wasting as an outcome (in addition to stunting) would be informative. Intervention studies in humans are ultimately needed to disentangle effects of toxins from effects of monotonous maize diets and associated poverty.

CHAPTER 5.

Fetal and neonatal toxicities of aflatoxins and fumonisins

Studies of early-life effects of exposure to mycotoxins in experimental animals may provide insight into relevant mechanisms of action that could contribute to short- and long-term toxicities in exposed infants in human populations. Some relevant observations are summarized here.

Aflatoxins

Fetal toxicity of aflatoxin B_1 (AFB_1) has been reported in rats and mice. Toxic effects include decreased fetal weight, external and skeletal malformations, and neural tube defects (NTDs) (IARC, 1993). Developmental NTDs are relatively common birth defects that result from the failure of the neural tube to close properly (Wilde et al., 2014). In humans, the neural tube closes within the first 30 days of gestation, and in mice within the first 9 days.

NTDs have been reported in rat embryos exposed to AFB_1 in vitro (IARC, 1993). Treatment of pregnant rats with AFB_1 resulted in the formation of benign and malignant tumours in the liver, stomach, intestine, endocrine organs, and central and peripheral nervous system in the offspring.

Intraperitoneal AFB_1 treatment of mice during pregnancy produced retardation in fetal development, including cleft palate and diaphragmatic malformation. Carcinogenesis in adult mice mainly targeted the lungs, whereas in infant mice high incidences of liver cell tumours were produced (IARC, 2002). The 20-fold lower level of DNA adducts in adult mice compared with neonatal mice is reflected in the lower incidence of hepatocellular carcinoma (HCC), primarily related to differences in AFB metabolism and the resulting generation of DNA-reactive intermediates (IARC, 2002; Shupe and Sell, 2004).

Studies in newborn male and female transgenic mice that examined mutations in target genes showed no differences in mutation level between sexes (Woo et al., 2011; Wattanawaraporn et al., 2012). As female mice have a much lower incidence of HCC, sex differences related to inflammatory responses, cytokine expression, and sex hormones could be responsible for the differences in tumour outcome. Sex differences in the occurrence of human HCC exist, and the effect of host responsive factors related to AFB and hepatitis B virus interactions and the differential role of metabolism, oxidative, and inflammatory parameters have been suggested as possible explanatory reasons (Wild and Montesano, 2009).

Fumonisins

Dietary folate sufficiency plays a crucial role in reducing NTD incidence in humans (Wilde et al., 2014). In areas of the world where maize is a dietary staple and where there is chronic fumonisin exposure, NTD rates are often very high compared with countries where maize consumption is low (Marasas et al., 2004; Gelineau-van Waes et al., 2009). Wilde et al. (2014) noted that in blocking folate transport, fumonisin was a plausible risk factor for NTDs. In 2012, the Joint WHO/FAO Expert Committee on Food Additives (JECFA) evaluated the existing human epidemiological studies linking fumonisin exposure to NTDs and concluded that the results, in combination with what is known about the toxicology of fumonisin, "indicate that fumonisin exposure in pregnant women may be a contributing factor to increased NTD risk in their babies" (Bulder et al., 2012).

Mechanistically, a case can be made for fumonisin intake as a risk factor since fumonisin inhibition of ceramide synthases disrupts the function of sphingolipid-dependent processes and signalling pathways necessary for normal neural tube closure. For example, studies in fumonisin-treated cells, mouse embryos, and mice in vivo show that folate transport is inhibited as a result of alterations in the membrane biophysical properties induced by inhibition of the biosynthesis of complex sphingolipids (Sadler et al., 2002; Marasas et al., 2004). In mice, NTD incidence induced by intraperitoneal exposure on gestation days 7.5 and 8.5 was significantly reduced by folate supplementation and almost completely prevented by restoration of lipid raft function through the administration of ganglioside GM1 (Gelineau-van Waes et al., 2005). At this gestational time point, the chorion (from the maternal side) and allantois (from the embryonic side) are still in the process of fusing, initiating formation of the mature placenta. Radiolabelled fumonisin B_1 (FB_1) crossed the developing placenta, resulting in accumulation of free sphingoid bases in the placenta and embryos, a finding indicative of fumonisin inhibition of ceramide synthase in the developing embryo. Both the NTD incidence in the mice and the degree of disruption of sphingolipid metabolism were strain-dependent, indicating a possible genetic linkage between NTD induction and disruption of sphingolipid metabolism (Gelineau-van Waes et al., 2005).

Subsequent studies showed that elevated levels of sphingoid base 1-phosphates could also be detected in the livers of fetuses from pregnant mice fed diets containing FB_1 (Riley et al., 2006). The levels of sphinganine 1-phosphate in the fetuses from the NTD-susceptible mouse strain were significantly higher than in the resistant strain. More recent studies in mice have shown that the sphingoid base analogue FTY720 can also induce high incidences of NTD in the susceptible mouse strain after oral exposure during the window of neural tube closure (gestation day 6.5–8.5). Both free sphinganine and FTY720 are phosphorylated by sphingosine kinase to form sphinganine 1-phosphate and FTY720 1-phosphate, which can accumulate to very high levels in maternal blood and placenta of mice of the susceptible strain treated with FB_1 and FTY720, respectively (Gelineau-van Waes et al., 2012). In pregnant mice dosed with FTY720, both FTY720 and FTY720 1-phosphate were shown to accumulate in exencephalic embryos examined on gestation day 9.5 (Gelineau-van Waes et al., 2012). The results provide proof in principle that, in addition to inhibition of folate transport, sphingoid base 1-phosphates also play an important role in NTD induction in fumonisin-treated mice.

Human embryonic stem cell-derived neural epithelial progenitor cells treated with FB_1 in vitro accumulate both free sphingoid bases and sphinganine 1-phosphate, which were shown to disrupt signalling pathways in these human cells (Callihan et al., 2012). Fumonisin inhibition of ceramide synthase has been shown in other human cells in primary culture (human umbilical vein endothelial cells and epidermal keratinocytes). Thus, fumonisin is an inhibitor of ceramide synthase in human cells in vitro, and (as in mouse in vivo) the accumulated sphinganine can be metabolized to the highly bioactive sphinganine 1-phosphate.

Taken together, the data from the mouse studies in vivo and studies with human cells in vitro support the hypothesis that if the fumonisin enters the developing embryo it will inhibit ceramide synthase and has the potential to disrupt sphingolipid metabolism. Alternatively, bioactive sphingoid bases and sphingoid base 1-phosphates, which are present at very high concentrations in the blood, could cross the placenta or act indirectly on the vasculature to cause changes in the developing embryo.

Many feeding studies in farm and laboratory animals have documented the dose-dependent relationship between fumonisin exposure and the tissue and blood levels of key sphingolipids known to regulate physiological processes and signalling systems that are essential for the animals' health (Marasas et al., 2004). Many of the processes potentially affected by altered levels of bioactive sphingolipids are also critical for the health of the mother,

developing fetus, neonate, and litter. For example, complex sphingolipids and sphingolipid metabolites are critical for intestinal nutrient uptake (Jennemann and Gröne, 2013), insulin and insulin-like growth factor 1 receptor (IGF-1R) signalling (Martin et al., 2009; Park et al., 2014), lymphocyte trafficking (Pappu et al., 2007), blood–brain barrier and vascular endothelial integrity (Cannon et al., 2012; Cruz-Orengo et al., 2014), and histone acetylation (Hait et al., 2009), among others.

In utero exposure to fumonisin in humans: scientific gaps and research needs

As noted above, in areas of the world where maize is a dietary staple and where there is chronic fumonisin exposure, NTD rates are often very high. For example, in South Africa, high NTD incidence has been reported in parts of rural Transkei (61/10 000) and in rural areas in Limpopo Province (35/10 000). In contrast, the incidence is much lower in urban communities such as Cape Town (1.06/10 000), Pretoria (0.99/10 000), and Johannesburg (1.18/10 000) (Marasas et al., 2004). The difficulties of accurately capturing population-based rates for NTDs, particularly in low-income countries, make these assessments complicated in regions where there is high fumonisin exposure.

There are many gaps in the understanding of the in utero exposure to fumonisins and possible effects on child health. Studies in mice have revealed that NTDs result from exposure very early in fetal development. At the moment there are no human data demonstrating the ability of fumonisin to cross the emerging human placenta as is the case in mice. It is unlikely that fumonisin would be detectable in umbilical cord blood, given the very small amount of fumonisin that has been detected in animal blood after exposure to relatively high levels of fumonisin (Riley and Voss, 2006; Bulder et al., 2012) and the rapidity with which FB_1 is cleared from human urine (Riley et al., 2012), suggesting that the half-life in the human body is very short.

Although it provides evidence for fumonisin inhibition of ceramide synthase, a shortcoming of using elevated sphinganine 1-phosphate in blood as a biomarker is that it will work well only when high and low fumonisin exposure groups are compared, based on concurrent comparison with the urinary FB_1 levels.

Progress in developing a better understanding of the potential for in utero exposure to either fumonisin or bioactive sphingolipid metabolites in humans is dependent on the discovery of new biomarkers that have a longer half-life or reflect long-term exposure. The half-life of sphingoid base 1-phosphates in human blood is likely to be short, based on the half-life of FTY720 1-phosphate and sphingoid base 1-phosphates in mouse blood (Gelineau-van Waes et al., 2012; Riley et al., 2015). Studies in rats and mice show that the half-life of elevated free sphinganine and sphinganine 1-phosphate is longer than that of FB_1 in the blood or urine; however, it is still elevated for only a few days to a week before returning to control levels (Bulder et al., 2012; Riley et al., 2015).

Fumonisin has been shown to inhibit folate transport in animal models. Folate supplementation has been shown repeatedly to reduce NTD incidence in humans. Thus, studies to assess folate, vitamin, and micronutrient sufficiency in populations consuming maize as a dietary staple are needed to better inform the design of educational approaches to improve the nutritional status of women. This information will also be useful for designing approaches to allow supplementation at either an individual or a community level.

Equally unknown are the possible consequences of fumonisin exposure or exposure to elevated sphingoid base 1-phosphates in utero on child health in early infancy or later in life. Studies on the susceptible mouse model have identified several molecular markers and targets in embryos from fumonisin-treated mice, but their relevance to human exposure is unknown.

In areas where maize is a dietary staple, future studies intended to reveal any possible linkage between maternal fumonisin exposure and reproductive toxicity and growth impairment in children will need to consider the possibility of co-exposure to other mycotoxins, and in particular aflatoxin.

CHAPTER 6.

Effects of aflatoxins and fumonisins on the immune system and gut function

There are few studies in humans that provide information on the impact of aflatoxin on the immune system. Those available have provided suggestive evidence of effects of aflatoxin similar to those observed in relevant animal models (IARC, 2002; Turner et al., 2003; Wild and Gong, 2010). No studies are available of the impact on immune function in populations of children highly exposed to fumonisin or of co-exposure to aflatoxin. Given the prevalence of mycotoxin exposures in populations vulnerable to infectious diseases, there is a need for well-designed studies of the impact of aflatoxin and fumonisin, alone or in combination, on the immune system and intestinal integrity.

Aflatoxins

In vivo studies in pigs exposed to aflatoxin B_1 (AFB_1) suggest that cytokine upregulation occurs at relatively low AFB_1 exposures (~0.9 mg/kg of feed) (Meissonnier et al., 2008). Interleukin-1 (IL-1) levels increased 1 day after dosing, due to production by peritoneal macrophages, in Fisher 344 rats given a single intraperitoneal injection of 1 mg/kg body weight (bw) AFB_1 (Cukrová et al., 1992). Also in Fisher rats, weaned animals were fed diets containing from 0 to 1.6 ppm AFB_1, 4 weeks on and 4 weeks off for 40 weeks, or the 1.6 ppm AFB_1 diet continuously (~0.1 mg/kg bw/day). The percentages of T and B cells in spleen were affected after the dosing cycles. Significantly increased production of IL-1 and IL-6 by lymphocytes in culture was seen in the second dosing cycle (12 weeks) and the second "off" cycle (16 weeks) at the higher doses. Inflammatory infiltrates were observed in the liver after 8 weeks of continuous and intermittent dosing and were increased in size and number at 12 weeks in both 1.6 ppm dose groups. This correlated with peak production of IL-1 and IL-6 (Hinton et al., 2003).

Exposure of Fisher rats to AFB_1 at 5–75 mg/kg bw by gavage for 1 week showed dose-dependent decreases in the percentage of splenic CD8+ T cells and CD3−CD8a+ natural killer (NK) cells. A general inhibition of the expression of IL-4 and interferon-gamma (IFN-γ) by CD4+ T cells, of IL-4 and IFN-γ expression by CD8a+ cells, and of tumour necrosis factor alpha (TNF-α) expression by NK cells was also found. These data suggest that AFB_1 elicits inflammatory responses by inducing cytokine expression (Qian et al., 2014).

Studies in cell lines suggest that AFB_1 inhibits the viability of hematopoietic progenitors and IL-8-induced

neutrophil chemotaxis (Roda et al., 2010; Bruneau et al., 2012). These effects, although identified in vitro, are likely part of the mechanism for AFB_1-related impairment of phagocytosis and bactericidal activity observed in animal models in vivo. Altered white blood cell function is likely to result in a longer and more severe bacterial/fungal infection with greater inflammation. Elevated levels of pro-inflammatory cytokines have been reported in humans, associated with AFB_1 exposure (Jiang et al., 2005). However, it is not clear whether this upregulation is predominantly direct or indirect (as a consequence of prolonged infection/inflammation). Direct upregulation of cytokines might occur through increased transcription factor binding or increased cytokine messenger RNA (mRNA) stability. Another potential mechanism of cytokine upregulation is related to infection in a compromised host. An impaired immune system, in the context of AFB_1 exposure, has been associated with increased viraemia, parasitaemia, increased susceptibility to infection, and reduced response to vaccines in animals (Bondy and Pestka, 2000; Meissonnier et al., 2006).

The intestine functions as a selectively permeable barrier, placing the mucosal epithelium at the centre of interactions between the mucosa and luminal contents, which include dietary antigens, microbial products, and nutrients (Groschwitz and Hogan, 2009; Turner, 2009). The intestine is where various immune mechanisms contribute to pathogen defence. Toxins that alter the integrity of intestinal epithelium are likely to have consequences for both nutrient absorption and pathogen exclusion. Intestinal epithelial cells transport nutrients and fluids and serve to restrict the access for luminal antigens to the internal milieu. Any damage leads to enhanced permeability of the cell layer. There are few recent studies on the impact of dietary AFB_1 on gut function in relevant animal models (Grenier and Applegate, 2013). A common in vitro model system for gut integrity is the Caco-2 cell line (human epithelial colorectal cells). In this model, aflatoxin (150 μM) decreased trans-epithelial electrical resistance (Gratz et al., 2007).

Fumonisins

Two studies were conducted in BALB/c mice with five daily subcutaneous injections of 2.25 mg/kg bw fumonisin B_1 (FB_1). The FB_1 treatment resulted in an increase in the T-lymphocyte population in the spleen of female mice only, compared with controls (Johnson and Sharma, 2001). At a dose of 2.25 mg/kg bw, FB_1 dramatically reduced the immature CD4+/CD8+ double-positive cell population in the thymus of female mice but not of male mice (Johnson and Sharma, 2001). In a second study under the same conditions, FB_1 treatment markedly reduced relative spleen and thymus weights in female mice but not in male mice. Decreased plasma immunoglobulin G (IgG) levels were seen in female mice, and the effect was smaller in male mice. In addition, concanavalin A- and phytohaemagglutinin-induced T-lymphocyte proliferation was significantly reduced in female mice exposed to FB_1. The results of this study suggest that FB_1 is immunosuppressive in mice. The magnitude of the effect was highly dependent on sex; female mice were more susceptible than male mice (Johnson et al., 2001).

Fumonisin has been demonstrated to alter intestinal barrier integrity (Bouhet et al., 2004) and immune function in several studies that affected animal health. Other effects on immune responses included alterations in cytokine expression, decreased antibody titre in response to vaccination, and increased susceptibility to secondary pathogens (Bulder et al., 2012). In swine, oral exposure to fumonisin resulted in sex-specific decreased antibody titres after vaccination and increased susceptibility to secondary pathogens (Oswald et al., 2003; Halloy et al., 2005; Marin et al., 2006). There is one study in swine exposed to pure fumonisin at a dose of 1.5 mg/kg bw for 7 days. FB_1 treatment induced a significant downregulation of the expression of IL-4 mRNA in the spleen and mesenteric lymph nodes (Taranu et al., 2005). Also, an extract of culture material containing fumonisin was incorporated in the basal diet to provide feed containing FB_1 at 8 mg/kg of feed for 28 days. The animals were immunized subcutaneously with Agavac, a vaccine made with a combination of formol-inactivated *Mycoplasma agalactiae* strains, followed by a booster shot 2 weeks later. Exposure to the contaminated diet diminished the specific antibody titre after vaccination against *M. agalactiae*. In contrast, ingestion of the contaminated feed had no effect on the serum concentration of the immunoglobulin subsets (IgG, IgA, and IgM). The authors concluded that FB_1 altered the cytokine profile, which in turn affected the antibody response (Taranu et al., 2005).

In pigs fed a diet containing fumonisin at about 0.25 mg/kg bw, multifocal atrophy and villi fusion, apical necrosis of villi, cytoplasmic vacuolation of enterocytes, and oedema of lamina propria were observed in intestinal tissue compared with controls. Lymphatic vessel dilation and prominent lymphoid follicles were also observed (Bracarense et al., 2012).

No information was provided on the functional impact of these morphological changes. Modulation of intestinal cytokine production was also observed in pigs exposed to fumonisin, as well as in intestinal cell lines (Bouhet et al., 2006; Bracarense et al., 2012). There have been at least two studies in mice showing FB treatment-induced disruption of sphingolipid metabolism in the small intestine. One study used subcutaneous injection (single dose, 25 mg/kg bw) and the other oral gavage (single dose, 25 mg/kg bw) (Enongene et al., 2000, 2002). This work illustrated the importance of sphingolipids and sphingolipid metabolites in the gut in relation to inflammation and barrier function, and also in the regulation of inflammatory response associated with endotoxin and microbial sepsis (Enongene et al., 2000, 2002).

CHAPTER 7.

Intervention strategies to reduce human exposure to aflatoxins and fumonisins

This chapter reviews a broad range of interventions associated with the reduction of aflatoxin and/or fumonisin exposure that have proven health benefits at a community level and are suitable for implementation in rural Africa and Central America. The interventions vary in resources required, complexity, and useful scale. For effective implementation, all require social consent and political will. Some interventions are complicated and resource-intensive, and others are simple to implement on a community or even household scale. Nonetheless, all are unified by the need for cultural and sex-specific training, access to robust technology for implementation, and sustainability. Some of the interventions require further work to verify their efficacy in areas of high aflatoxin exposure.

The Working Group assessed the question of effective interventions in low-income countries using studies where there was reliable direct or indirect evidence of improvement of health, including reduced mycotoxin biomarker levels. The evaluation of evidence about public health interventions includes examining the credibility of the evidence as well as its completeness and its transferability at an individual, community, or national level. The "best quality" evidence (i.e. indicating that an intervention is ready for implementation) is for an approach that has reached a mature stage of development, results in significant intervention effects, and addresses the needs of important stakeholders (Rychetnik et al., 2002). Fifteen interventions were placed into one of four categories: (1) sufficient evidence for implementation, (2) needs more field evaluation, (3) needs formative research, and (4) no evidence or ineffective. Recommendations on how to approach the necessary further investigation and potential scale-up were also considered. The results of these evaluations are summarized in Table 7.1. The following text provides an analysis of the respective interventions.

Regulation

Although they are not explicitly discussed as interventions, corporate, international, and governmental regulatory frameworks can be important drivers in the reduction of mycotoxin levels in food and feed. The available evidence shows that the development of a functioning food safety system begins in the corporate sector, both for domestic consumption and for export crops

Table 7.1. Summary of the Working Group's evaluation of interventions associated with the reduction of aflatoxin and/or fumonisin exposure

Intervention	Category of evidence[a]	Context	Gap (research/translation)	Combination/issues/comments
Dietary diversity	—[b]	**Dose effect reduction of hepatocellular carcinoma**	• Investment in appropriate crops for the target region, both suitable for the climate and culturally acceptable	**Comment:** Difficult in food-insecure situations or in food-, arable land-, or water-insecure countries
Genetic resistance		**Contamination**		
Aflatoxin in maize	3		• Movement of resistance in agronomic lines • Identification of resistance genes	**Combination:** Biocontrol; agronomic and post-harvest practices **Issues:** Small research community; large environmental effect on phenotype expression; resistance is polygenic
Fumonisin in maize	2		• Movement of resistance in agronomic lines • Identification of resistance genes	**Combination:** Agronomic and post-harvest practices **Issues:** Small research community; large environmental effect on phenotype expression; resistance is polygenic
Aflatoxin in groundnuts	4		• Identification of sources of resistance • Movement into agronomic lines	**Combination:** Biocontrol; agronomic and post-harvest practices **Issues:** Large environmental effect on phenotype expression limits resistance expression over large areas; small research community; resistance is polygenic; resistance is not well described
Biological control		**Contamination**		
Atoxigenic strains	2		• Frequency and outcomes of genetic recombination • Consistency of efficacy evaluated across geography and users	**Combination:** Agronomic and post-harvest practices **Comment:** Ongoing translational research in Africa and the USA
Primary prevention		**Dose effect**		
Dioctahedral smectite clay	2		• Dose and duration on efficacy and safety • Effects on infants, children, and pregnant women	**Combination:** Clay amended with chlorophyllin and other trapping agents **Issue:** Formulation strategies **Comments:** Possible enhanced efficacy during outbreaks; potential to mitigate aflatoxins and fumonisins
Chlorophyllin	2			
Lactobacillus	3			
Yeast glucan	4			
Post-harvest		**Dose effect/ contamination**		
Package	1		• Knowledge translation is cultural • Modules need to be developed in partnership with farmers, area agricultural extension workers, traditional leaders, church groups, health workers, and civil society	**Comments:** Ready to be implemented; use in chronic-exposure situations as an ongoing intervention package; needs to be applied as a multifactorial intervention package
Sorting	1		• Done in all cultures for all crops; however, best practices need to be formally taught at the village level	**Issue:** Fate of the rejected food **Comment:** Important for complementary food
Nixtamalization	1		• Requires adequate water for washing • Has not been adapted in Africa or Asia	

Table 7.1. Summary of the Working Group's evaluation of interventions associated with the reduction of aflatoxin and/or fumonisin exposure (continued)

Intervention	Category of evidence[a]	Context	Gap (research/translation)	Combination/issues/comments
Chemoprevention		**Dose effect**		
Broccoli sprout extract	2		• To date, phase II clinical trials for efficacy; need for scaling to longer-term interventions • Translation to local, culturally acceptable foods with these enzyme inducers • Biomarker studies to date; no health end-point studies yet	**Comment:** Opportunity for use in acute-exposure situations; native plants; dietary diversification
Dithiolethiones	2			
Green tea polyphenols	2			

[a] Categories of evidence for public health interventions: (1) sufficient evidence for implementation, (2) needs more field evaluation, (3) needs formative research, and (4) no evidence or ineffective.
[b] This is a proven intervention (see text) but could not be designated as 1 (sufficient evidence for implementation) because of the complexity of achieving this goal in most circumstances.

(Reardon et al., 1999; Kussaga et al., 2014). As capacity and appropriate legal frameworks and enforcement structures are put in place, contamination levels in crops eventually decrease. However, the positive impact on subsistence farmers is usually limited, with the benefits generally going to larger farmers (Hansen and Trifković, 2014).

Where regulatory systems are established, implementation of intervention strategies and technologies is usually robust and foodborne exposure is low. Where regulatory systems are not fully functional, a basic developmental goal should be to put systems in place and get them operational. Enforcement of risk-based food law is critical to public health and economic viability, and drives the development and sustained use of intervention technologies.

Dietary diversity to mitigate mycotoxin exposure

Dietary diversity is a good way to improve nutrition and health (FAO, 1997; Frison et al., 2006; Lovo and Veronesi, 2014). Aspects important for a healthy diet include the number of different foods, the quantities, and the health (nutritional) value of those foods available for consumption (Drescher et al., 2007). Dietary data from the United Republic of Tanzania estimated the effect of crop diversification on child growth and projected a positive and significant impact on child nutritional status, particularly for girls and on children's height (Lovo and Veronesi, 2014).

A lack of dietary diversity is directly related to levels of mycotoxin exposure. In rural Africa and parts of Latin America, a high percentage of calories come from maize, which is commonly contaminated by aflatoxins and/or fumonisins. In East Africa, aflatoxin exposure has also been directly correlated with reported daily intake of maize, and fumonisin exposure occurs almost entirely from maize (Kimanya et al., 2008). Another major source of exposure to aflatoxin is through the consumption of groundnuts (Liu and Wu, 2010; IARC, 2012). Access to a greater variety of foods will lower the risk of exposure by lessening the intake of these commonly contaminated foods (Groopman et al., 2008). Replacing foods at high risk of mycotoxin contamination with those at lower risk would improve access to foods with better nutritional value.

An excellent example of improved health outcomes after a switch from a food source at high risk of aflatoxin contamination to one at lower risk occurred in Qidong, China. A government policy to grow foods that are eaten locally, combined with a prohibition on interregional shipments of food products, had forced residents of Qidong County to produce and consume primarily maize for several decades. Liberalization of the transboundary provincial trade policy allowed rice to be imported from other regions of the country, replacing maize as the staple cereal. Since aflatoxin contamination is much lower in rice than in maize, the result was reduced aflatoxin exposure and a precipitous drop in liver cancer incidence (Chen et al., 2013).

Food diversity and exposure risk can also be driven by socio-economic factors. In West Africa, Egal et al. (2005) reported that the average frequency of maize consumption is 5–7 days per week. Maize is currently the most common cereal staple, having displaced the native cereals sorghum and millet and other sources of starch (Miracle, 1966). Consumption of groundnuts, another common source of aflatoxins, was positively correlated with household and maternal wealth variables and varied by agro-ecological zone. In Ghana, Shuaib et al. (2012) showed interesting evidence of an inverse relationship between a woman's income and the level of aflatoxin biomarkers in her blood. This suggested that greater purchasing power may improve the opportunity for diversifying food choices.

Changing food preferences where there are no economic constraints can be a matter of social marketing and awareness. However, changing food preferences and access for people living in food-insecure conditions presents an enormous challenge. In 1950, by far the major source of dietary starch in sub-Saharan Africa was sorghum and millet (40%), followed by cassava (30%) and maize (15%) (Miracle, 1966). The subsequent shift towards maize is part of a global trend; over the past 50 years, consumption of sorghum and millets has declined by 50% and consumption of cassava by 40% (Khoury et al., 2014). In turn, this may have had a major role in increasing aflatoxin exposures. In West Africa, for example, aflatoxin concentrations in pearl millet and sorghum were substantially lower than those in maize (Bandyopadhyay et al., 2007).

Genetic resistance to aflatoxin and fumonisin contamination of maize

Aflatoxins

Genetic resistance to aflatoxin and fumonisin contamination exists in maize populations, but it is complex and involves multiple genes, and genetic engineering requires moving resistance genes into agronomically acceptable genotypes (Moreno and Kang, 1999; Eller et al., 2008; Warburton et al., 2013; Zila et al., 2013; Warburton and Williams, 2014).

Resistance to ear-feeding insects is associated with lower levels of aflatoxins and fumonisins (Miller, 2001; Munkvold, 2003). Transgenic expression of *Bacillus thuringiensis* (Bt) toxins reduces insect damage and fumonisin contamination (de la Campa et al., 2005; Barros et al., 2009; Ostry et al., 2010; Abbas et al., 2013; Pray et al., 2013). The effectiveness of Bt in reducing aflatoxin contamination is inconclusive (Abbas et al., 2013).

Proteomic, transcriptomic, and histological analyses of the interaction between the fungus and the maize seed show striking similarities to other well-characterized systems, suggesting that resistance is achievable. The new genetic technologies, along with improved breeding populations and phenotyping strategies, have dramatically increased the number of genetic markers associated with resistance to aflatoxins and fumonisins and have identified putative resistance genes and proteins (Lanubile et al., 2010; Brown et al., 2013; Campos-Bermudez et al., 2013; Dolezal et al., 2013, 2014; Warburton and Williams, 2014).

Progress has been made in selecting breeding lines of maize with resistance to aflatoxin accumulation that show high and repeatable resistance under different environments (Mayfield et al., 2012; Williams and Windham, 2012). Additional resistance has come from the Germplasm Enhancement of Maize Project, which is a public–private programme that uses exotic germplasm from across the world, including from the International Maize and Wheat Improvement Center (CIMMYT) (Li et al., 2002; Henry et al., 2013). Use of the maize core diversity panel, which captures most of the maize diversity in breeding programmes worldwide (Flint-Garcia et al., 2005), has identified more than 30 lines showing good resistance to mycotoxins in up to seven environments (Warburton et al., 2013; Warburton and Williams, 2014). These maize germplasm lines are publically available, and several already have been included in a joint United States Agency for International Development/United States Department of Agriculture (USAID/USDA) project, together with two CGIAR centres, with the goal of developing resistant hybrid cultivars (Warburton and Williams, 2014). As part of a USA–Africa collaborative strategy, the International Institute of Tropical Agriculture and USDA released six inbred lines adapted to Africa with enhanced resistance to aflatoxin accumulation (Menkir et al., 2006, 2008).

In summary, maize hybrids with improved resistance to *Aspergillus flavus* and aflatoxins are being used, but the level of resistance is not yet adequate to prevent unacceptable aflatoxin contamination in some fields. Putative resistance-associated genes have been identified by gene expression profiling studies and could be evaluated for their role in resistance to aflatoxin contamination.

Fumonisins

Many genotypes have been identified with some resistance to fumonisin accumulation (Mesterházy et al., 2012; Santiago et al., 2013), including germplasm lines adapted to Argentina (Presello et al., 2011), Central and West Africa (Afolabi et al., 2007), and South Africa (Small et al., 2011), but no hybrids are available with adequate resistance. Heritability for resistance to fumonisin accumulation is higher than that for resistance to aflatoxin contamination (Zila et al., 2013), and a moderate to high genotypic correlation between ear rot and fumonisin content suggests that resistance to the fungus and to fumonisin production may be closely linked (Eller et al., 2008; Presello et al., 2011; Zila et al., 2013). This correlation has allowed selection for resistance to fumonisin accumulation based on ear rot scores (Robertson et al., 2006; Eller et al., 2008; Santiago et al., 2013), thus making screening quicker and less expensive.

Genome-wide association studies on the maize core diversity panel have identified three novel loci associated with 3–12% of the genetic variation associated with resistance to ear rot (Zila et al., 2013). Three putative resistance genes co-localized with the genetic markers. The large number of genetic markers available on the diversity panel is allowing the dissection of complex quantitative traits, such as resistance to mycotoxin accumulation.

Fumonisin accumulation is consistently decreased when Bt maize hybrids effectively reduce insect damage. This can make the difference between maize products that are relatively safe and those that are not (de la Campa et al., 2005; Pray et al., 2013).

Genetic resistance to aflatoxin contamination of groundnuts

Genetic resistance to aflatoxin contamination in groundnuts is complex: heritability is low to moderate, there is a poor correlation between fungal growth and aflatoxin contamination, and results from in vitro seed assays do not correlate with those from field assays (Holbrook et al., 2008; Arunyanark et al., 2010; Girdthai et al., 2010b; Hamidou et al., 2014).

Germplasm with some resistance is available, but genotypes do not show consistent response across locations, due to large interaction effects between the genotype and environment on aflatoxin contamination (Liang et al., 2006; Arunyanark et al., 2010; Girdthai et al., 2010a, 2010b; Hamidou et al., 2014).

One key environmental effect is drought stress, and many programmes have focused on breeding for drought tolerance as a way to improve resistance to aflatoxin contamination. A field study in West Africa examined 268 genotypes over four locations and confirmed that drought stress intensity increases aflatoxin contamination; however, the investigators did not show a significant relationship between drought tolerance and aflatoxin contamination (Hamidou et al., 2014), possibly due to other site-specific environmental effects.

An improved understanding of resistance mechanisms should help improve selection of resistant germplasm. Genome sequences of the two diploid progenitors of groundnut are now available (http://peanutbase.org/browse_search), which may facilitate molecular mapping and breeding for disease resistance.

Biological control of aflatoxins

In the USA, biocontrol strategies have been developed to reduce aflatoxin contamination in cottonseed (Cotty, 1994), groundnuts (Dorner and Lamb, 2006), maize (Dorner et al., 1999), and pistachio nuts (Doster et al., 2014) using strains of *A. flavus* that do not produce aflatoxins (i.e. atoxigenic strains). In commercial practice in the USA, these atoxigenic strains are applied to the field during crop development (Cotty, 1994; Dorner and Lamb, 2006). Under appropriate conditions, the spread of the introduced strain throughout the field displaces the native, toxic strains (Mehl et al., 2012; Atehnkeng et al., 2014). Strains formulated into biological control products may be single clones (Bock and Cotty, 1999) or be composed of more than one strain to improve local adaptability (Atehnkeng et al., 2014).

Several factors have been identified that affect efficacy. Dew and moisture will allow for the atoxigenic strains to produce spores over several days (longer if conducive conditions persist). If the seeds are placed on dry soil, an adequate production of spores may not occur, but they will stay inert and viable until moisture is available (Bock and Cotty, 1999). A late application of atoxigenic strains on maize (after silking) may not be effective. In the event of a heavy rain shortly after the inoculum is spread, the biological control product may not stay evenly distributed on the surface of the field. In a review of the use of atoxigenic strains of *A. flavus* in the USA, Abbas (2011) indicated that this technology is emerging as a useful management practice for reducing aflatoxin concentrations in maize.

Use under African conditions

In one study in Nigeria, the inoculation of a mixture of four endemic atoxigenic strains of *A. flavus* in maize plots in four agro-ecologies over 2 years resulted in significant reductions in aflatoxin concentrations at harvest and after storage (Atehnkeng et al., 2014). At harvest, the reduction in aflatoxin ranged from 57.2% (27.1 ppb in untreated plots vs 11.6 ppb in treated plots) to 99.2% (2792.4 ppb in untreated plots vs 23.4 ppb in treated plots). The applied atoxigenic strains remained with the treated crop, and the reduction in aflatoxin concentration in grains after poor storage ranged from 93.5% (956.1 ppb in untreated vs 66.2 ppb in treated) to 95.6% (2408.3 ppb in untreated vs 104.7 ppb in treated).

In Nigeria, a similar percentage of maize samples were contaminated by both aflatoxin and fumonisin (Adetuniji et al., 2014; Adetunji et al., 2014), which is not uncommon. In situations where conditions are permissive for both aflatoxin and fumonisin in the field, interventions that are effective for both toxins are needed. Aside from Bt maize, which is not yet widely used in Africa, there are few interventions for pre-emptive prevention of fumonisin in the field. Preliminary trials have shown potential for development of biological control treatment for *Fusarium verticillioides* (Sobowale et al., 2007).

Genetic recombination with *A. flavus* has been shown to increase genetic variation within the populations (Olarte et al., 2012; Horn et al., 2014). Sexual recombination leading to the acquisition of toxin genes is possible, but the implications of this are not clear with respect to biological control (Abbas et al., 2011). Studies to date show that aflatoxin production is heritable and is not lost during sexual recombination; however, hybridization between toxic and atoxigenic strains produced progeny of no or lower aflatoxin production (Olarte et al., 2012).

Cyclopiazonic acid can also be produced by A. flavus

Cyclopiazonic acid (CPA) has been shown to be toxic and immunosuppressive in various strains of mice and rats as well as swine and poultry (Burdock and Flamm, 2000; De Waal, 2002; King et al., 2011). One of the commercial atoxigenic strains used in the USA, AF36, produces CPA. It is possible to select for strains of *A. flavus* that produce neither aflatoxin nor CPA (King et al., 2011). Efforts need to be made to minimize or eliminate CPA production in biological control strains before use (Abbas et al., 2011; King et al., 2011).

Research needs

The use of atoxigenic strains to help manage aflatoxin in maize and groundnuts in Africa, and other parts of the world, will require an investment to optimize, adapt, and deploy the technology in a sustainable manner.

Given the large number of exploratory investigations in Africa, studies are needed to evaluate the impact of the low rate of genetic recombination, which will then inform the deployment of the technology in diverse settings.

Sorting

In developed countries, sorting and grain cleaning techniques are required to reduce mycotoxin contamination, notably in grains contaminated by ergot and in nuts. Ergot sclerotia are removed by specific gravity seed cleaning equipment, a practice that has been in place for a long time. In groundnuts, after basic clean-up of the crop by commercial farmers, high-capacity electronic optical sorters are used to remove nuts contaminated by aflatoxin (Whitaker et al., 2005). For maize, normal grain cleaners reduce aflatoxin and fumonisin by 50–60% (Malone et al., 1998; Pacin and Resnik, 2012), far less than the reduction from hand sorting (Brekke et al., 1975).

Soon after the discovery of aflatoxin in 1961, sorting emerged as a regular and effective practice to improve safety for groundnuts. The need for efficient ways to remove aflatoxin-contaminated nuts prompted experiments on the concentrations of aflatoxin in kernels from shells that were not visibly mouldy. This revealed that visual sorting was an efficient way to segregate more- versus less-contaminated kernels in the laboratory. However, parts of some nuts that appeared sound contained substantial levels of aflatoxin (Cucullu et al., 1966). In the USA, after 3–4 hours of training on visual signs of contamination with *Aspergillus*, people with no prior experience were asked to visually sort samples of groundnuts that had already been classified according to their quality (sound, damaged, intermediate) by federal inspectors according to the official grading procedure. In the best grade of groundnuts, misclassification occurred, which the authors ascribed to mostly false-positives, with some false-negatives and sampling error (Dickens and Welty, 1969).

By 1968, another step was introduced into the United States inspection system: examination by the inspectors of the damaged kernels for *Aspergillus*. After training, each inspector was given a folder with two sets of coloured photographs that showed what to look for and what not to look for. Before the development of the current methods

of inspection, this low-technology approach was proven useful (Goldblatt, 1973). Whitaker et al. (1998) demonstrated that visual sorting of groundnuts provided a practical first-action regulatory method. They found that sound mature kernels and sound half kernels contained about 7% of the aflatoxin, with the damaged kernels containing the rest. Studies on grains contaminated with *Fusarium* toxins indicate that these strategies work best where there is ongoing training (Desjardins et al., 2000; van der Westhuizen et al., 2010). A study in the Philippines found that manual sorting reduced aflatoxin concentrations in lots of raw groundnuts from 300 ng/g to less than 15 ng/g (Galvez et al., 2003). Research conducted in Kenya (and Haiti) demonstrated that manual sorting of groundnuts purchased at local markets could reduce lot aflatoxin concentrations by about 98% (Filbert and Brown, 2012).

In the case of maize in Africa, manual sorting is moderately effective at the village level for segregating kernel lots for decreased concentrations of aflatoxin. Removing visibly mouldy, insect-damaged, and broken grains by hand reduced aflatoxin concentrations by 40%, based on reports from a study in Benin (Fandohan et al., 2005). Studies in South Africa and the United Republic of Tanzania have demonstrated that hand sorting of maize kernels by local farmers by removing the visibly infected or damaged kernels reduced fumonisin concentrations by 20% (Kimanya et al., 2009; van der Westhuizen et al., 2010).

The willingness to hand sort grains and nuts has been shown to depend on the available supply (Kimanya et al., 2008; van der Westhuizen et al., 2010; and references cited therein). A study in Ghana found that household income and agricultural training increased the quality of the nuts consumed (Adu-Gyamfi, 2013). In South Africa, the effectiveness of hand sorting on fumonisin reductions has been documented by biomarkers (van der Westhuizen et al., 2011).

In developed countries, sorting of contaminated grains is the primary tool used to reduce mycotoxin contamination in grains and nuts after harvest and can be effective at all scales of production.

Research needs

There is a need to adapt commercial optical sorting equipment for groundnuts for the African value chain for both large and small operations.

Targeted training in manual sorting for rural women would appear to be a good investment. In Africa, food security is the major barrier to implementation of sorting (Fandohan et al., 2008). Safe alternative uses for rejected lots need further research (e.g. Filbert and Brown, 2012).

Nixtamalization

In Mexico and Central and South America, nixtamalization has been the usual practice for millennia. Hydrolysis of fumonisin during commercial production of masa virtually eliminates fumonisin. Masa is made by boiling maize meal with the addition of lime, which is then washed out. The ratio of maize to lime to water used and the boiling, soaking, and rinsing practices vary (De La Campa et al., 2004).

In the USA, fumonisin concentration is low in commercial tortillas from major companies (Voss et al., 2001). In contrast, in the USA, masa products from artisanal production facilities often contain some fumonisin (De La Campa et al., 2004; Dvorak et al., 2008). Where there is sufficient washing of the lime-treated product in the traditional process before consumption, concentrations of fumonisin and aflatoxin are lowered (De Arriola et al., 1988; De La Campa et al., 2004; Méndez-Albores et al., 2004; Guzmán-de-Peña, 2010). In Latin America, variability in the process means that there can be residual parent fumonisin in the tortillas (e.g. Dombrink-Kurtzman and Dvorak, 1999; Meredith et al., 1999) that leads to fumonisin exposure (Gong et al., 2008a).

Research needs

In Latin America, nixtamalization has been shown to reduce exposure to aflatoxin and fumonisin. A knowledge translation package based on factors known to reduce fumonisin in the residual masa (De La Campa et al., 2004) would be beneficial.

Post-harvest storage intervention strategies to reduce aflatoxin and fumonisin exposure

Mycotoxin contamination of crops can occur in the pre- and post-harvest agricultural system due to inadequate agricultural practices. Fungal growth and toxin production can occur in the field (e.g. fumonisin, aflatoxin), in storage (aflatoxin), or in both. High humidity (> 85%), high temperatures (> 25 °C), insect and rodent activity, improper drying of crops, and water infiltration in the storage structure will result in the growth of *A. flavus* and *Aspergillus parasiticus* and aflatoxin accumulation (Adegoke and Letuma, 2013).

Most developing countries are located in the world's tropical zones and are subjected to monsoons and high temperature and humidity levels, which contribute to large post-harvest crop losses.

Inadequate storage practices account for 20–50% of these losses. Despite being a major United Nations priority since 1946 (Schulten, 1982), such losses remain a global problem, increasing the risk of food insecurity (food availability, hunger, and nutritional value) and poverty (Hell et al., 2008; Jayas, 2012; Kimatu et al., 2012; Gitonga et al., 2013; Guillou and Matheron, 2014). The double burden of both chronic exposure to mycotoxins and food insufficiency increases both mortality and morbidity, especially in children (Bryden, 2007; IARC, 2012). Adequate post-harvest measures that are practical, economic, and culturally acceptable will therefore address food safety and security and improve public health.

In subtropical climates, maize in the field is typically infected by *A. flavus*, and unless it is dried very quickly, aflatoxin concentrations increase after harvest (IARC, 2012). The stored post-harvest crop ecosystem is therefore an integral part of mycotoxin prevention strategies (Marín et al., 2004; Choudhary and Kumari, 2010; Chulze, 2010). Most of the conditions associated with the post-harvest period can be controlled, unlike those affecting the pre-harvest phase. Strategies to reduce mycotoxin levels during storage mainly consist of: adequate drying of crops before storage; using clean, dry, and enclosed storage facilities; proper water drainage; well-aerated stores; and eliminating insect activity and other pests such as rodents and birds (Lanyasunya et al., 2005; Turner et al., 2005; Hell et al., 2008).

Before storage, harvested field crops should be dried as soon as possible to reduce fungal growth; safe moisture levels recommended for cereals are 10–13% and for oilseeds are 7–8% (Hell et al., 2008). Common storage practices for crops include: on the field; on the floor in homes; on top of or under the roof of houses; in jute or polypropylene bags, wire cribs, pits, and metal bins; and in conical structures or other constructed structures, with or without roofing, made from wood, bamboo, thatch, or mud (Hell et al., 2010; Narrod, 2013; Abass et al., 2014).

Evidence-based post-harvest storage intervention strategies among subsistence farmers are limited. Turner et al. (2005) conducted a field study among groundnut farmers in West Africa (600 volunteers from 20 villages) to reduce aflatoxin exposure by implementing a specific intervention package, and to assess the impact of the intervention by monitoring aflatoxin B_1 (AFB_1) levels in groundnuts and blood aflatoxin–albumin adducts (AF–alb) as a measure of exposure. The intervention package included hand sorting of kernels (with removal of damaged kernels), drying kernels on natural fibre mats, estimating the completeness of a sun-drying period, storing kernels in natural fibre bags, supplying wooden pallets to store the bags on, and using insecticide (acetilite). Significant reductions in both AF–alb in blood (58% reduction) and groundnut contamination levels (70% reduction) were observed. This is the only study of its kind that showed the reduction of aflatoxin exposure in the groundnut-consuming population (Turner et al., 2005).

In Africa, maize is matured under dry conditions and is commonly left in the field to dry on the stalk, whereas in South-East and East Asia, maize is sometimes harvested wet and piled in stacks and left on the field to dry for a period of time (Pitt et al., 2013). Maize may also be shelled, and this, together with drying practices, increases aflatoxin levels. However, crops dried adequately away from the field and off the ground are less susceptible to insect damage and fungal growth.

Sun-drying of maize and groundnuts is common practice in Africa and, together with the use of platforms, has been shown to reduce the growth of toxigenic fungi such as *Aspergillus*, *Fusarium*, and *Penicillium* (Hell et al., 2008). In Ghana, the method of inverted windrowing of groundnut pods after harvest ensures exposure to direct sunlight and circulating air. This cost-effective method dries the pods rapidly and sufficiently to ensure reduction of aflatoxin levels (Amoako-Attah et al., 2007). For groundnuts, drying on raised surfaces or on mats to a kernel moisture content of 8% is required to reduce the risk of aflatoxin contamination (Waliyar et al., 2013).

Kaaya and Kyamuhangire (2010) investigated the effect of biomass-heated natural convection dryers on maize quality during storage in Uganda. During that study, insect damage, mould infection, aflatoxin contamination, and the maize germination potential were determined. The use of these dryers proved to be protective against insect damage, reduced mould and aflatoxin contamination, and had no effect on the grain germination potential. They also were shown to be highly effective in eliminating crop loss due to insect damage. Additional benefits included the reduced need for insecticides to protect the crop, the extension of crop storage duration by 1.8–2.4 months, the improvement of availability of food by more than 1 month, and an increase in jobs and income.

A suggested replacement for sun-drying is the use of solar dryers, because they dry crops faster and more efficiently and provide a controlled environment that offers improved sanitation (Sharma

et al., 2009; Ogunkoya et al., 2011). The lack of success of using solar-based drying among rural commercial farmers has been attributed to the cost, complicated operational procedures, and the reluctance to change from traditional methods (Ekechukwu and Norton, 1999). Small-scale farmers require solar dryers that are more affordable to purchase or construct and need little maintenance (Ogunkoya et al., 2011). Of the solar drying technologies available, including the active (forced-convection) solar dryers and the passive (natural-circulation) types, the use of a ventilated greenhouse dryer has been suggested for rural small-scale farmers, due to its low cost, simplicity, and on-site construction and operation (Ekechukwu and Norton, 1999).

The use of hermetically sealed storage bags, such as those of the Purdue Improved Crop Storage project, is apparently effective for insect control, increasing insect mortality by 95–100% in stored maize (Baoua et al., 2014; Hell et al., 2014). The efficiency of hermetic technologies to prevent fungal growth and consequent mycotoxin contamination seems to be dependent on the type and specific characteristics of the crop. Storage of groundnuts in Super Grain Bags (bags made of multilayer polyethylene that have a two-track zipper and are sealed using a zipper slider) reduced the growth of aflatoxin-producing fungi during an experimental study (Navarro et al., 2012). Mutegi et al. (2013) showed that groundnuts stored in polyethylene bags were 7–13% more contaminated than samples stored in polypropylene and jute bags. Jute bags are considered more feasible compared with polyethylene and polypropylene only if crops are properly dried before storage; polyethylene and polypropylene bags are poorly aerated and do not absorb moisture. The use of natural fibre jute bags has been suggested to be more suitable to maintain crop quality (Turner et al., 2005).

Research needs

Strategies to improve post-harvest storage of crops should be an urgent research priority (Anankware et al., 2012). Ideally, technologies should be economically feasible, require low labour intensity, be practical and sustainable, reduce the need to use chemicals, and be convenient, widely available, and easy to transport (Hell et al., 2010; Baoua et al., 2014). The interventions should also be developed for both rural small-scale and commercial farmers. In sub-Saharan Africa, 80% of farms are smallholder, mostly subsistence farms (Mboya and Kolanisi, 2014), and a distinction should be made as to what technologies are feasible for commercial versus small-scale farmers in rural areas.

The cultural acceptability of a proposed intervention in the different agricultural systems is also important. Therefore, post-harvest strategies in developing countries should be comprehensively field-tested and validated to assess their efficacy, economic feasibility, cultural acceptability, and sustainability (Strosnider et al., 2006; De Groote et al., 2013; Jones et al., 2014). To ensure compliance, it will be important to monitor large-scale implementation.

Apart from the lack of feasible and inexpensive strategies, other obstacles to improving post-harvest storage of crops include the absence of governmental commitment and the shortage of trained personnel, such as agricultural extension workers (Hell et al., 2010). Establishing strategies to safeguard crops during storage will inevitably require cooperation and communication between governments, research entities, nongovernmental organizations, other stakeholders (market agencies, farmers' and consumer groups), manufacturers, and the farmers.

In Africa, farmers' awareness of the health risks associated with aflatoxin and how to reduce exposure is influenced by their socioeconomic status, education, farm size, extension participation, market orientation, economic motivation, and perceptions (Kumar and Popat, 2010; Adegoke and Letuma, 2013). The role of women in rural agro-ecological zones in developing countries should also be considered, because they play an important role as mothers, educators, and businesswomen managing household nutrition, farming, and the selling of smallholder crops. Women in certain areas of Ghana and Nigeria were able to produce less maize compared with men. This was due to a lack of access to fertile soil and new technologies or innovations (Udoh et al., 2000; Adu-Gyamfi, 2013). In Ghana and Nigeria, women have less influence on decision-making compared with men (Ogunlela and Mukhtar, 2009; Adu-Gyamfi, 2013). In South Africa, the situation is different; women head 60% of the rural households in the Eastern Cape Province and manage the farms (Burger et al., 2010). More research on gender and mycotoxin management is needed to properly develop education campaigns and ensure equitable access to information by both men and women.

Post-harvest interventions to reduce mycotoxin exposure should include education programmes and awareness campaigns that will facilitate best practices. Working in rural South Africa, Mboya and Kolanisi (2014) (260 smallholder farm households) found that few people understood the health risks associated with mycotoxins. This was also the case in a much larger study

(sample size, 2400) in Benin, Ghana, and Togo (James et al., 2007). Sustainability of appropriate agricultural practices will be more effective through continuous campaigns (Strosnider et al., 2006; Jolly et al., 2009). The emphasis should be on crop quality rather than on productivity in domestic markets (Kumar and Popat, 2010).

The following is a summary of recommended procedures using evidence-based, culturally acceptable, and validated prevention strategies.

- Develop knowledge translation modules in partnership with farmers, area agricultural extension workers, traditional leaders, church groups, health workers, and civil society, with a focus on women.
- Be prepared to implement prevention strategies on a larger scale.
- Use recommended procedures in chronic-exposure situations as an ongoing intervention package.
- Apply as a multifactorial intervention package to include hand sorting, rapid and proper (elevated) drying, proper storage, elevation of stored crops, and insect control.
- Consider that designs for solar or biomass dryers and storage structures preferably built from locally available materials are urgently needed.

Interventions useful in emergencies

A distressing number of cases of acute aflatoxicosis have occurred, notably in the past decade. Those who are most likely to consume foods contaminated with aflatoxins suffer the most severe effects, including disease and death after acute exposure (Lewis et al., 2005). Thus, feasible interventions and therapies to diminish human and animal exposure to aflatoxins during aflatoxin outbreaks are imperative.

Numerous strategies to sequester aflatoxins in the gastrointestinal tract and reduce their bioavailability have been evaluated for their potential as practical, cost-effective, and sustainable solutions to the aflatoxin problem. Aside from avoiding ingestion of contaminated food, none of these primary intervention strategies provides complete protection. However, a refined calcium montmorillonite clay (NovaSil [NS]) and chlorophyllin have been widely studied in animals and humans for safety and efficacy, with promising results. Similar research is under way to evaluate the efficacy of other enterosorption strategies, including various bacteria and indigestible carbohydrates such as glucans, glucomannans, cellulose, and peptidoglycans.

Aflatoxin enterosorbents

Studies describing materials that can tightly adsorb aflatoxins onto internal and/or external surfaces, causing a reduction in toxin uptake and bioavailability, have been recently reviewed (Kensler et al., 2013; Miller et al., 2014). The technical feasibility, costs, and efficacy of various mitigation strategies (including the use of enterosorption and trapping agents) have also been reported (Khlangwiset and Wu, 2010). It has been suggested that inclusion of toxin enterosorbents in the diet can decrease morbidity and mortality during outbreaks of acute aflatoxicosis. The most common materials used as toxin enterosorbents and trapping agents are discussed briefly below.

Chlorophyll/chlorophyllin

Chlorophyll and chlorophyllin are naturally occurring constituents of the human diet that have been shown to be effective anticarcinogens in several animal models (Dashwood et al., 1998). They are hypothesized to act as interceptor molecules by trapping carcinogens, such as AFB_1, thereby diminishing bioavailability by impeding their absorption (Breinholt et al., 1995).

In a 4-month clinical trial in China, ingestion of 100 mg of chlorophyllin at each meal led to an overall 55% reduction in median urinary levels of aflatoxin–N7-guanine adducts compared with placebo (Egner et al., 2001). In a crossover study among four human volunteers in the USA, data suggested that chlorophyll or chlorophyllin consumption may limit the bioavailability of aflatoxins, as shown in animals (Jubert et al., 2009). Prophylactic therapy with chlorophyllin or supplementation of diets with foods rich in chlorophylls may represent a practical measure to reduce the likelihood of developing aflatoxicosis (Kensler et al., 2013).

Clays

The use of clay-based products as enterosorbents for aflatoxins is a frequent strategy to reduce aflatoxin exposure in animals. Dioctahedral smectite clays (especially montmorillonite) are the common sorbents used for this purpose. Earlier studies showed that inclusion of a calcium montmorillonite clay (NS) in animal feed reduced the adverse effects associated with aflatoxin exposure in multiple animal species and decreased the level of aflatoxin M_1 (AFM_1) in milk from lactating dairy cows and goats (Phillips et al., 2008). Equilibrium adsorption isotherms, molecular modelling, and in vivo studies have been used to demonstrate that NS binds AFB_1 and fumonisin B_1 in the gastrointestinal tract, thereby reducing systemic bioavailability

(Phillips et al., 2008; Robinson et al., 2012).

Initial human trials in Ghana and in Texas (USA) showed no adverse health effects in humans (Phillips et al., 2008; Johnson et al., 2009; Mitchell et al., 2013). Based on animal and human studies, NS clay does not significantly alter the levels of vitamins and minerals. Overall, use of NS clay during outbreaks of acute aflatoxicosis appears to be a safe and practical strategy for vulnerable populations at high risk for exposure (Mitchell et al., 2014).

Other aflatoxin-sequestering materials that have been investigated include lactic acid bacteria (El-Nezami et al., 2000, 2006; Hernandez-Mendoza et al., 2009; Dalié et al., 2010; Pizzolitto et al., 2011) and yeast (Baptista et al., 2002; Diaz et al., 2004; Stroud, 2006; Kutz et al., 2009; Pizzolitto et al., 2011; Fruhauf et al., 2012).

Research needs

The young of all species are the most vulnerable to aflatoxins; thus, children are the most likely to suffer the consequences of aflatoxin outbreaks. The trials reported to date have been in adults, and there is a knowledge gap in emergency strategies for protecting infants and children.

Further studies are warranted to assess the effects of aflatoxin dose and duration of exposure on efficacy and the safety of NS clay and chlorophyllin in the vulnerable, including malnourished infants, children, and pregnant women.

Other research needs include: determining the effects of mixtures of NS, chlorophyllin, and other enterosorbents; assessing the effectiveness of combinations of aflatoxin enterosorbents and chemoprotectants; identifying sustainable and effective delivery strategies to treat acute aflatoxicosis; and conducting phased clinical trials.

Chemoprevention studies

Dithiolethiones (oltipraz)

Oltipraz, a substituted 1,2-dithiole-3-thione, was originally developed by the pharmaceutical industry as a possible treatment for schistosomiasis and was extensively evaluated in clinical trials in the early 1980s. Subsequent studies demonstrated that oltipraz and some structurally related 1,2-dithiole-3-thiones were potent inducers of enzymes associated with the maintenance of reduced glutathione pools, as well as enzymes important to carcinogen detoxification, in multiple tissues of rats and mice (Ansher et al., 1983, 1986).

Aflatoxin biomarkers were used as intermediate end-points in a phase IIa chemoprevention trial of oltipraz in Qidong, China (Kensler et al., 1998; Wang et al., 1999). This was a placebo-controlled, double-blind study in which participants were randomized to receive placebo, 125 mg of oltipraz daily, or 500 mg of oltipraz weekly. In participants receiving the 500 mg weekly dose, urinary AFM_1 levels were reduced by 51% compared with the placebo group. Median levels of aflatoxin–mercapturic acid (a glutathione conjugate derivative) were elevated 6-fold in the 125 mg group but were unchanged in the 500 mg group. Increased aflatoxin–mercapturic acid levels reflect induction of aflatoxin conjugation through the actions of glutathione *S*-transferases. The apparent lack of induction in the 500 mg group probably reflects masking caused by diminished aflatoxin-8,9-epoxide formation for conjugation through the inhibition of CYP1A2 seen in this group. This initial study demonstrated for the first time that aflatoxin biomarkers could be modulated in humans in a manner that would predict decreased disease risk.

Sulforaphane

Although the oltipraz clinical trial demonstrated the proof of principle for increasing pathways leading to aflatoxin detoxification in humans, the practicality of using a drug-based method for prevention in developing countries is limited. Fortunately, oltipraz is not the only agent that affects enzyme changes through the Nrf2-Keap1 pathway. Many foods have high levels of these enzyme inducers (Talalay and Fahey, 2001; Fahey and Kensler, 2007).

A beverage formed from hot water infusions of 3-day-old broccoli sprouts, containing defined concentrations of glucosinolates as a stable precursor of the anticarcinogen sulforaphane, was evaluated for its ability to alter the disposition of aflatoxin (Kensler et al., 2005). Sulforaphane has been extensively examined for its chemopreventive properties and is a potent activator of the Nrf2-Keap1 pathway, leading to increased expression of carcinogen-detoxifying enzymes (Fahey et al., 2002; Dinkova-Kostova et al., 2007). In a study in Qidong, China, 200 healthy adults drank infusions containing either 400 µmol or less than 3 µmol of glucoraphanin nightly for 2 weeks. Urinary levels of aflatoxin–N7-guanine adducts were similar between the two intervention arms. However, the measurement of urinary levels of dithiocarbamates (sulforaphane metabolites) indicated striking interindividual differences in bioavailability. This outcome may reflect individual differences in the rates of hydrolysis of glucoraphanin to sulforaphane by the intestinal microflora of the study participants. Accounting for this variability, a significant inverse association was observed for excretion

of dithiocarbamates and aflatoxin–N7-guanine adducts in individuals receiving broccoli-sprout glucosinolates (Kensler et al., 2005).

This preliminary study illustrates the potential use of an inexpensive, easily implemented, food-based method for secondary prevention in a population at high risk of aflatoxin exposure. A follow-up intervention seeking to minimize the interindividual variability in the pharmacokinetics of the glucoraphanin precursor is currently in progress.

Green tea polyphenols

Many studies have demonstrated that green tea polyphenols (GTPs) inhibit various chemically induced cancers in experimental animals (Moyers and Kumar, 2004; Yang et al., 2006). Qin et al. (1997) studied the effects of GTPs in drinking-water for 2 or 4 weeks to protect against the development of AFB_1-induced hepatocarcinogenesis in the rat. The data on GTPs in experimental animals provided the impetus to translate this strategy to human clinical trials. In an initial study in an aflatoxin-exposed high-risk group in Guangxi, China, the effects of GTPs were assessed in urine samples collected from a randomized, double-blinded, placebo-controlled phase IIa chemoprevention trial (Luo et al., 2006). All participants tested positive for AF–alb and took GTPs capsules daily at a dose of 500 mg or 1000 mg, or a placebo, for 3 months. Analyses were performed on blood and urine samples collected during this clinical trial to evaluate the efficacy of GTPs in modulating aflatoxin biomarkers; reductions in AF–alb and urinary AFM_1 levels were observed (Tang et al., 2008). After the 3-month trial, both of the GTPs intervention groups were found to have reduced AF–alb levels compared with the non-intervention controls.

Research needs

This research has established that chemoprevention with the above-mentioned agents is effective in relevant animal models and that the mechanism applies in humans. Similar plant polyphenols and sulforaphanes occur in several plant species found in developing countries that are affected by aflatoxin. Research is needed to determine which locally grown and consumed plants contain sufficient levels of these naturally occurring chemopreventive agents to induce protection from aflatoxin exposure, and to conduct experimental trials.

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Disclosures of interests

Dr Ranajit Bandyopadhyay reports that his laboratory at the International Institute of Tropical Agriculture (IITA) benefited from research funding from Nestlé and currently benefits from funding from a number of public sector and non-profit organizations on matters related to the subject of the meeting.

Dr Martin Kimanya reports receiving personal consultancy fees from Abt Associates.

Dr Isabelle Oswald reports that her laboratory at the French National Institute for Agricultural Research (INRA) benefited from research funding from Biomin on matters related to the subject of the meeting.

Dr Timothy D. Phillips reports receiving personal consultancy fees from BASF; Dr Phillips reports that his laboratory at Texas A&M University benefits from research funding from BASF on matters related to the subject of the meeting; Dr Phillips reports holding intellectual property rights in a patent owned by Texas A&M University.

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ISBN 978-92-832-2510-2