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The Relationship Between Aflatoxins and Stunting: A Summary of Current Research

Aflatoxins are natural compounds produced by the toxigenic molds *Aspergillus flavus* and *A. parasiticus* and related species. They are highly toxic to humans and animals and well documented to cause liver disease and cancer and contribute to immune system suppression. Aflatoxin-producing molds affect grain and other food crops—maize and groundnuts in particular. Also, the toxins can be carried along the food chain. Several studies have shown a potential correlation between aflatoxin exposure and childhood stunting, although additional research is needed to establish a causal relationship. Because of the lifelong health and developmental problems associated with childhood stunting, clarification of the relationship is important.

A Potential Relationship Between Aflatoxin Exposure and Childhood Stunting

Childhood stunting, a chronic form of malnutrition, is potentially associated with many health problems, including an increased rate of infectious illnesses, impaired learning capabilities, and reduced work productivity. Stunting in children under five has decreased in the past 20 years, yet still remains a significant public health challenge in much of the developing world. It is higher in south Asia and sub-Saharan Africa than elsewhere in the world, for example, and globally it affects at least 163 million children.¹

It is suspected that a relationship exists between aflatoxins and stunting. Only a small number of observational studies have been conducted, but these initial studies have found a strong association between aflatoxin exposure and growth retardation.² A paper published in 2002 identified a

correlation between exposure to higher levels of aflatoxins and lower growth rates, based on comparing aflatoxin albumin adduct levels in blood samples from children in Benin and Togo with the World Health Organization (WHO) classification of child stunting (height for age Z score < -2).³ A follow-up study in 2004 presented even stronger evidence, showing that aflatoxin exposure was associated with slowed child linear growth.⁴ Studies in The Gambia linked exposure in pregnancy, and at time of delivery, with smaller babies during the first year of life.⁵ Studies in Iran, Kenya, and the United Arab Emirates have shown similar findings, outlined in a review published in 2011.⁵ A paper published in 2014 found some association between aflatoxin exposure and weight and height among breastfed infants under six months of age in Northern Tanzania.⁶

Despite quite successful international efforts to reduce childhood stunting, such as improved maternal and child health and nutrition in the first 1,000 days of life, the prevalence of stunting has not fallen as dramatically as predicted. Therefore, research efforts to identify currently unknown causes of growth retardation are underway, including additional research on the contribution of aflatoxins to stunting, relative to other factors.

1 R.E. Black, et al., Maternal and child undernutrition and overweight in low-income and middle-income countries, *The Lancet*, 2013, 382 (9890): 427–451.
2 J. Leroy, Childhood stunting and aflatoxins, *Aflatoxins: Finding Solutions for Improved Food Safety* (Washington, DC: International Food Policy Research Institute, 2013).

3 Y.Y. Gong, et al., Dietary aflatoxin exposure and impaired growth in young children from Benin and Togo: Cross sectional study, *BMJ*, 2002, 325: 20. Available online at: <http://www.bmj.com/content/325/7354/20?tab=related>.
4 Y.Y. Gong, et al., Post-weaning exposure to aflatoxin results in impaired child growth: A longitudinal study in Benin, West Africa, *Environmental Health Perspectives*, 2004, 112 (13): 1334–1338
5 P. Khalangwiset, G. S. Shepard and F. Wu. Aflatoxins and Growth Impairment: A Review, *Critical Reviews in Toxicology*, 2011 41(9): 740–755.
6 H. Magoha, et al. Association between aflatoxin M1 exposure through breast milk and growth impairment in infants in Northern Tanzania. *World Mycotoxin Journal*, 2014; 7 (3): 277–284.

Current Research on Aflatoxins and Stunting

The following is a summary of some of the major research currently underway that is exploring the relationship between mycotoxin (including aflatoxin) exposure and childhood stunting. All of these are observational studies, associating aflatoxin exposure, often measured by biomarkers in blood samples, with stunted fetal, infant, and child growth. If each of these studies finds evidence of a correlation between aflatoxins and stunting, they together would provide a strong evidence base for a causal relationship.

Understanding Mechanisms and Identifying Biomarkers for the Relationship Between Aflatoxin Exposure and Child Stunting in West Africa

A group of researchers led by Yun Yun Gong of Queen's University Belfast in the United Kingdom has begun work to explore, through biomarkers, the mechanistic pathways by which aflatoxin may lead to child growth faltering in sub-Saharan Africa. Relevant biomarkers will be identified for applications in child cohort and intervention studies. The researchers will determine the mechanism by which aflatoxins inhibit growth in early life using blood samples and growth measurement from more than 300 children in The Gambia. Changes in the insulin-like growth factor axis, epigenetic marks, and gene expression will be examined. Candidate biomarkers will be validated in an *in vitro* cell model of a human liver, which is the primary target of aflatoxins.

Association Between Aflatoxin Exposure and Childhood Stunting in Bangladesh

The Centre for Nutrition and Food Security in Bangladesh—part of The International Centre for Diarrhoeal Disease Research (icddr,b)—is conducting a two-year study on the association between aflatoxin exposure and childhood stunting. The purpose of the study is to improve scientific and public health understanding of how aflatoxins affect the growth of children under five in Bangladesh. The study is measuring the aflatoxin albumin adducts in sera samples collected at 7, 15, 24 and 36 months of age from a birth cohort. This study is also collecting food security data, dietary variables, breastfeeding status, gut enteropathy, morbidity data, and micronutrient status, which should control most of the variables associated with child growth and development. The research builds on a five-year, multi-site study conducted by the Malnutrition-Enteric Diseases Consortium and administered by the Foundation for the National Institutes of

Health, in the United States. The study partners also include the University of Venda in South Africa and the University of Virginia and Johns Hopkins University in the United States.

Mycotoxin as a Risk Factor in Childhood Growth Impairment Worldwide

Under the leadership of Felicia Wu, from the Department of Agriculture, Food and Resource Economics at Michigan State University in the United States, research will be conducted on how dietary mycotoxin exposure, in conjunction with other risk factors for diarrheal diseases, affects child growth development in low-income nations. This project is a companion project within the Malnutrition-Enteric Diseases Consortium, mentioned previously. Sites have been established worldwide in locations with populations that have a high prevalence of malnutrition and enteric diseases for epidemiological studies, in order to gain a better understanding of malnutrition, enteric diseases, and their relationship with gut function and inflammation, as well as their effects on physical and cognitive development in young children. The study aims to undertake an integrated approach, including toxicology, immunology, exposure, epidemiology, and risk assessment, so as to explore the most critical questions concerning the role of dietary mycotoxins in child growth impairment in Tanzania and Nepal.

Assessing Aflatoxin Exposure and Malnutrition Among Children in Southern Africa

Researchers at Cornell University in the United States are collaborating with the Zvitambo Institute for Maternal and Child Health Research in Zimbabwe to investigate the role of mycotoxin exposures in more than 4,000 mother–infant dyads during pregnancy and the first 18 months of post-natal life, and the relationship of those exposures to birth outcomes and pre- and post-natal stunting. The study will be conducted in the context of the SHINE Trial, a community-based cluster-randomized trial of an integrated WASH (water, sanitation, and hygiene) intervention and also an infant nutrition intervention in two rural districts. The study aims to assess fumonisin and deoxynivalenol exposure as well as that of aflatoxin, hypothesizing that multiple toxins may be even riskier than exposure to only aflatoxins. The data will be combined with survey data on food security, diet diversity, and agricultural practices relevant to mycotoxin risks, as well as biological data on gut enteropathy and immune function.

Additional Research Needs

A clear understanding of the relationship between aflatoxins and stunting would help to build an even stronger case for aflatoxin prevention activities among the international community. The health impacts of aflatoxin

through aflatoxicosis and liver cancer are well documented,^{7,8,9,10} and make a compelling case for immediate, well-coordinated action. However, stunting continues to be an institutional priority for a number of international and multinational organizations (including the WHO and UNICEF) and philanthropic donors. A well-documented link between aflatoxin exposure and stunting could further build support to prioritize aflatoxin control actions.

In order to improve understanding of the relationship between aflatoxin and stunting, additional research is needed in the following areas:

- 1. Mechanism for stunting:** The studies to date have largely been focused on identifying a correlation between aflatoxin exposure and stunting. Current knowledge about the biological effects of aflatoxins on immune suppression, protein synthesis, and the metabolism of micronutrients suggests a potential mechanism, but additional research is needed to explain how aflatoxin exposure impacts growth.
- 2. Additional studies on human health:** Although the studies conducted thus far are generally consistent, and the current research outlined above holds promise for further contributions toward understanding a potential causal relationship, several areas of research are still required. For example: (1) How strong is the effect of aflatoxins on child stunting, and can we quantify the size of the effect? (2) How do aflatoxins' effects on stunting compare to micronutrient deficiencies? Are there any synergistic effects on stunting? (3) How do aflatoxins' effects on stunting compare to that of infectious disease? Are there any synergistic effects on stunting? (4) Do agriculture- and public-health-based interventions reduce exposure and result in improved child growth? Randomized trials on the latter question are needed, and could provide the ultimate causal evidence between aflatoxins and stunting. Evidence on causality will necessitate wide-ranging studies across geographies and scales. And, the results of these types of studies will help to guide proper prevention strategies for child stunting in Africa.
- 3. Using animal health data to make the public health case:** Existing studies conducted on a variety of animal species consistently found that exposure to aflatoxins led to reduced weight gain, and these animal models can be used to illustrate the mechanism of aflatoxin-associated stunting. However, there is a need for additional information on how applicable the existing research on animals is to growth retardation in children.

Conclusion

Although direct causality and the mechanisms by which mycotoxins cause growth retardation outcomes are not fully understood and are likely complex, there is accumulating evidence that the adverse impacts of aflatoxins likely extend beyond the well-documented connection to liver disease and liver cancer. Research is underway to further investigate the relationship between aflatoxins and stunting, but additional work is needed. Studies are often labor-intensive and require extensive laboratory infrastructure. Therefore, coordination of research efforts is important for effectively sharing resources and building the knowledge platform needed to understand the full range of health impacts caused by aflatoxin exposure.

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- 8 Y. Liu and F. Wu, "Global burden of aflatoxin-induced hepatocellular carcinoma: A risk assessment, *Environmental Health Perspectives*, 2010, 118 (6): 818–824. Available online at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898859/>.
- 9 K.A. Krishnamachari, et al. Investigations into outbreak of hepatitis in parts of Western India, *Indian Journal of Medical Research*, 1975, 63: 1036–1049.
- 10 K.A. Krishnamachari, et al., Hepatitis due to aflatoxicosis: An outbreak in Western India, *The Lancet*, 1975, i: 1061–1062.



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