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FORUM

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Reduced Foodborne Toxin Exposure Is a Benefit of Improving Dietary Diversity

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ABSTRACT

Naturally occurring foodborne toxins are common in subsistence diets of low-income human populations worldwide. Often, these populations rely on one or two staple foods for the bulk of their calories, making them more susceptible to chronic intake of certain toxins. Exposure to common foodborne toxins is associated with diverse conditions such as cancer, immunotoxicity, growth impairment, and neurological deficits. Interventions focused solely on reducing toxin levels have proven difficult to sustain. Using case studies of two foodborne toxins, aflatoxin and cassava cyanide, this article addresses the heightened risk of particular diseases from eating monotonous diets based in maize, groundnuts, and cassava: common in sub-Saharan Africa and parts of Asia. We also discuss the potential role of increased dietary diversity in counteracting these diseases. Increased dietary diversity can reduce consumption of toxins and increase intake of nutrients that could counteract the toxicity of such chemicals. In Qidong, China, a population that previously consumed a monotonous maize-based diet and increased dietary diversity since the 1980s has experienced a dramatic reduction in liver cancer mortalities. That liver cancer decreased as dietary diversity increased is the catalyst for the hypothesis that dietary diversity could have a direct impact on reducing health effects of foodborne toxins. Future research, agricultural development, and food policy reforms should take into consideration the multifaceted benefits associated with improved dietary diversity. Collaborations between toxicologists, nutritionists, and policymakers are important to development of sustainable interventions to reduce foodborne toxin exposure and promote health through increased dietary diversity.

Key words: foodborne toxins; nutrition; diet; aflatoxin; cassava cyanide; global health

Consumption of monotonous diets rich in carbohydrates but low in protein and micronutrients are common among poverty stricken communities. A profound public health benefit could be achieved through increased dietary diversity. Dietary diversity, a measure of the variety of individual food items or food groups consumed, has long been studied in the nutritional community in the context of health outcomes (Ruel, 2003). Generally, dietary diversity reflects dietary quality (Arimond and Ruel, 2004), adequacy of micronutrient intake (Moursi *et al.*, 2008), and dietary energy availability (Hoddinott and Yohannes, 2002). Low dietary diversity scores are related to poor nutritional status (Chua *et al.*, 2012), a risk factor for multiple diseases common in low-income populations. Of particular importance is the dietary diversity and nutritional status of children residing in low-income coun-

tries where childhood death from malnourishment and disease are the highest. In 2004, 39% of child deaths were caused by micronutrient deficiencies, underweight, suboptimal breastfeeding, and preventable environmental risks (Mathers *et al.*, 2009).

In addition to improved micronutrient status through greater dietary diversity, another benefit that has received little to no attention is decreased human exposure to specific foodborne toxins. This concept is particularly important among populations in low-income nations who rely heavily on only a few dietary staples such as maize, groundnuts, cassava, and rice; which can be highly contaminated with naturally occurring toxins. Such staples are often utilized in weaning children and can account for large portions of the diet throughout a person's lifetime. Therefore, exposure to foodborne toxins and the resulting health effects are often chronic in nature. Because cereals and grains make up the largest portions of the diet worldwide, toxins that naturally occur in these staples present the most risk for chronic disease. Fungal growth and infection of cereal and grain plants can result in contamination of food stuffs with various mycotoxins that are known carcinogens, immunosuppressants, nephro- and hepatotoxins, and teratogens (CAST, 2003). Environmental conditions have a profound effect on fungal growth and subsequent mycotoxin contamination, making populations in certain climates more susceptible to exposure. The climatic conditions within tropical areas of the globe result in a high risk for mycotoxin contamination in both the field and during storage and handling, enhancing the difficulty for farmers and distributors to provide good quality grain products. The majority of areas where exposure to mycotoxins is continuous do not have the infrastructure and economic backing to sustain appropriate regulations, handling, and storage technologies to reduce mycotoxin contamination and consumption. In addition to mycotoxins, the environment in which certain staples are grown can affect levels of toxins such as metals. For example, consumption of large quantities of rice products by children has been considered to be the greatest exposure route for arsenic in children under 3 years of age (EFSA, 2009). Arsenic in water used on rice patties can accumulate in the grains causing various chronic effects over a lifetime, including cancer, skin lesions, neurologic, respiratory, cardiovascular, and developmental effects (Argos *et al.*, 2012; Naujokas *et al.*, 2013; Smith and Steinmaus, 2009; States *et al.*, 2011). Plants also can naturally produce chemicals to protect themselves from consumption by pests, including humans. Some of these plants comprise tubers and roots, but can actually be eaten once properly prepared and cooked. In areas where food insecurity and/or communities focus on a single cash crop for income, consumption of large quantities of potentially toxic or contaminated foods is seemingly unavoidable. Increasing both agricultural and dietary diversity could dilute the potential for chronic toxin consumption by such populations.

Increasing dietary diversity in these populations not only reduces exposure to foodborne toxins, but may allow for intake of dietary constituents that counteract the adverse effects of these toxins. Here, we describe how improved dietary diversity could directly and indirectly counteract the adverse health effects of two foodborne toxins: aflatoxin and cyanogenic glycosides. Although consumption of certain nutritional supplements such as folate, protein, selenium, etc., have been associated with decreasing the effects of other known food contaminants (i.e., arsenic, lead, cadmium, etc.), exposure to these toxins are known to occur through multiple routes and foods (Basu *et al.*, 2011; Gamble *et al.*, 2005, 2006; Hall *et al.*, 2009; Pilsner *et al.*, 2009; Steinmaus *et al.*, 2005), making the effect that dietary diversity would have on their related public health outcomes difficult to address and beyond the scope of this manuscript. Additionally, we suggest potential public health benefits achieved through policy changes in agricultural biodiversity, global food security, and nutrition education in the developing world.

AFLATOXINS

Aflatoxins are a group of chemically related toxins produced primarily by the foodborne fungi *Aspergillus flavus* and *A. parasiticus*. These fungi are particularly prevalent in tropical and subtropical regions, infecting food crops both in the field and postharvest. Aflatoxins, in particular AFB_1, contaminate multiple staple foods including maize and groundnuts. Roughly 5 billion people worldwide are exposed to uncontrolled aflatoxin contamination (Strosnider *et al.*, 2006).

For decades, it has been known that AFB_1 exposure causes liver cancer in humans and a variety of animal species. The International Agency for Research on Cancer has classified naturally occurring mixes of aflatoxins as a Group 1 human carcinogen (IARC, 2002). Currently, the United States Food and Drug Administration and the European Commission have set action limits of 20 and 4 μg/kg for food stuffs, respectively (FAO, 2004a). Observed contamination of aflatoxin in maize from Africa and Southeast Asia often exceed these action levels. Based on estimated consumption of maize and peanuts, populations with the highest exposure risk could consume upward of 200 ng/kg body weight of aflatoxins per day making the risk for aflatoxin-induced hepatocellular carcinoma (HCC) in Africa and Southeast Asia range from 1740 to 17,300 cases annually (Liu and Wu, 2010). Additionally, concomitant exposure to aflatoxin and the hepatitis B virus (HBV) is common in developing countries, and has been shown to greatly increase liver cancer risk in Asia and Africa to upward of 78,000 cases per year (Kirk *et al.*, 2005; Liu and Wu, 2010; Liu *et al.*, 2012; Lunn *et al.*, 1997; Qian *et al.*, 1994; Ross *et al.*, 1992). There is also an increasing body of evidence that aflatoxins modulate the immune system (Jiang *et al.*, 2005, 2008; Turner *et al.*, 2003) and may lead to stunted growth in children (Gong *et al.*, 2002, 2004; Khlangwiset *et al.*, 2011), potentially exacerbating health risks due to inadequate protein and micronutrient intake that predominates in impoverished communities.

Current strategies for reducing aflatoxin exposure in food include preharvest (strategies that reduce fungal infection of crops in the field), postharvest (improved drying and storage practices to prevent aflatoxin accumulation in stored food), and dietary interventions to enhance aflatoxin detoxification and elimination once ingested (Khlangwiset and Wu, 2010). However, many of these strategies have not been sustainable over long periods of time and may not be economically feasible in poverty stricken communities. Less attention has been given to developing dietary diversity, which could reduce total aflatoxin exposure and its harmful effects.

A recent study has shown that decreased maize consumption, in favor of rice and other foodstuffs, has resulted in markedly lower aflatoxin exposures, and subsequently, dramatically declining liver cancer mortality rates in Qidong, China (Chen *et al.*, 2013). Prior to the 1980s, agricultural policies had restricted Chinese counties from trading food with one another, as food self-sufficiency was required of each county. Because the soil in Qidong was unsuitable for growing rice, maize was the primary staple grown, under environmental conditions that led to high aflatoxin contamination. As a result, Qidong became a "liver cancer hot spot," where 1 in 10 adult men died of liver cancer, often by age 45.

When market reforms were introduced in the 1980s, the Qidongese increased their dietary diversity, turning from maize to rice and other foodstuffs from neighboring counties. As a result, aflatoxin exposure has plummeted in the last 30 years; correspondingly, the age-standardized rate of liver cancer mortality has decreased by 45% in the Qidong population since the 1980s (Chen *et al.*, 2013). This effect is independent of the recent deployment of a universal HBV vaccination program in China. Introducing dietary diversity into populations where aflatoxin-contaminated maize and groundnuts are dietary staples could not only reduce liver cancer risk, but could also reduce other adverse effects associated with aflatoxin exposure, such as growth faltering.

Hepatocarcinogenesis of AFB_1 is now a well understood mechanism that requires activation of the parent compound through oxidation by cytochrome P450s (Eaton and Gallagher 1994; Ishii *et al.*, 1986). The intermediate product, aflatoxin-8,9-epoxide, is highly reactive and can form a promutagenic aflatoxin-N^7-guanine adduct within the DNA. Knowledge of the metabolic pathway and the mechanism of action provide a basis for modulation of aflatoxin's carcinogenic potential through chemopreventive agents available in foods. Improved dietary diversity could have the impact of introducing such protective phytochemicals (Kensler *et al.*, 2004). Compounds found in cruciferous vegetables, onions, and garlic can reduce aflatoxin-induced cancer by enhancing glutathione-S-transferase (GST) expression, which mediates conjugation of the reactive intermediate aflatoxin-8,9-epoxide and diverts its interaction with DNA. Randomized clinical trials utilizing a broccoli sprout beverage rich in the phytochemical sulforaphane demonstrated protective alterations in aflatoxin excretion (Kensler *et al.*, 2011). Chlorophyllin, a derivative of chlorophyll, is a natural constituent of green vegetables in the human diet that has shown anticarcinogenic effects in animals (Dashwood *et al.*, 1998). Chlorophyllin appears to protect against aflatoxin by sequestering aflatoxin during the digestive process and hence impeding aflatoxin's absorption (Egner *et al.*, 2001).

Because aflatoxin is one of the most important risk factors for one of the deadliest cancers worldwide, liver cancer, reducing its presence in human diets is critical. Possibly even more critical from a global health standpoint is the potential association between aflatoxin exposure and growth impairment in children, which can lead to a variety of adverse health conditions that last well beyond childhood.

CYANOGENIC GLYCOSIDES

The presence of cyanogenic glycosides in bitter cassava (cassava cyanide) presents another example in which increasing dietary diversity may not only reduce consumption of the risky foodstuff, but may provide nutrients that biochemically counteract the foodborne toxins. The Food and Agriculture Organization (FAO) estimates that cassava comprises an essential part of the diet for 500 million people worldwide (FAO, 2004b).

Cassava, particularly the bitter variety grown in resource-poor settings, contains cyanogenic glycosides that protect the root against pest consumption. Based on developmental toxicity studies with the major cyanogenic glycoside found in cassava, linamarin, the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) set an acute reference dose (ARfD) of 90 μg/kg body weight for cyanide equivalents. Chronic consumption of cassava, which can contain linamarin from 15 to 1000 mg/kg, can result in adults exceeding the ARfD by a three-fold factor (Feeley *et al.*, 2012). To reduce cyanide, cassava root is typically processed by sun drying or soaking. These traditional practices could take up to 7 days to reduce glycosides to levels safe for human consumption. Unfortunately, during times of food shortages, cassava processing may be shortened or eliminated (Boivin *et al.*, 2013).

Cassava cyanide exposure can lead to a variety of adverse neuromuscular and neurocognitive effects. Konzo in particular is an ongoing public health concern in poor areas dependent on cassava. It often occurs in the most remote areas of Africa, leading to a lack of attention by health authorities and the research community. A paralytic disease, konzo is characterized by a permanent, nonprogressive loss of motor function typically in the legs. Severe cases can result in a lifetime inability to walk. The loss of motor function is caused by exposure to cyanogenic glycosides in cassava causing selective upper motor neuron damage.

A recent publication shows that neurocognitive deficits can occur even in children who do not develop konzo, if they are living in a konzo-endemic region (Boivin *et al.*, 2013). In the Democratic Republic of Congo, children with konzo performed the most poorly on neurocognitive and neuromotor tests; but even children without konzo who lived in a konzo-endemic region performed significantly more poorly than children not living in an endemic area. This implies that in high-risk regions, average exposures to cassava cyanide that may not result in konzo can still cause other adverse cognitive effects in children.

The neurotoxic mechanism for cyanogenic glycosides has not yet been clarified, however, there is evidence that the effects occur either within the corticomotor neurons or the descending motor pathways (Tylleskar *et al.*, 1993; Tshala-Katumbay *et al.*, 2002). Cyanogenesis occurs in cassava when the plant tissue is damaged and initiation of this process involves the conversion on linamarin by linamarase to acetone cyanohydrin. Acetone cyanohydrin in cassava is unstable and will decompose to acetone and hydrogen cyanide at pH >5 and/or at temperatures exceeding 35°C (Nzwalo and Cliff, 2011). The high pH within the gut is hypothesized to induce the conversion of acetone cyanohydrin to cyanide, thus causing cyanide toxicity and ultimately konzo and other neurological diseases.

Yet not everyone who consumes cassava worldwide is at risk of developing konzo or neurocognitive deficits. Konzo is associated with the combination of specific conditions: dependence on cassava in the diet, low sulfur amino acid intake, and conditions of hardship (drought, famine, conflict) that drive populations to consume inadequately processed cassava (Nzwalo and Cliff, 2011). In particular, the combination of low sulfur amino acid intake with high cassava intake appears to play a role in all major konzo epidemics recorded (Banea *et al.*, 2013). Detoxification of cyanide within the body involves transformation of cyanide into thiocyanate by the enzyme rhodanese which requires sulfur donors. Dietary sulfur amino acids, which are deficient in cassava, provide protective capacity from cyanide toxicity through promoting detoxification pathways and excretion of thiocyanate in the urine (Nzwalo and Cliff, 2011; Tor-Agbidye *et al.*, 1999). Improving dietary diversity, where possible, can reduce two of these three risk factors. It will not only reduce the total amount of bitter cassava consumed per individual—hence, reducing the burden of cyanogenic glycoside intake—but could also introduce sulfur, which aids in detoxification of cyanide in the body. Dietary sulfur amino acids from protein sources—eggs, dairy, meat, and legumes—are important in the detoxification of cyanide in the body.

CONCLUSIONS

Dietary diversity and foodborne toxins have traditionally been studied in separate fields: nutrition and toxicology. It is important to consider their interactions, which are relevant to the health of billions of the most vulnerable human populations worldwide. Nutritionists with a focus on global health should consider that another benefit of increasing dietary diversity is to reduce the overall burden of foodborne toxins and to counteract these toxins' adverse effects in the body. Food toxicologists who develop interventions to reduce toxin levels in food crops should consider the enhancement of dietary diversity among their suite of interventions. Dietary diversity promotion and education in poor populations and among research scientists should focus on this dual benefit in order to optimize interventions and research programs.

We have described two foodborne toxins common in monotonic diets: aflatoxin and cyanogenic glycosides. Not only would increasing dietary diversity in populations where maize, groundnuts, and cassava decrease the overall intake of these toxins; it would also increase the likelihood of consuming nutrients that could counteract their adverse effects to improve health. Thus, governmental programs that make production of diverse crops profitable to farmers and diverse foodstuffs accessible to consumers should be considered a priority in developing countries. Such governmental policy changes were shown to be effective in reducing both aflatoxin exposure and consequently primary liver cancer in the Qidongese in China (Chen *et al.*, 2013).

Education in rural areas and developing nations on the health impacts of a diverse diet through advertising, marketing, and public health workshops are needed to inform communities of the long-term benefits of consuming a diverse diet and, likewise, potential risks to human health of a monotonous diet. Additionally, governmental policies and education should focus on added benefits of introducing agricultural biodiversity, like decreased residual pesticide exposure, as a means of inciting interest in the population and incentivizing societies to maintain such practices. Educating farmers on the benefits to soil health and crop yield, thus increasing their profits, through rotation and intercropping systems would not only benefit the farmers but would influence dietary diversity and population health as well. Development of more diverse cropping systems has proven to yield similar profit margins as monocropping systems while also decreasing external synthetic inputs such as pesticides, herbicides, and fertilizers. Thus, diverse agriculture systems can lower residual pesticide contamination of freshwater and soil that can negatively impact human health (Davis *et al.*, 2012; Lechenet *et al.*, 2014).

Improving human health through dietary diversity will involve a multilevel approach that influences agricultural production, extension, marketing, education, and policy development (Frison *et al.*, 2006). The International Plant Genetic Resources Institute has been working to increase dietary diversity in developing areas for several years, and has identified multiple challenges to the diversification and use of "neglected and underused species" of crops. Included in these challenges is a lack of investment by funding agencies in research projects with comprehensive nutrition goals (Frison *et al.*, 2006). The vast majority of dietary intervention strategies focus on increases of a single dietary nutrient, such as protein, vitamin A, or iron. Singularly focused interventions may have limited efficacy in sustainably improving population health.

Changes in food consumption practices are difficult to achieve in populations, as these practices are often passed down from generation to generation, and food is a central part of many cultures. Improving dietary diversity, however, does not necessitate a complete change in food traditions; rather, augmentation of dietary staples with additional foodstuffs as regularly as possible. Initiatives to increase crop biodiversity in developing countries have the benefit of improving nutrition and decreasing exposure to foodborne toxins and carcinogens. This dual impact needs to be emphasized in policy decision-making among global agricultural and public health communities.

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