GENERAL INTEREST PAPER

Evaluating the Applicability of a Risk-based Approach (Decision Tree) to Mycotoxins Mitigation

P. R. Hanlon,[1*] R. Bandyopadhyay[2] and G. P. Brorby[3]

[1]*Abbott Nutrition, 3300 Stelzer Road, Columbus, OH 43219, USA

[2]International Institute of Tropical Agriculture (IITA), Ibadan 200001, Nigeria

[3]ToxStrategies, Inc., 952 School St., PMB 302, Napa, CA 94559, USA

SUMMARY

Mycotoxins are secondary metabolites of naturally occurring fungi often associated with the production and storage of certain grains. Humans have thus been exposed throughout history to mycotoxins inherent in many foods consumed as part of standard diets. The primary aim of this work was to evaluate a hypothesis on whether a foundational framework (decision tree) previously developed by the North American Branch of the International Life Sciences Institute (ILSI North America) Food and Chemical Safety Committee for a risk-based approach to mitigation of process-formed compounds could be applied to other not-readily-avoidable substances, such as mycotoxins. It was concluded that the ILSI North America decision tree was generally applicable to mycotoxins, although with the recognition that specific steps and/or specific mycotoxins may require the development of additional criteria, especially within developing nations.

OVERVIEW

The North American Branch of the International Life Sciences Institute (ILSI North America) Food and Chemical Safety Committee (referred to hereafter as the committee) developed and supported a symposium on the risk-based assessment of mycotoxins mitigation at the Combined Conference of the World Mycotoxin Forum and International Union of Pure and Applied Chemistry International Symposium on Mycotoxins held in Winnipeg, Canada, in June 2016. The hypothesis proposed at this symposium, and summarized in this publication, was to evaluate whether a foundational framework (decision tree) previously developed by the committee for a risk-based approach to mitigation of process-formed compounds could be applied to other not-readily-avoidable substances, such as mycotoxins.

Mycotoxins can have a significant influence on human health because of their immunosuppressive, mutagenic, carcinogenic, genotoxic, and hepatotoxic effects that lead to various diseases. In addition to health concerns, mycotoxins in the food supply give rise to a range of economic and trade implications. Only relatively recently have regulatory agencies implemented food safety measures to reduce consumer exposure to mycotoxins. These measures include establishing regulatory limits, creating action levels, and developing codes of practice (COPs), with the ultimate goal of reducing risk *(13, 18, 47)*. Because risk comprises both hazard and exposure, evaluating the impact of these mitigation efforts must also focus on overall risk, not simply on exposure reduction, which may not accurately reflect whether an actual reduction in risk has been achieved.

APPLICATION OF RISK-BASED DECISION MAKING TO MYCOTOXINS

The ILSI North America decision tree for a risk-based process for mitigation of process-formed compounds is shown in *Fig. 1* *(23)*. Our hypothesis is that the decision tree could also be applied to other not-readily-avoidable compounds, and mycotoxins were identified as a potential example. The initial analysis of potential applicability of the decision tree to mycotoxins is described in the following sections for each component of the process (prioritization, assessment of current risk, development of mitigation plans, evaluation of secondary effects of mitigation, and recommendations). Additionally, this paper includes discussion of the specific challenges that may be faced by the developing world, because this represents an area where there are significant differences in how process-formed compounds and mycotoxins could be addressed.

Prioritization (boxes 1–3) for process-formed compounds versus mycotoxins

The goal of the prioritization step is to rank all compounds under consideration by risk, using rapid methodology and available data to prioritize compounds based on the likelihood of their presenting a risk to human health. This is a valuable exercise to conduct for not-readily-avoidable compounds such as mycotoxins as well as for process-formed compounds, but there are differences in the way these two sets of compounds would be evaluated.

In the case of both mycotoxins and process-formed compounds, the identification and quantification of "new" compounds often drives the prioritization of risk

*Author for correspondence: Phone: +1 614.624.3213; Email: paul.hanlon@abbott.com

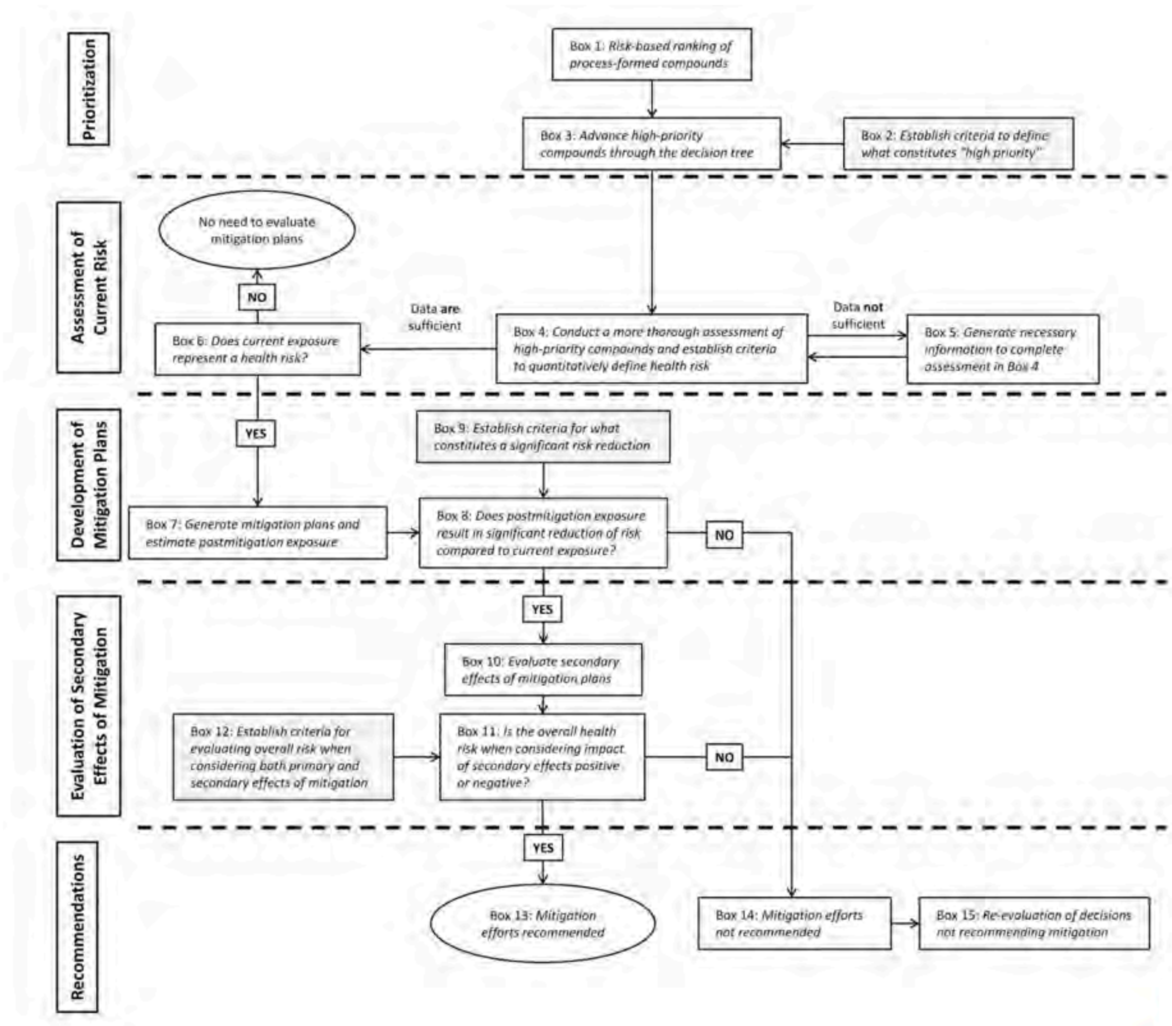

FIGURE 1. ILSI North America Decision Tree. Reprinted from Hanlon et al. *(23)*.

management measures. For example, newer analytical platforms such as "dilute and shoot" sample preparation protocols coupled with liquid chromatography–tandem mass spectrometry have made rapid analysis possible for a few hundred fungal and bacterial metabolites, including all major mycotoxins, simultaneously in a large number of samples *(9)*. Once these new methodologies identify a "new" substance, risk management measures are developed to reduce consumer exposure, in the absence of a quantitative analysis of whether these measures will reduce risk. This is an application of the absolute precautionary principle, in which mitigation measures are recommended in cases of incomplete information on risk *(40)*. This paper proposes a comprehensive analysis of the chemosphere as the first step (prioritization) in determining which compounds require more information to inform risk management decisions, as opposed to an application of the precautionary principle to all "new" compounds identified by chemical analysis of food.

Dozens of mycotoxins have been identified, and the world of mycotoxins continues to expand with the increased evaluation of "masked" mycotoxins (i.e., plant metabolites of mycotoxins not routinely screened or regulated) *(10)*. However, the number of known mycotoxins is still only a fraction of the vast number of process-formed compounds that have been identified. For example, it has been estimated that at least 800 compounds can be formed through the heating of food *(25)*. The prioritization of mycotoxins may be simpler than process-formed compounds simply because of the significantly lower number of compounds under consideration.

Additionally, more information is typically available for mycotoxins than for process-formed compounds, because of both the smaller number of mycotoxins and the prioritization of research on mycotoxins. Techniques such as the threshold of toxicological concern or structure-activity relationships may need to be employed more frequently for process-formed compounds, as compound-specific toxicological information is lacking for a greater percentage of these compounds. Also, not only does compound-specific information exist for a greater percentage of mycotoxins, but those mycotoxins for which compound-specific information is lacking are often structurally similar to mycotoxins for which extensive data exist.

Ultimately, the objective of this step of the decision tree is to narrow the focus of the remaining steps to the highest-priority compounds. As described previously *(23)*, risk management decisions will need to be made about how to prioritize compounds (an absolute number, or a certain percentage of all compounds). However, the prioritization step could be applied to mycotoxins in a manner similar to that used for process-formed compounds.

Assessment of current risk (boxes 4–6) for process-formed compounds versus mycotoxins

The goal of this step is to refine the assessment for those compounds that were identified as being of higher priority from the first step to determine whether the compounds truly present a risk to human health at the levels at which they are currently present in the diet. This would include refinement of both the hazard assessment and the exposure assessment; in both cases (as outlined in the decision tree, Box 5), the assessor should evaluate whether additional data are needed to refine these assessments. Refining the hazard assessment would include evaluating compound-specific data to generate a health-based guidance value or a point of departure for calculating a margin of exposure (MOE). Depending on the compound, the level of estimated exposure, and likely toxicity, this step may drive additional toxicological safety studies, which could include subchronic toxicity studies, toxicokinetic studies, *in vitro* genotoxicity assays, and/or other studies designed to address specific toxicological endpoints potentially relevant to these compounds.

Similarly, the exposure assessment should be refined at this stage to properly compare estimated exposure against the health-based guidance value or MOE. For example, guidance documents from the European Food Safety Authority *(19)* and the World Health Organization (WHO)/International Programme on Chemical Safety *(58)* recommend refinement of exposure estimates by use of probabilistic models when screening methods indicate that exposure could exceed health-based guidance values. While worst-case deterministic (i.e., single point) estimates of exposure can be helpful in the prioritization stage to screen large numbers of compounds, when conducting quantitative risk assessments, probabilistic models that allow for more accurate estimation of both occurrence and consumption should be used to determine whether mitigation is needed.

Mycotoxins are likely to be associated with fewer data gaps than process-formed compounds when it comes to hazard, and possibly even exposure. However, estimates of occurrence (and therefore exposure) for mycotoxins are likely to have additional uncertainties and greater magnitudes of those uncertainties than process-formed compounds. For example, seasonal or climatic variability, geographical variability, and world trade of commodities will all contribute variability to estimates of mycotoxin occurrence, leading to challenges in the calculation of exposure, and thus of risk.

Understanding of risk associated with mycotoxins, process-formed compounds, and other chemical contaminants could benefit from greater alignment on the definition of what constitutes a significant risk (Box 6). Despite the fact that risk is the critical factor for determining whether mitigation would be recommended, there are inconsistencies in how it is defined. For example, establishing mitigations to protect the 90th percentile is not precise, as the 90th percentile of a specific population must be defined (e.g., all consumers, only users, or only users within a specific demographic category or age range?).

This type of quantitative risk assessment has been conducted by numerous risk assessment agencies for a variety of mycotoxins. For example, Joint FAO/WHO Expert Committee on Food Additives (JECFA) risk assessments for mycotoxins are used by the Codex Committee on Contaminants in Foods (CCCF) to develop maximum levels (MLs) for foods in which they can occur at levels that significantly contribute to the total exposure of consumers. The CCCF also uses the JECFA risk assessments to identify situations where the development of COPs is warranted as a way of proactively reducing mycotoxin levels in the food supply *(13)*. Many other regulatory agencies around the world implement similar processes.

When the ILSI North America decision tree *(Fig. 1)* is used, only compounds that currently pose a significant risk to consumers would proceed further through the evaluation process. If a chemical, mycotoxin, or process-formed compound does not pose a significant risk to consumers, the recommendation from this process would be to halt further activity, including development of control measures, as resources would be better spent addressing other compounds that pose a greater risk to consumers.

Assessment of current risk (boxes 4–6) for developing countries versus developed countries

The quantitative risk assessment for mycotoxins (and other compounds) relies heavily on consumption data and occurrence rate; thus, determining whether consumers are at significant risk will be heavily influenced by country-specific considerations. The extent of exposure to mycotoxins differs not only between developed and developing nations but also between developing nations and regions within a nation. The diets of people are based on a relatively small number of crops, and the total diversity of crops contributing significantly to diets worldwide has narrowed *(30)*. Nevertheless, there are numerous foods and spices on which rural households depend, and several of these foods and spices are prone to mycotoxin contamination *(5, 20,* *21, 41)*. Mycotoxin exposure assessment using a total diet study approach has been carried out in several developed nations *(32, 43)*, but such studies have not been reported in developing nations, with a few exceptions *(31)*.

Maize is a common constituent of food in most parts of Africa, where per capita consumption can be more than 400 g/day (such as in Kenya), compared to less than 10 g/day in Europe, resulting in variations in mycotoxin exposure between developed and developing nations. Therefore, one would expect that MLs for mycotoxins in food would be less stringent in Europe than in Africa *(42)*. On the contrary, the opposite situation exists; for example, the ML for total aflatoxins in Europe is 4 µg/kg compared to 10 µg/kg in Kenya.

In developed nations, consumption of food purchased from organized markets is the norm, but most African rural households consume homegrown crops. People dependent on organized markets in developed nations usually have low exposure to mycotoxins because regulations can be conveniently enforced in such markets *(55)*. However, regulations for homegrown food are rare unless extreme contamination levels leading to health scares are reported *(56)*. The extent of mycotoxin exposure is also determined by the time of year. Generally, mycotoxin concentrations are at their lowest level in newly harvested food crops and increase as grains stay longer in storage *(51)*. In developed economies, mycotoxin concentrations in foods are kept below the ML irrespective of the time of year, because of compliance with regulations. However, in developing nations, mycotoxin exposure is usually low soon after a crop is harvested but increases with time until a new crop is harvested *(45, 53)*.

Socioeconomic status is likely to impact the extent of mycotoxin exposure. Contaminated and discolored grains are usually discounted at the market, compared to cleaner, low-aflatoxin grains. In Kenya, people are willing to pay more for grains that are tested and certified as aflatoxin safe *(16)*. However, individuals of low socioeconomic status cannot pay the higher cost and are therefore exposed to an estimated five to seven times more aflatoxin than those of higher socioeconomic status *(33)*.

Development of mitigation plans (boxes 7–9) for process-formed compounds versus mycotoxins

The objective of this step in the process is both to develop mitigation plans and to evaluate the impact of those mitigation plans on consumer risk, not just on exposure. Historically, most (if not all) mitigation has focused on reducing exposure because of the difficulty of modifying the hazard associated with a compound *(1, 29)*. Although it is possible to target hazard reduction for mitigation, in all likelihood the majority of mitigation plans will remain focused on reducing exposure.

The concentration of process-formed compounds in food can be impacted by a number of factors, as has been documented by multiple analyses of acrylamide *(1, 11)*. Similarly, the concentration of mycotoxins can be impacted at multiple points along the supply chain, from agricultural practices, to transportation and storage, through processing *(29, 44)*. For all of these factors, pinpointing the effectiveness of mitigation efforts to a single factor is extremely challenging because of the significant impact of geographical and climatic changes.

Another difference between mitigation measures appropriate for mycotoxins and process-formed compounds is that because mycotoxins are generated by living organisms, they are more likely to accumulate during crop growth, harvest, storage, transport, and other points prior to the consumption of foods. While specific mitigation measures can be taken to reduce the population of the fungi responsible for their generation, this biological component is much less relevant for most process-formed compounds. In contrast, most process-formed compounds are created by specific processes, and once that process ends, the generation of the compounds ceases. As food manufacturers have more control over the steps that create process-formed compounds, but relatively little control over factors such as how long a food product may be stored by a consumer prior to consumption, this can lead to additional challenges in assessing the impact of mitigation for mycotoxins.

A proactive strategy for assessing mitigation, for either mycotoxins or process-formed compounds, can be only as successful as the accuracy of the estimates of the impact of the different mitigation options. Historical data on the effectiveness of mitigation plans on the same compound or similar compounds can increase the accuracy of the prediction of the effectiveness of new mitigation plans. In this regard, mycotoxins could have an advantage over process-formed compounds, as mitigation plans have been established *(6, 17)*, COPs have been developed for multiple mycotoxins *(13)*, and efficacy trials have been conducted mostly for a single mycotoxin *(45)* and rarely for multiple mycotoxins *(36)*. In contrast, many process-formed compounds are created by unique processes and often have chemical structures that are not similar to the compounds for which mitigations have been established.

Another challenge shared by both mycotoxins and process-formed compounds is that both suffer from a lack of alignment from risk managers on what constitutes a "significant" risk to human health; thus, there is a lack of criteria that define whether a specified reduction in exposure would result in a "significant" reduction in risk. This concept, identified during development of the process-formed compounds decision tree *(23)*, would also be applicable to mycotoxins, as discussed during the mycotoxin symposium in 2016.

Under precautionary risk management practices, any efforts that are likely to reduce exposure to a substance should be implemented in cases where there is incomplete information about risk *(40)*. Unfortunately, this is often incorrectly interpreted by the public to imply that any reduction in exposure makes food safer (reduces risk).

However, both the magnitude of the reduction of exposure and where exposure is located on the dose-response curve are important.

For many compounds, a threshold can be established below which adverse effects will not occur, either because the compound has no physiological effect below a certain concentration or because the body's homeostatic mechanisms can reverse the effects of the compound *(14)*. If current exposure is below that threshold, then further reduction of exposure would not reduce consumer risk, regardless of the magnitude of reduction in exposure. Above the threshold, the magnitude of that reduction is critical to understanding whether there will be a significant impact on consumer risk, recognizing that not all reductions in exposure will significantly impact consumer risk. This is certainly an area where more research is needed and the cooperation of risk assessors and risk managers will be required.

Development of mitigation plans (boxes 7–9) for developing countries versus developed countries

Several aflatoxin reduction methods, from preharvest stages until the crops are consumed, have been recommended in developing countries. Developed countries have several sophisticated mitigations available to reduce the occurrence of mycotoxins in the food chain, including crop management practices, genetically modified crop varieties, grain dryers, sophisticated grain storage, optical sorting, mycotoxin testing, multiple regulatory standards, and decontamination processes, among others. Upon examination of the current peer-reviewed knowledge of various mycotoxin management practices, a WHO/International Agency for Research on Cancer Expert Working Group recommended four practices that are ready for large-scale implementation in developing countries for improving health outcomes *(54)*. These practices are dietary diversity, package of many postharvest practices (e.g., improved storage), sorting, and nixtamalization (in maize in Latin America). One of the key determinants of this short list of four broad practices was the availability of data to demonstrate the impact of various mycotoxin management practices on reducing human exposure.

Various pre- and postharvest practices that reduce aflatoxin contamination have been identified and can be applied in developing countries *(27, 49)*. Aflatoxin contamination of groundnuts is significantly reduced by adjustments in planting dates, frequent irrigation *(50)*, and water conservation practices in the field to reduce drought stress, a predisposing factor for aflatoxin proliferation in West Africa. Liming of soil and application of cereal crop residues and farmyard manure have also been shown to be effective *(48)*. Atoxigenic strain-based biological control of aflatoxin is also a proven preharvest technology that can reduce aflatoxin accumulation by 67% to 95% *(3)*. The beneficial effect of biocontrol passes from the field to the store and to the time that the grain is consumed *(6)*.

The fact that good grain drying and storage practices reduce aflatoxin contamination in maize in West Africa has long been known *(27)* and has been corroborated by many other studies, such as in Tanzania *(28)*. Although improved traditional storage structures have been recommended for use in West Africa *(26)*, newer types of storage containers, such as triple-layer hermetic bags *(37)* and metal silos, can stop the proliferation of aflatoxin in these structures if the grains are stored dry. Dietary interventions, primarily the use of calcium montmorillonite clay, do not reduce aflatoxin in the ingested food, but absorption of the toxin in the gut is lowered because aflatoxin binds with the clay and is excreted. Ingestion of clay powder before every meal reduced the aflatoxin biomarker in urine by 58% compared with placebo in Ghana *(52)* and was almost halved in Kenya *(4)*. It has been recommended that clay be used as an emergency measure in areas and at times when aflatoxin poisoning has occurred or is likely to occur. However, use of clay as a mycotoxin binder is not permitted by the U.S. Food and Drug Administration (FDA) at present, even in animal feed, although it can be used as an anticaking agent. Extensive research has demonstrated that some types of clays have no unintended effects on the human body *(39)*. Several chemoprevention agents such as chlorophyllin and oltipraz have also been recommended *(59)*.

Regulations that limit trade of commodities based on established MLs are an effective tool to minimize entry of harmful levels of aflatoxins in food and feed. Appropriate sampling and testing protocols and rigorous implementation of regulations must be in place for this method to succeed. While market-based trade in developed nations has been able to effectively implement regulations, smallholder farming in developing economies makes implementation of regulations challenging. Regulatory authorities in some nations, such as Nigeria, have taken the approach of monitoring packaged goods alone for implementation of regulations.

There is no "silver bullet" for mycotoxin mitigation. A combination of pre- and postharvest management methods must be integrated to obtain high levels of mycotoxin reduction. However, the number of practices that could be recommended to a farmer, who is already constrained by time and resources, is too high for adoption as a package. Therefore, comparative assessments of various practices can contribute to selection of those locally relevant practices that are simple but are highly cost-effective at various stages of crop handling from the field to consumption *(60)*.

Unfortunately, empirical data on the relative efficacy of various management practices for mycotoxin reduction are rarely available. As an exception, Matumba et al. *(35)* compared the efficacy of hand sorting, flotation, and dehulling, singly and in combination, for the reduction of mycotoxins in a single study. They demonstrated that hand sorting was most effective (96% reduction), followed by dehulling (83% reduction) and washing (63% reduction). When all three practices were used together, mycotoxin reduction increased marginally (by 3% to 99%) over use of sorting alone.

The availability of mycotoxin mitigation technologies does not automatically translate to the adoption and use of these practices by growers and others in crop value chains. Plans to implement technologies must be combined with the appropriate policy and institutional frameworks to overcome barriers to adoption of these technologies. The desire to achieve public health benefits provides the foundation for implementing plans for reducing mycotoxins. Only a few documented instances of implementation of mycotoxin reduction plans exist in Africa. The Grains Quality Improvement Project was created in 2007 in Ghana and Nigeria after about 50% of locally sourced crops were rejected because of mycotoxin contamination *(8)*. The project implemented a three-pronged approach with maize farmers to reduce the rejection rate. This approach included implementing good agriculture and storage practices, training farmers to improve capacity for mycotoxin management, and raising awareness of the harmful effects of mycotoxins among farming communities. A similar approach has been used in Malawi in the groundnut value chain *(17)*. Crop rejection was reduced from 50% in 2007 to 2% in 2014. The AgResults Aflasafe Pilot in Nigeria used a different multipronged approach to reduce aflatoxins in the maize value chain *(6)*. The elements of this approach consisted of farm-based organizations working with groups of farmers who were made aware of the dangers of aflatoxins and providing access to inputs (including the biocontrol product Aflasafe), technical services, training on good agricultural practices including aflatoxin management, aggregation of grains and aflatoxin testing services, and market linkages. More than 6,000 farmers following the integrated management approach in 2015 received a 13%–15% premium for the sale of aflatoxin-safe crops in the market.

Evaluation of secondary effects of mitigation (boxes 10–12) for process-formed compounds versus mycotoxins

This step in the process includes an evaluation of potential secondary effects, both positive and negative, of mitigation, to determine whether the overall impact of mitigation will be positive with regard to lowering the overall risk to consumers. Implementation of mitigation efforts that significantly reduce risk due to the targeted contaminant, but that disproportionally increase the risk that comes from another contaminant, a lack of nutrients, microbiological risk, or other factors should not be implemented, as the objective is to reduce overall consumer risk.

As the mitigation methods available for process-formed compounds and mycotoxins are quite different, the secondary effects of mitigation efforts for these two classes of contaminants are also likely to be different. Many of the mitigation efforts to control mycotoxins, such as changes in agricultural practices and storage or transportation of grains, will have similar impacts on all classes of mycotoxins. In these cases, the implementation of mitigation plans for mycotoxins would likely have positive secondary effects on the risk due to other mycotoxins. In contrast, for process-formed compounds, implementation of mitigation efforts could reduce a specific compound (and possibly similar compounds) but the impact on other, structurally unrelated compounds could be more difficult to predict. For example, some methods to reduce 3-monochloropropanediol in vegetable oils can lead to an increase in the concentrations of glycidyl esters *(22)*.

For mycotoxins, a possible secondary effect of mitigation would be the reduced availability of food. As described previously, once foods are contaminated, mycotoxin levels can be very difficult to reduce, leaving destruction of contaminated foodstuffs as the only mitigation available. This highlights another challenge, in that it can be difficult to compare two very different types of risk (e.g., risk from a contaminant versus risk due to reduced food availability). Recently, the WHO conducted an evaluation of the global burden of disease caused by a variety of food contaminants *(24, 34)*, which, by ranking the relative risks of different contaminants in terms of disease burden worldwide, could help inform these decisions.

Evaluation of secondary effects of mitigation (boxes 10–12) for developing countries versus developed countries

The European Union's strict regulations for mycotoxins require rejection of grains that do not meet the MLs. The exporters are then provided the choice of repatriating the consignment or paying the cost of destroying it. Both are costly and damaging, because the interceptions are notified across nations. Upon repeated interceptions, stringent controls are placed on further imports from the country, including bans in extreme cases. Exporting countries are responsible for ensuring that policies and practices are in place to meet the standards of the importing countries. As a consequence, the best-quality grains are exported out, leaving the poor-quality grains in the country and exposing the local population to higher levels of aflatoxins *(34)*.

Some recommended practices for mycotoxin mitigation may have unintended consequences, both positive and negative. The above example highlights a situation in which a specific mitigation effort (setting an ML) has a positive impact in some countries (countries with low MLs reduce mycotoxin concentrations in their own food supply) and a negative effect in other countries (countries that are forced to export their grains with the lowest mycotoxin levels increase the mycotoxin concentrations in their own food supply).

Some of the recommended good agricultural practices not only reduce mycotoxins but also benefit crops in other ways. Timely planting, irrigation, water conservation, crop rotations, and soil amendments are normal recommendations for increasing crop production. Rapid drying and good storage practices reduce postharvest losses due to insects.

Other practices, such as sorting, can have mixed consequences. Sorting of good-quality from lower-quality grains is very effective in reducing mycotoxins in the final product in both developed and developing countries. However, as a result, aflatoxin is necessarily concentrated in the culled grains because almost all of the lower-quality grains are fractioned in the "cull." In the developed world, there are adequate regulatory safeguards for segregation and decontamination of the culls, but this is not the case in the developing world. In addition, several developing nations are making efforts to increase exports of groundnuts to the European Union, where aflatoxin MLs are very low. Often, developing countries cannot meet the EU ML of 4 μg/kg for food and thus target the bird feed standard of 20 μg/kg, and even that lower standard sometimes cannot be met. Thus, grains destined for export are sorted, but the fate of culled grains in the exporting country is largely unknown. It is likely that a significant proportion is returned to the domestic market or taken by the women doing the sorting operations to be used for home consumption, as feed for animals, or for sale on the street. Because the culls are usually discolored, and hence cheaper in the market, poor consumers purchase the discolored grain *(16)* and are therefore exposed to disproportionately high levels of the toxin *(34)*.

In a few African nations, such as Kenya, public health officials conduct frequent monitoring of aflatoxin in maize at various points in the maize value chain, such as household stores, grain aggregation points, and markets. When the total aflatoxin level is above 10 μg/kg or the aflatoxin B1 level is above 5 μg/kg, the grain consignments are declared unfit for consumption and are sometimes destroyed, which can lead to food insecurity and increased food prices. The rejected grains are still of value for nonfood uses, either through decontamination procedures or by channeling contaminated grains into uses that can tolerate high levels of aflatoxin. For example, in the United States, maize containing up to 300 μg/kg aflatoxin is allowed by the FDA for use in feed of mature beef cattle, but no such differential regulatory standards for different uses exist in developing nations. Some of the decontamination procedures are ammoniation *(2)* and ozonation *(15)*. Ammoniated grain lots are unfit for human consumption but are nutritive as cattle feed if used immediately after ammoniation. While ammoniation is a recommended practice, ozonation has not gained acceptance. Neither of these two methods is currently used in the developing world because of cost and safety issues, but ammoniation has promise for adoption in the feed industry. Nixtamalization, an age-old alkaline treatment process for preparing dough in Latin America *(38)*, is being introduced in aflatoxin-prone areas of Africa and has been recommended for widespread implementation *(54)*.

Recommendations (boxes 13–15) for process-formed compounds versus mycotoxins

The objective of this step of the process is to finalize the decision on mitigation, whether that includes a recommendation to implement a specific mitigation plan (or combination of plans) or a recommendation to not implement mitigation at this point. This process is being developed to drive criteria-based decision making that can be utilized by risk managers. A recommendation to not implement any mitigation would be based on data demonstrating that none of the evaluated mitigation plans would result in a significant reduction in overall consumer risk.

For both mycotoxins and process-formed compounds, any recommendation to not implement mitigation should be re-evaluated when new data or new mitigation technologies become available. Such a recommendation will be, by necessity, representative of a particular point in time; therefore, every attempt should be made to clearly articulate the particular limitations of the mitigation plans evaluated, to facilitate future reviews when new technologies applicable to these limitations have come to light.

Similarly, for both process-formed compounds and mycotoxins, if a specific mitigation plan is recommended and then implemented, there should also be a mechanism in place to review the effectiveness of the plan. Not only is this important for the specific compound for which the mitigation plan was developed, but analysis of the effectiveness will also help inform the development of future mitigation plans by providing data in terms of what the magnitude of risk reduction would be if similar mitigation plans were implemented for other compounds.

Recommendations (boxes 13–15) for developing countries versus developed countries

Nearly all mycotoxin mitigation practices come at a cost—in terms of both time and money—that must be borne by farmers and others in the crop value chain. Incentives to adopt mitigation measures may include health, income, and reputational outcomes. In the developed world, effective monitoring and enforcement of regulations to protect consumers from mycotoxin exposure plays a dominant role in achieving food safety. Growers, aggregators, and processors implement mycotoxin mitigation practices to meet these standards. The reality of millions of smallholder farmers, less organized supply chains, and an inadequate capacity for regulations in developing nations requires the use of different approaches based on local needs *(57)*.

For rural smallholder farmers who are less involved in market trade, public funds are justified to implement mitigation practices, because the indirect cost of the increased public health burden of not doing so would be high. Examples of public intervention include creating awareness about mycotoxins in the food supply, training farmers about management practices, and implementing programs and policies that provide access to technologies such as biocontrol, dryers, and improved grain storage. In a trade-based system, institutional support to encourage private-sector investments for mycotoxin mitigation is more likely to be successful.

Three approaches—public, private, and public-private—can be followed, as described by Bandyopadhyay et al. *(6)* for aflatoxin biocontrol. In the public model, public institutions provide improved seeds, fertilizers, and biocontrol products at a subsidy; technical services such as training for pre- and postharvest management for growing productive and safe crops; and sometimes, buy-back opportunities. This model is being followed in some parts of Kenya and Nigeria by the respective governments. Some organizations in the private sector and farm-based businesses have followed the path of corporate social responsibility and fair trade objectives to manage mycotoxins in smallholder settings to achieve the objectives of maintaining food safety at the farmer level, establishing a reputation for adhering to high standards, and boosting profits for the company *(8, 17)*. An example of the public-private hybrid model is AgResults (www.agresults.org), a collaborative initiative between the Bill and Melinda Gates Foundation and the governments of Australia, Canada, the United Kingdom, and the United States that incentivizes and rewards high-impact agricultural innovations that promote food security, health, and nutrition. These results are accomplished through the design and implementation of pull mechanisms, an innovative finance mechanism that provides economic incentives to the private sector to enter into markets that serve those living in extreme poverty. AgResults is currently providing incentives to the private sector to scale up adoption of the highly effective biocontrol *(6)* and grain storage technologies for aflatoxin control, which have some constraints to adoption. The incentives are provided to offset the constraints and only if evidence is presented to demonstrate the technology was actually adopted. The incentive is withdrawn after a predetermined period.

Several methods are already available for mycotoxin mitigation. Awareness must be created among decision makers about the grave consequences of mycotoxins on health, trade, and the national economy so that they support mitigation actions. Implementation of the proven practices in the crop value chains for mycotoxin mitigation should receive high priority, together with creating conditions that make adoption of such practices economically attractive. The Partnership for Aflatoxin Control in Africa (PACA), based in the African Union, is leading efforts among high-level policy makers and coordinating continent-wide actions for aflatoxin mitigation. PACA also needs to take on the role of promoting monitoring of aflatoxin mitigation efforts in partnership with the national government and private enterprises.

DISCUSSION

In this paper, we assessed the applicability of the ILSI North America risk-based decision tree for mitigation of process-formed compounds to the control of mycotoxins. While the decision tree is applicable, several unique challenges are associated with a risk-based approach to mycotoxin mitigation. These include the likelihood that certain populations, primarily in developing nations, may be at an increased risk due to disposition of rejected commodities. Climate change, which has the potential to profoundly affect the prevalence and concentration of mycotoxins in various parts of the world *(7, 46)*, is outside human control and could further complicate the assessment of future exposure in response to different mitigation strategies. Consequently, substantial effort will be required to monitor the effectiveness of mitigation measures going forward.

It is important to consider the role of MLs or other guidance or advisory levels as incentives for improving processes that will ultimately reduce dietary exposure versus being effective tools, in and of themselves, for reducing exposure. Clearly, the presence of mycotoxins (or other contaminants) cannot be managed (or even evaluated) without being measured; thus, MLs provide the incentive to at least monitor those mycotoxins in the food supply. However, MLs affect world trade, and the need to meet lower MLs to trade with certain countries provides additional incentive to improve processes that lower mycotoxin levels in various commodities [e.g., *(12)*]. Even domestically, farmers who want to meet market requirements may keep some of their crop, thus also improving home consumption. These positive outcomes must be balanced with the reality that more commodities will be rejected, and the disposition of those rejected commodities must be managed to prevent disadvantaged communities from being disproportionately adversely affected.

Despite the challenges, application of the decision-tree approach with defined criteria could provide many benefits to the control of mycotoxins. Historically, mycotoxins have been controlled through common mechanisms (COPs and/or the setting of MLs), under the assumption that these measures are likely to decrease not only exposure but ultimately consumer risk as well. Application of specific criteria that forces decision making to be based on risk reduction, rather than reduction in occurrence, could help ensure prioritization of the mitigation efforts that are the most effective at reducing risk. These criteria would also improve mechanisms for evaluating the effectiveness of mitigation efforts that have already been implemented, again ensuring that conclusions about the effectiveness are based on risk reduction.

Application of the ILSI North America decision tree to mycotoxins, in whole or at least in part, will help shift the focus of mitigation efforts from simply reducing exposures to ensuring that such expenditures of resources actually reduce overall health risk to the consumer. The symposium identified several important and unique considerations for applying risk-based decision making to mycotoxin mitigation, particularly in developing nations. Public-private partnerships will play an important role in successfully reducing the public health impacts of dietary exposure to mycotoxins on a global scale.

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Author contributions

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