Executive summary

Mycotoxins are fungal toxins that contaminate staple foods consumed by many of the poorest and most vulnerable populations in the world. These toxins have the potential to contribute to a diversity of adverse health effects in humans, even at low concentrations. Given the ubiquitous nature of exposure in many countries, an urgent need exists for a coordinated international response to the problem of mycotoxin contamination of food. The topic has been marginalized for far too long. One priority is development of a better understanding of the consequences of consuming large quantities of toxin-contaminated food daily, as is often the case in subsistence farming areas in developing countries. A second priority is development of effective, accessible, and practical intervention measures to prevent or minimize exposure in the populations at the greatest risk.

The knowledge and methodologies exist to control mycotoxins in food. However, these are currently only applied with any rigour in some high-income countries with well-established analytical methods to screen for mycotoxins and with strong regulatory controls. In low-income countries, the situation is often in marked contrast: subsistence or small-scale farmers produce foods for local consumption that may be heavily contaminated with mycotoxins; these foods are untested; and regulatory controls either do not exist or are not enforced.

In low-income countries, the main consequence of mycotoxin awareness may be the commercial sale of the best quality food and local consumption of the worst. Grains and other foods for export must comply with quality requirements and sanitary regulations, which are established by the target markets. Contaminated commodities may also be exported from high-income countries to those where regulations either are not in place or are ineffective or unenforced. Because of a lack of resources for an efficient control system, these contaminated imports can be diverted to the poorest sectors of society. One man's meat is truly another man's poison. As a result, for example, some populations are exposed daily to aflatoxins at levels well above those legally permitted in other countries; these are toxins that the international health community has recognized for two decades as being human carcinogens.

In low-income countries, exposure to mycotoxins at high levels is often closely associated with inequality and poverty. Therefore, affordable and feasible solutions should be a part of the international development agenda. Much can be done; much should be done. Failure to act in a timely manner could pose a grave risk to consumers in low-income countries where basic commodities like wheat, maize, and groundnuts are potentially contaminated with harmful levels of mycotoxins and are consumed in large quantities.

This book from the International Agency for Research on Cancer, the specialized cancer agency of the World Health Organization, aims to sensitize the international community to the mycotoxin problem in a format that is accessible to a wide audience and is useful to decision-makers across a broad spectrum of disciplines, including agriculture, public health, marketing, and economics. The editors hope that this book will be a stimulus to governments, nongovernmental and international organizations, and the private sector to initiate measures designed to minimize mycotoxin exposure in high-risk populations. The book not only provides a scientific description of the occurrence and effects of mycotoxins but also goes further by outlining approaches to reduce mycotoxin exposure aimed at improving public health in low-income countries. This executive summary briefly outlines the book's content and provides some context to its preparation.

Mycotoxin occurrence

Mycotoxins are secondary fungal metabolites that contaminate many of the most frequently consumed foods and feeds worldwide. Therefore, human and animal exposure to one or more of this broad group of toxins is widespread. The types of fungi – and therefore mycotoxins – found in different regions depend on climatic conditions. The main mycotoxins of significance for human disease are aflatoxins, fumonisins, ochratoxin A, deoxynivalenol, and zearalenone. These toxins are produced by just a few species of fungi from the common genera *Aspergillus, Penicillium*, and *Fusarium*. These fungi may either grow on the crop or invade the crop after harvest and produce toxins during drying and storage.

Wheat is the most important cereal for human consumption, as the staple food for nearly half of the world's population, followed by rice and maize. With some exceptions (e.g. parts of West Africa), consumption of the remaining staple crops, including sorghum and millet, is minor by comparison. Natural contamination of the three major crops by mycotoxins can be a serious food safety problem in some regions, but the crops differ in susceptibility to the various fungi that produce toxins. The incidence of mycotoxins also depends on a wide variety of agronomic and climatic conditions as well as on whether a particular cultivar is grown within the area to which it is adapted.

Of the *Aspergillus* species occurring in warmer climates, *A. flavus* produces aflatoxins in maize, groundnuts, tree nuts, and, less frequently, other commodities, whereas *A. parasiticus* is common in groundnuts. Fumonisins are produced mainly by *Fusarium verticillioides*, a fungus that is ubiquitous in maize. Ochratoxin A is produced mainly by *A. carbonarius,* which is commonly found in grapes, dried vine fruits, wine, and coffee, and by *A. ochraceus* and related species, which produce this toxin in coffee and sometimes in stored grains. *Penicillium verrucosum* also produces ochratoxin A but occurs only in cool temperate climates, where it infects small grains. *F. graminearum* is the major producer of deoxynivalenol and zearalenone in maize, wheat, oats, and barley and produces these toxins whenever it infects these grains before harvest. Indeed, wheat can be highly affected by deoxynivalenol in southern China and parts of South America as well as in cooler, damper climates in Europe and Canada. Maize is at considerable risk for contamination by aflatoxin, fumonisin, deoxynivalenol, and zearalenone, sometimes all four at once. Significant contamination of maize with aflatoxins and fumonisins occurs in the tropical and subtropical growing areas of the world. Rice is not infected before harvest by any of the major toxigenic fungi and seldom, if ever, contains significant mycotoxins immediately after harvest, drying, and hulling. However, rice can be contaminated by aflatoxins if post-harvest storage systems are inadequate.

Mycotoxin measurement

Investigating the health and economic impacts of mycotoxins requires measuring their occurrence. However, accurately assessing the level of one or more mycotoxins in a crop or food commodity is a major challenge because the mycotoxins are heterogeneously distributed, which makes representative sampling extremely difficult. Therefore, considerable care and planning are needed in sampling and sample preparation to ensure the accuracy of the estimated levels of contamination. In any investigation of mycotoxin levels in relation to health effects or for regulatory purposes, careful attention must be paid to the need for accurate estimates of contamination. Representative sampling can pose particular problems in the context of small-scale farmers or subsistence farming communities, where only smaller sample sizes can be obtained, and thus sampling approaches must be adapted accordingly.

Once an appropriate sample has been prepared, an analytical procedure must be selected to measure the mycotoxin(s). Many modern methods require highly sophisticated technology and skilled technicians. Although these techniques are applicable in settings of developed economies handling bulk commodities, a need still exists for methods that are applicable to smaller-scale farms, where resources are limited and rapid decisions are needed about the contamination of foods to be consumed locally. Validated thin-layer chromatography and immunoassays are existing technologies capable of meeting this challenge. Indeed, one of the outstanding requirements in the management of mycotoxins is the production of reliable and easily applicable tests for use in low-income countries. Commercial companies and development agencies should consider production of appropriate testing kits, sampling equipment (e.g. grinders), and training models specifically tailored for use in these regions.

Effects in food-producing animals

Animals suffer a variety of adverse effects from consuming mycotoxin-contaminated feeds, and these in turn may pose problems to those communities that rely on the animals for food. Several indices can be used to associate a disease in animals with a particular mycotoxin through awareness of the outward adverse signs typical of exposure to a given mycotoxin. As well as the direct effect in animals, mycotoxicoses in domestic animals can be a warning sign of a risk of high-level contamination of foods for human consumption.

Aflatoxins can cause acute toxicity in many species, most notably evident in poisoning outbreaks in poultry. In addition, chronic exposure leads, among other effects, to reduced weight gain, decreased egg production, impaired immunity, and altered susceptibility to infectious agents. Fumonisins were first identified through the occurrence of equine leukoencephalomalacia and, later, the occurrence of porcine pulmonary oedema. The main target organ of ochratoxin A is the kidney, and nephropathy is accompanied by renal dysfunction and oedema; this is most common in pigs but has also been reported in horses. Ochratoxicosis in poultry is associated with feed refusal and high mortality. Deoxynivalenol can provoke feed refusal, e.g. in cattle, pigs, and chickens, and pigs are particularly sensitive; high intakes are also associated with emesis. Zearalenone causes a variety of reproductive problems as a consequence of estrogenism.

In relation to cancer, aflatoxins are hepatocarcinogenic in several different species, and fumonisins have been shown to induce kidney tumours in mice and liver tumours in rats. Ochratoxin A is also carcinogenic in rats and mice, inducing kidney carcinoma in rats and both liver and kidney tumours in mice. In contrast, there is little evidence of carcinogenicity of deoxynivalenol. Zearalenone treatment increased incidences of liver cell and pituitary tumours in mice, consistent with a hormonal mode of carcinogenic action; no carcinogenic effect was seen in rats.

Effects in humans

Despite the fact that the potential adverse effects of mycotoxins on human health have been recognized for centuries, much remains to be defined. For aflatoxins, a strong causal association with liver cancer has been identified, with a particularly elevated risk in people chronically infected with hepatitis B virus (HBV). Acute aflatoxin poisoning, termed aflatoxicosis, is also a known consequence of exposure to high dietary toxin levels. The recently identified association between aflatoxin exposure early in life and impairment of child growth is an important observation that, together with possible immunomodulatory effects, demands greater scrutiny to evaluate its importance in many vulnerable populations worldwide. If the link between aflatoxin exposure and child growth impairment is causal, this will transform the public health impact of minimizing exposure.

For fumonisins, studies indicate a possible role in oesophageal cancer and in neural tube defects, but further investigation is needed as a priority. For deoxynivalenol and other trichothecenes, exposure has been linked to acute poisoning outbreaks in large numbers of subjects. The effects of chronic exposure need to be defined, given the extent of exposure occurring worldwide. For ochratoxin A and zearalenone, the human health effects remain largely undefined and also merit greater attention. However, investigating the effects of mycotoxins on human health is challenging, not least because of the difficulties in measuring exposure, and this is also reflected in the relative paucity of epidemiological studies on the toxins mentioned above. Newly established biomarkers of exposure at the individual level are proving valuable in improving exposure assessment and should be prioritized in terms of development and validation as well as application in studies of etiology.

As with other environmental toxins, individual differences in susceptibility to mycotoxins are likely. Susceptibility may be influenced by genetic, demographic, nutritional, infectious, or immune factors. For example, individuals may differ in the way in which mycotoxins are metabolized or, alternatively, other co-exposures may be critical, as mentioned above for aflatoxin exposure and HBV chronic carriers. The consequence of these interactions is that the same mycotoxin exposure may have different effects in different populations or individuals. The influence of malnutrition on susceptibility to toxicity induced by mycotoxins has been little studied. In developing countries, most people consuming maize as a monocereal staple diet also lack sufficient levels of micronutrients and thus may have enhanced susceptibility to adverse effects of contaminating mycotoxins. Young children may be particularly susceptible, as may be the fetus. In fact, there is a dearth of data on the possible effects of mycotoxins in women and children in populations where mycotoxin exposures are highest. Increased awareness of the risks posed to vulnerable populations by mycotoxins should stimulate more research on the interactions with other risk factors and elicit caution when risk assessments are conducted.

Risk assessment and management

The well-documented toxicity of mycotoxins in animals and humans has provided the impetus for the conduct of risk assessments on all the major mycotoxins (aflatoxins, fumonisins, ochratoxin A, deoxynivalenol, and zearalenone) by various regulatory agencies. These risk assessments have had a variety of impacts in relation to the global burden of diseases related to mycotoxins as well as regulatory measures on food supply and international trade. Overall, in line with the limited evidence from epidemiology referred to already, many uncertainties remain. The health end-points used to set regulatory levels need to be periodically reviewed, given that mycotoxins may cause a diverse set of effects. For example, with aflatoxins the risk assessments have been dominated by the association with liver cancer, but the recent studies on child growth impairment, if confirmed, may provide an important additional parameter for consideration. These adverse effects may occur at exposure levels below those that induce cancer, in which case the current regulatory levels may provide inadequate protection, even if adhered to.

Many differences are also apparent in risk management strategies and government regulations and technologies to reduce levels of mycotoxins in the food-chain. However, it is evident that regulatory measures have very little impact on remote rural and subsistence communities.

Economics of mycotoxins

In the past, the biology and economics of mycotoxins have been considered separately, but if the mycotoxin problem is to be addressed, a rounded consideration is needed of the broader consequences of these environmental contaminants. Therefore, the economic impacts of mycotoxins should be thought of in two ways: (i) the direct market costs associated with lost trade or reduced revenues due to contaminated food or feed, and (ii) the human health losses from the adverse effects mentioned above.

Losses related to markets occur within systems in which mycotoxins are being monitored in the food and feed supply. Such monitoring systems can result in a commodity with excessively high mycotoxin levels being rejected for sale or having a lower market value, but human exposure to the toxins is thus reduced. Losses related to health occur when mycotoxins are present in food at levels that can cause illness, and such losses can be measured using disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs). It is estimated that aflatoxin-related liver cancer alone may cause more than 2 million DALYs annually worldwide. The total socioeconomic burden of all mycotoxins and all associated diseases and conditions is likely to be much higher. From a market standpoint, in the USA alone, mycotoxins cost crop growers more than 1 billion US dollars annually. Similar losses are sustained by producers in three Asian countries – Thailand, the Philippines, and Indonesia – from aflatoxin alone.

An important component, which merits more research, is the economic assessment of costs of interventions to reduce mycotoxins compared with benefits, in terms of either improved markets or improved human health. The cost-effectiveness of an intervention is evaluated by comparing the cost of implementing the intervention in a given population, per DALY saved, with the per capita gross domestic product for the country in which the intervention is applied. Aside from direct economic considerations, interventions that are feasible in low-income countries should be prioritized.

Reducing exposure to mycotoxins

Approaches to minimize mycotoxin levels in food are varied, encompassing good agricultural and manufacturing practices as well as approaches at the household or individual level. In general, interventions at the different stages include pre-harvest, post-harvest, and dietary approaches. What is needed most is the evaluation and adaptation of these approaches into cost-effective, simple, and sustainable intervention methods, predominantly at the population level, suitable for low-income countries.

One possibility to reduce mycotoxin exposure is avoiding contaminated foodstuffs by modifying the diet. However, this is dependent on having the necessary wealth and access to different foods to enable choice. It also presupposes that lack of food is not driving the need to eat contaminated food. Some examples exist where economic development has resulted in a change in diet and lower mycotoxin levels, notably in parts of China where a shift from maize to rice consumption has lowered aflatoxin intake. This option is not an obvious one for other populations to follow but does demonstrate both the detrimental effects of overreliance on a potentially contaminated crop and the positive effects of resources flowing to low-income countries, permitting a greater dietary diversity. Nevertheless, any such changes are likely to be slow in coming.

The possibility has been explored of using dietary interventions that either reduce mycotoxin bioavailability or modulate metabolism in ways that reduce the harmful effects of ingested toxins. For example, some enterosorbent clays and micronutrients have been added to the diet to adsorb aflatoxins in the gastrointestinal tract, thus reducing absorption. An alternative approach, also for aflatoxins, has involved the use of chemopreventive agents (e.g. chlorophyllin) that increase the detoxification of reactive metabolites in the body. Although these approaches can be used to target exposed individuals, their application as a broader, sustainable public health intervention is unclear.

A wide range of agricultural strategies, both pre-harvest and post-harvest, exist that may reduce the quantity of aflatoxin in food. Genetic modification of crops to reduce insect damage or enhance fungal resistance offers a promising opportunity for some toxins. Biocontrol by inoculating fields with non-toxigenic fungi is another approach, already in use in some high-income countries. Post-harvest interventions include the removal of infected and/or insect-damaged food components by hand sorting, preferably combined with correct drying and storage conditions, which avoid fungal proliferation and toxin production. Significant reductions in exposure can be achieved by simply removing and discarding visibly mouldy maize or groundnuts, for example. In addition, under some circumstances the food commodity can be processed to reduce mycotoxin levels; an example is chemical deactivation via nixtamalization. Each of these agricultural and individual approaches is more or less accessible to different populations, depending upon available resources and cultural acceptance of the practice.

Food security versus food sufficiency

Human exposure to mycotoxins is determined by the level of contamination in a given food commodity and the quantity of that commodity consumed. Thus, in some areas of the world mycotoxin levels are relatively high but exposure is modest because of a varied diet. In other areas, a similar level of contamination may translate into a much higher exposure because the diet is more uniform. This is why communities relying on dietary staples such as wheat, groundnuts, or maize, which are frequently contaminated by mycotoxins, are particularly vulnerable. These communities tend to be in regions where national regulations on mycotoxins either do not exist or are seldom implemented.

While facing mycotoxin contamination and high levels of exposure, these same regions often face challenges of adequate food production and preservation combined with a generally poor nutritional status of the population. Food availability may have a strong seasonality, which threatens the adequacy of nutrition at the household and national level. Importation of food may be constrained by currency problems, among other things. This is the context in which many countries have to face the challenge of mycotoxins as they balance the adequacy of the food supply with the safety of food.

One key problem is the general lack of awareness about the presence and health effects of mycotoxin contamination of food, compared with the immediacy of not having enough to eat. As a consequence, in many cases food security simply translates to having sufficient food for everybody throughout the year, as viewed from both household and government perspectives. This constant concern about food sufficiency is itself, therefore, a barrier to addressing the issue of mycotoxins as a component of food security. At the household and community level, misconceptions about food security result from a lack of information and nutritional education. At the government level, the information may also be lacking, but the overriding focus is on food supply, whereas the problem of food security is a matter that awaits economic development.

At an international level, the responsibility to safeguard the health of a specific population from mycotoxins is placed on the importing governments because of the way mycotoxin regulations are applied. This leads to heterogeneity as a result of economic factors, international trade agreements, and other factors, such as the protection of certain agricultural commodities by government subsidies. The result of these varying pressures is that mycotoxin regulation varies among countries, from strict implementation based on the latest risk assessments through to a total lack of implementation and control. Therefore, the various influences on regulatory decisions in a specific country are often played out against a background of tension between the health authorities and the political and economic powers controlling international trade and industry.

Despite the political, structural, and economic challenges to mycotoxin control outlined here, the means and the motivation for change already exist. Subsistence and small-scale farmers are familiar with problems of the quality of seed varieties, pests (e.g. insects, rodents), and storage management. The understanding that fungi damage crops exists and solutions are welcomed, even though an understanding that fungi produce mycotoxins and that these can have adverse health effects remains uncommon.

A limited awareness of the danger of mycotoxins in foodstuffs is also apparent among the local traders who, in some regions of the world, may purchase from local growers and sell to customers or larger businesses. In fact, regulations applied by importing developed countries to crop exports from developing countries are often the point where governments and large traders are brought face to face with the mycotoxin problem.

Overall, therefore, it is important, through education, to improve awareness of the problems of mycotoxin contamination of foods and to promote the potential solutions within different sectors of society, including householders, farmers, and traders as well as governments and nongovernmental and international organizations.

Responses to the mycotoxin problem – seven priorities

This executive summary provides a flavour of how this book addresses the major issues and of the complexity of the mycotoxin problem in low-income countries. However, mycotoxins are one problem embedded within many other challenges to health, resulting from poverty and inequality.

Therefore, mycotoxins can only really be addressed by taking into account the local situation with respect to food sufficiency, economic pressures, competing health problems, and the social environment. In this context, we propose the following seven priority areas for mycotoxin control worldwide.

1. Education leading to improved awareness of mycotoxins across different sectors of society, including householders, farmers, traders, governments, and nongovernmental and international organizations.
2. Better description of the prevalence and level of mycotoxin exposure in the regions of the world most affected, as a basis for prioritizing control and estimating risk.
3. Development of accurate and applicable mycotoxin testing kits, sampling equipment, and training models for use in low-income countries, to permit rapid assessment of mycotoxin contamination of staple foods.
4. Conduct of epidemiological studies to assess the acute and chronic health effects of mycotoxin exposure; priorities include the impact of mycotoxins on child growth and immune status.
5. Identification of individuals and groups who are particularly susceptible to mycotoxins so that the risk assessment can be focused on those at greatest risk for adverse health effects.
6. Development and evaluation of cost-effective, simple, and sustainable intervention methods suited to low-income countries.
7. Detailed economic assessments of interventions, in terms of either improved markets or improved human health.