

# Approaches to the risk analysis of mycotoxins in the food supply

**T. Kuiper-Goodman**

Tine Kuiper-Goodman is in the Toxicological Evaluation Section, Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Health Canada, Ottawa.

A number of cereal and other crops are susceptible to fungal attack, either in the field or during storage. The fungi involved may produce mycotoxins as secondary metabolites. The level of mycotoxins in foods can fluctuate widely and vary significantly from year to year. These fluctuations depend on many factors, including adverse conditions that favour fungal invasion and growth either in the field or during storage. Mycotoxins are a diverse group of chemical substances. When present at high enough levels in the diet, many have caused acute and/or chronic adverse health effects in animals and humans. Mycotoxins can affect many target organs and systems, notably the liver, the kidney and the nervous, endocrine and immune systems. There is much concern about chronic effects brought about by low levels of exposure, and several mycotoxins have been classified by the International Agency for Research in Cancer (IARC) as human carcinogens or potential human carcinogens (IARC, 1993).

Although there are geographic and climatic variations in the production and occurrence of mycotoxins, exposure to these substances occurs all over the world and much of the world's food supply is contaminated to some extent. Monitoring of mycotoxins is needed in areas where high levels cause problems that could have adverse effects on health. Although these toxicants can never be completely removed from the food supply, risk analysis based on sound scientific knowledge makes it possible to define the levels in food (tolerances, guideline levels and maximum residue levels) that are unlikely to be detrimental to health. This will aid the harmonization of mycotoxin regulations and control procedures, and facilitate international trade in food. Considerable efforts have already been made to assess the health risks posed by just a few of these chemicals. In terms of exposure and the severity of the chronic lesions (especially cancer) they cause, mycotoxins appear, at present, to pose a higher risk than anthropogenic contaminants, pesticides and food additives (see Table). In addition, the implications of exposure to several mycotoxins at once may need to be considered.

## Rating health risks from foods

Acute		Chronic
	<b>High</b>	
Microbiological		Mycotoxins
Phycotoxins		Anthropogenic contaminants
Some phytotoxins		Some phytotoxins
Mycotoxins		Unbalanced diet
Anthropogenic contaminants		Phycotoxins
Food additives		Microbiological
Pesticide residues		Food additives
		Pesticide residues
	<b>Low</b>	

Source: Kuiper-Goodman, 1998.

## RISK ANALYSIS

At the time of two previous meetings on mycotoxins – held by FAO, the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) in Bangkok in 1987 and Nairobi in 1997 – the application of risk analysis to mycotoxin problems was not well developed. The lack of a unified approach among countries resulted in a wide variety of guidelines and regulations regarding mycotoxins. During the last ten years, much progress has been made in the approaches to risk analysis for all of the chemicals that may cause concern for food safety, including mycotoxins, and a leading role has been taken by international organizations such as WHO and FAO (especially through the Codex Alimentarius Commission [CAC] and the Joint Expert Committee on Food Additives [JECFA]), the International Agricultural Research Centres, the Organisation for Economic Co-operation and Development (OECD) and the International Life Sciences Institute (ILSI), as well as several national agencies (CAC, 1998; JECFA, 1996; IARC, 1991; IPCS, 1990). Although it has been recognized that common approaches and common terminology are essential for harmonization, this goal has not yet been achieved.

In dealing with the problems associated with mycotoxins, a framework of risk analysis similar to that recently proposed by FAO and WHO (FAO/WHO, 1995) needs to be used. According to this framework, risk analysis is made up of three parts: risk assessment, risk management

and risk communication (see Figure). Each of these major spheres of influence overlaps with the others. Such an approach considers scientific principles related to human and animal health, including comparisons with other risks (as part of risk communication), as well as socio-economic factors (as part of risk management). The aim is to achieve practical solutions, such as guidelines regarding maximum residue levels, procedural guidelines aimed at preventing the problem (e.g. Hazard Analysis and Critical Control Point [HACCP]) or a combination of both. Ideally, such guidelines are acceptable to the countries that produce food commodities as well as to the countries that receive them.

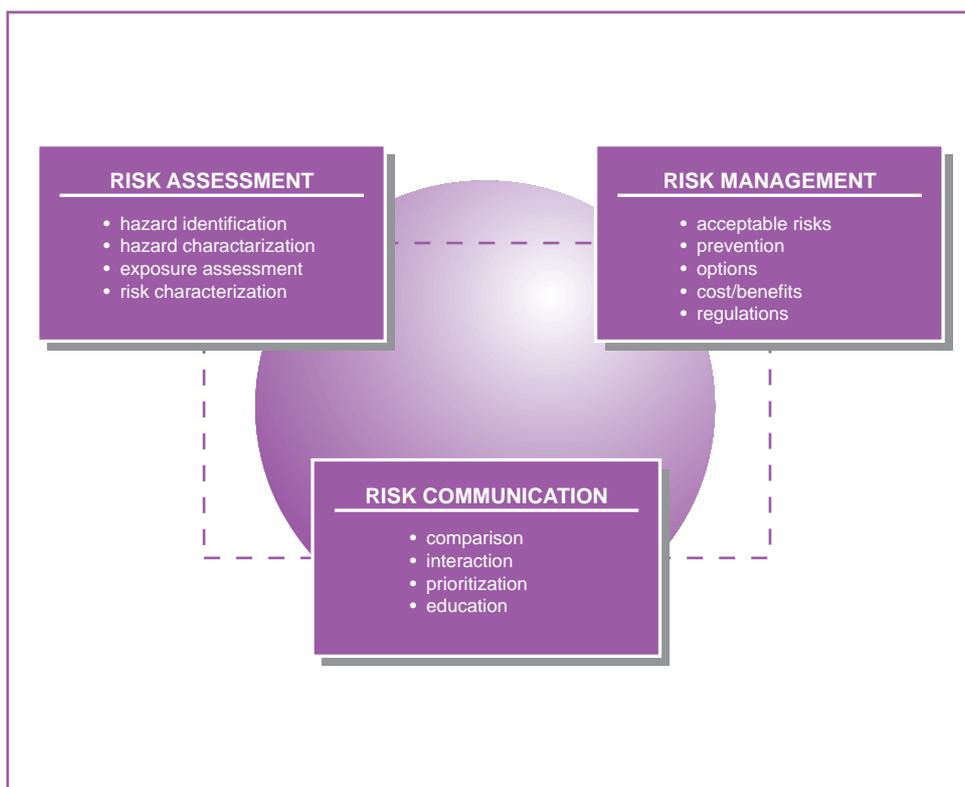
Since the last FAO/WHO/UNEP meeting, new mycotoxins have been discovered (fumonisins) and for some of the other mycotoxins important new data related to toxicology, epidemiology and human exposure have become available (as a result of improved detection methods and the use of biomarkers). This has resulted in new and updated evaluations by IARC (IARC,1993) and JECFA (JECFA,1996), as well as national agencies (Kuiper-Goodman, 1985; Kuiper-Goodman, Scott and Watanabe, 1987; Kuiper-Goodman and Scott, 1989; Olsen *et al.*, 1991; Bowers *et al.*, 1993; Kuiper-Goodman, 1996; Kuiper-Goodman *et al.*, 1996). Scientific evaluations have become the basis for recommendations regarding the international regulation of mycotoxin levels (aflatoxins, ochratoxins, patulin, zearalenone) made by the Codex Committee on

Food Additives and Contaminants (CAC, 1999) and the European Union (EU).

Several factors make it difficult to use a harmonized approach. One of these factors relates to the conflict between national interests and trade interests. Countries need to be autonomous and serve their own interests. However, the interests of producing countries do not necessarily coincide with those of recipient countries and the presence of mycotoxins in food commodities could lead to trade barriers, unless all parties agree on the approach for deriving safe levels and can see that their own interests have been addressed. Other impeding factors relate to data interpretation and analysis and differences in food intake patterns among countries. These are discussed later in this article.

#### RISK ASSESSMENT

Ideally, risk assessment involves a complete toxicological assessment, an epidemiological assessment, an exposure assessment and a risk characterization. However, in the risk management of mycotoxins it may be necessary to take action before all this information is available. In this article, “hazard” is defined as the intrinsic property of a biological, chemical or physical agent to cause adverse health effects under specific conditions. This definition implies some certainty that, under similar conditions, the agent will cause similar adverse health effects. “Risk” is defined as the



*Risk analysis framework for food safety*

estimated likelihood of an adverse health effect, weighed for its severity, occurring in humans as a result of exposure to a biological, chemical or physical agent in food.

#### Hazard identification

Many economically important mycotoxins have carcinogenic properties that affect several organs. They may also cause developmental effects, including birth defects, and affect the immune system; some also exhibit hormonal activity or are neurotoxic. In addition to these diverse organ- or site-specific actions, a disturbance of the gastrointestinal system, skin irritation and haematological effects have been observed. These studies usually determine empirically the “no-observed-adverse-effect level” (NOAEL), which can be regarded as a “threshold”.

Several of the carcinogenic mycotoxins appear to have both initiating and promoting properties and also contribute to tumour progression, as reflected in both tumour pathology and genotoxicity test results. It has been presumed that there is no threshold for this process. Other mycotoxins seem to exert predominantly tumour-promoting activity, a mode of action for which it is presumed that a threshold does exist. Under hazard characterization, these two types of carcinogens are treated differently and this has an impact on how safe levels are determined. However, the distinction between the two groups of carcinogens is not always clear. Thus, mycotoxins have a wide spectrum of toxicological effects, and may affect many diverse cellular processes. This diversity of biological effects demands a case-by-case evaluation and may require a variety of extrapolation techniques (see next section, Hazard characterization).

The widespread occurrence of mycotoxins has made them a cause of human as well as animal mycotoxicoses (ergotism, liver cancer, yellow rice disease, alimentary toxic aleukia [ATA], turkey-X-disease). Risk assessment, therefore, also uses information from epidemiological studies of exposed humans.

#### Hazard characterization

Hazard characterization is the extrapolation phase of risk assessment. Its aim is to make a predictive characterization of the hazard to humans, based on animal studies (species extrapolation) under low exposure conditions (extrapolation from high to low dose). The endpoint of hazard characterization is the estimation of a “safe dose” such as a provisional tolerable daily intake (PTDI) or equivalent – the word “tolerable” indicates that, generally, mycotoxins do not serve a useful purpose to humans. In general, (P)TDIs are determined only when there is likely to be a threshold

in the relationship between dose and effect, based on knowledge of the mechanism and mode of action. To derive a TDI for humans, it has been common practice to divide the NOAEL by a safety factor of 100 when extrapolating from animals to humans. This takes into consideration a factor of 10 for interspecies differences and another factor of 10 for intra-species (in this case, intra-human) variation. When there are significant irreversible effects for which thresholds have been established (as is the case for non-genotoxic carcinogens) or insufficient data, additional uncertainty factors may be added. Sometimes the setting of a (P)TDI is deferred until sufficient data are available. Alternatively, and as an interim measure, a margin of safety approach is sometimes used, as in the interim risk assessment for fumonisins.

For genotoxic carcinogens the default position has been that there is no threshold dose below which effects, such as initiation of the carcinogenic process, will not occur, and a TDI is generally not determined. Non-threshold carcinogens are not allowed as food additives. When such chemicals cannot be completely avoided (as is the case for some mycotoxins), a variety of approaches have been used. Mathematical models, most of which presume that the effects of low doses are linear, have been used to extrapolate the possibility of adverse effects at low doses. The dose corresponding to a risk level of  $10^{-5}$  or  $10^{-6}$  has, in some jurisdictions, been considered as posing a negligible risk. Other jurisdictions consider that, for genotoxic carcinogens or even genotoxic agents (e.g. patulin) for which the carcinogenic potential has not been established, the most appropriate method of regulation is to determine levels that are “as low as is reasonable” (ALAR) or as low as is technologically achievable. Alternatively, regulation can be based on biological factors, such as mode of action and weight of evidence, which examine the severity of the resulting lesion. This information can be combined with an estimate of tumour potency such as the  $TD_{05}$ . Dividing the  $TD_{05}$  by an uncertainty factor of 5 000 gives a value that is equivalent to a risk level of 1:100 000 and provides estimates of safe intake that are similar to those derived using low-dose linearized models (Kuiper-Goodman, 1990). This approach can, therefore, be used for both genotoxic and non-genotoxic agents, which is especially useful when there is some uncertainty regarding the mode of action (threshold versus non-threshold, e.g. ochratoxin A) (Kuiper-Goodman, 1996). The value of 5 000 for the uncertainty factor can be decreased when additional biological information indicates that there is less cause for concern. Estimates for a “safe dose” may also be derived from appropriate epidemiological studies, such as for aflatoxins,

when they are available. Efforts need to be made to establish more international harmonization in dealing with mycotoxins for which a non-threshold mode of action is postulated.

Although difficult to determine, the TDI can be viewed as an intrinsic property of mycotoxins, which takes into consideration both the potency of the effects measured and the biological factors regarding the severity, relevance and significance of the effects for humans.

#### Exposure assessment

Reliable and validated analytical methods are currently available for only a few mycotoxins. Improved methods have recently been established with the development of specific antibodies for use in enzyme-linked immunosorbent assays (ELISAs) and the utilization of immuno-affinity columns for sample clean-up. Problems are caused by the non-homogenous distribution of mycotoxins in food commodities, which therefore require appropriate sampling.

Exposure to mycotoxins depends on the level of these substances in different foods and on the intake of those foods. There can be large national and regional differences in the intakes of foods, so exposure assessments are country-specific and this is an impediment for harmonization. For mycotoxins, the monitoring data for food commodities of concern collected over several years usually provide the input for data on levels. Estimates may then be refined by considering further modifications to the levels of mycotoxins, in the food that is actually consumed, by including information on manufacturing and processing both by industry and in the home. In Canada, exposure estimates can be based on the average intakes of the total population, of the 90<sup>th</sup> percentile value of the total population, or of only those persons who actually consume the food being assessed. They may be made for different age or target groups, depending on the scenario being investigated (i.e. acute intake versus chronic intake). Exposure varies according to age, with young children, generally, being exposed at a much higher rate in terms of body weight for commodities such as milk (up to sevenfold) and peanut butter (up to fourfold) that may contain aflatoxins or their metabolites. Exposure assessments can sometimes also be based on measurements of biomarkers in humans (aflatoxins, ochratoxins), and the intake can then be estimated on the basis of pharmacokinetic relationships.

It is also necessary to address the potential hazards to human health that arise from the presence of mycotoxins in animal food products. At high levels in feed, mycotoxins

may cause illness or death of farm animals through the development of such animal toxicoses as aflatoxicosis. Carry-over studies in livestock have only been conducted for major mycotoxins, and more information on bio-availability to humans of the parent compound and its metabolites, including bound metabolites (conjugates, protein-bound), is needed. At lower levels in feed, mycotoxins may have no apparent effect on livestock production, but their residues and related substances might move up the food chain. This indirect intake of mycotoxins and related substances from the consumption of animal food products may pose a health hazard to humans. In a previous review it was found that the risk to humans associated with indirect exposure from animal-derived food products is generally somewhat lower than that from direct exposure from cereal and other food crops that may contain mycotoxins (Kuiper-Goodman, 1991).

Since mycotoxins affect mainly staple foods, exposure in market-based economies, where different sources are mixed, tends to be lower but is usually of long duration. In farming communities, high exposure of shorter duration may sometimes occur. Little is known about the differences in associated long-term risks between these two types of exposure. Probabilistic exposure assessments have recently been introduced and help to visualize the distribution of exposure under diverse scenarios. International agreement on how to derive appropriate parameters is needed.

#### Risk characterization

Risk characterization is the qualitative and/or quantitative estimation, including the attendant uncertainties, of the severity and probable occurrence or absence of known and potential adverse health effects on an exposed population. It is based on hazard identification, hazard characterization and exposure assessment. Risk characterization can also be the establishment of levels of daily exposure at which the risk is insignificant over a lifetime (i.e. exposure needs to be below the TDI or other measure of safe dose). This latter definition may be more relevant, bearing in mind the uncertainties that have already been discussed. For substances for which a TDI cannot be determined, the safety margin between human exposure and adverse effects seen in animal species may serve as an indication of the likelihood of ill effects occurring in humans, and this may be used in risk management. This was the case in the recent evaluation of fumonisins (Kuiper-Goodman *et al.*, 1996). As well as considering the average population, risk characterization also needs to consider those groups that are most vulnerable to exposure, such as children (because

of their lower body weight), and other groups for which there may be differences in bio-availability, metabolism or genetic disposition, such as the elderly. In this regard, the adequacy of a tenfold safety factor to address differences in human susceptibility arising from human variability needs to be examined.

Detailed risk assessments have been performed for only a few mycotoxins (aflatoxins, deoxynivalenol, ochratoxin A, zearalenone, fumonisins) (Kuiper-Goodman, 1985; Kuiper-Goodman, Scott and Watanabe, 1987; Kuiper-Goodman and Scott, 1989; Olsen *et al.*, 1991; Bowers *et al.*, 1993; Kuiper-Goodman, 1996; Kuiper-Goodman *et al.*, 1996) and these evaluations need to be re-examined from time to time taking into account new information on both exposure and basic toxicology as well as improved understanding of the mechanism of action.

#### RISK MANAGEMENT

With regard to mycotoxins, there are a variety of risk management options that help to ensure a safe food supply. These range from prevention of mould growth and setting of regulatory limits, to diversion into alternate uses. Enormous economic costs are associated with all of these options.

One impediment to harmonization in trade relates to the setting of maximum residue limits (MRLs) for mycotoxins. MRLs are now generally based on scientific evaluations. They cannot be exceeded in traded goods, but levels of mycotoxins somewhat above these levels can be tolerated on a low-incidence basis. A large percentage of incidences of mycotoxin occurrence are well below the MRL. The export of commodities is a continuous process, so it is not possible to base allowable levels on the weighted average of the actual levels, adjusted for several commodities, or to revise the allowable levels for various commodities on a yearly basis. However, in the final risk assessments, exposure assessments for mycotoxins can be based on actual residue levels (and not on the MRL) as a worst case scenario. The concern of regulators is that, if a higher MRL were to be allowed, it would become the acceptable level for industry and blending upwards to this level would occur, thus increasing exposure. For this reason blending is not allowed in many jurisdictions.

#### CONCLUSIONS

There have been a wide variety of regulations pertaining to mycotoxins. Initially, many of these were not based on sound scientific evaluation. As yet, there is a lack of agreement among countries, but in recent years the Codex Committee on Food Additives and Contaminants (CCFAC)

has been moving towards harmonization by inviting position papers on proposed regulatory limits for several mycotoxins (aflatoxins, ochratoxins, patulin and zearalenone) and, based on comments from its member countries, it is hoped that a consensus can be reached. The ultimate aim is to achieve optimal regulations for human safety which do not become trade barriers. ♦

#### REFERENCES

- Bowers, J., Brown, B., Springer, J., Tollefson, L., Lorentzen, R., & Henry, S.** 1993. Risk assessment for aflatoxin: an evaluation based on the multistage model. *Risk Anal.*, 13(6): 637-642.
- CAC.** 1999. *Report of the thirtieth session of the Codex Committee on Food Additives and Contaminants.* ALINORM 99/12. Rome, FAO/WHO.
- FAO/WHO.** 1995. *Application of Risk Analysis to Food Standard Issues: Report of the Joint FAO/WHO Expert Consultation.* Geneva, WHO.
- IARC.** 1991. *Mycotoxins, endemic nephropathy and urinary tract tumours*, ed. M. Castegnaro, R. Plestina, G. Dirheimer, I.N. Chernozemsky & H. Bartsch. IARC Scientific Publications No. 115. Lyons, France.
- IARC.** 1993. Ochratoxin A. In *Some naturally occurring substances; Food items and constituents, heterocyclic aromatic amines and mycotoxins.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 56, 489-521. Lyons, France.
- IPCS.** 1990. *Selected mycotoxins: ochratoxins, trichothecenes, ergot.* International Program of Chemical Safety (IPCS). Environmental Health Criteria No. 105. Geneva, WHO.
- JECFA.** 1996. *Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) 1956-1995, first through forty-fourth meetings.* Geneva, FAO/WHO, ILSI Press.
- Kuiper-Goodman, T.** 1985. Potential human health hazards and regulatory aspects. In P.M. Scott, H.L. Trenholm & M.D. Sutton, eds. *Mycotoxins: a Canadian perspective.* NRC Publication No. 22848. Ottawa, Canada, National Research Council (NRC) of Canada.
- Kuiper-Goodman, T.** 1990. Uncertainties in the risk assessment of three mycotoxins: aflatoxin, ochratoxin, and zearalenone. *Can. J. Physiol. Pharmacol.*, 68: 1017-1024.
- Kuiper-Goodman, T.** 1991. Risk assessment to humans of mycotoxins in animal-derived food products. *Vet. Hum. Toxicol.*, 33(4): 325-333.
- Kuiper-Goodman, T.** 1996. Risk assessment of ochratoxin A: an update. In *ILSI Europe Workshop on Occurrence and*

*Significance of Ochratoxin A in Food*. Brussels, International Life Sciences Institute (ILSI) Europe.

- Kuiper-Goodman, T.** 1998. Food safety: mycotoxins and phycotoxins in perspective. *In* M. Miraglia, H.van Egmond, C. Brera & J. Gilbert, eds. *Mycotoxins and phycotoxins – developments in chemistry, toxicology and food safety*. Oxford, United Kingdom, International Union of Pure and Applied Chemistry (IUPAC).
- Kuiper-Goodman, T. & Scott, P.M.** 1989. Risk assessment of the mycotoxin ochratoxin A. *Biomed. Environ. Sci.*, 2: 179-248.
- Kuiper-Goodman, T., Scott, P.M., McEwen, N.P., Lombaert,**

**G.A. & Ng, W.** 1996. Approaches to the risk assessment of fumonisins in corn-based foods in Canada. *In* L.S. Jackson, J.W. DeVries & L.B. Bullerman, eds. *Fumonisin in food*, p. 369-393. New York, Plenum Press.

- Kuiper-Goodman, T., Scott, P.M. & Watanabe, H.** 1987. Risk assessment of the mycotoxin zearalenone. *Regul. Toxicol. Pharmacol.*, 7: 253-306.
- Olsen, M., Thorup, I., Knudsen, I., Larsen, J.-J., Hald, B. & Olsen, J.** 1991. Health evaluation of ochratoxin A in food products. *Nordiske Seminar- og Arbejds- rapporter*, Vol. 545. Copenhagen, Nordic Council of Ministers. ♦

### Approaches to the risk analysis of mycotoxins in the food supply

Mycotoxins are fungal metabolites that are present in a large part of the world's food supply. They pose a potential threat to food safety. At lower levels, the possible chronic toxicity of many mycotoxins (aflatoxins, ochratoxins, fumonisins, zearalenone) is usually of greater concern than acute toxicity, since some of these substances are very potent carcinogens and exposure to them is widespread. While the complete elimination of mycotoxins from foods would be an impossible goal, it is important to ensure that their levels do not threaten health. In recent years, a variety of interrelated approaches have been developed to assess the hazards, monitor exposure and determine the associated risks. These processes need to be transparent so that the hazards and the need for risk management and intervention are clear. Risk assessments provide the scientific background and understanding for sound policy decisions that protect the public at an affordable cost and allow for public/international discussion, scrutiny and harmonization. Because there are differences in the significance of biological effects and in the available data, there is at present no single approach that can be used for all problems regarding mycotoxins, and a case-by-case approach is needed.

### Méthodes d'analyse des risques liés aux mycotoxines dans les approvisionnements en produits alimentaires

Les mycotoxines sont des métabolites fongiques qui sont présents dans une grande partie des produits alimentaires dans le monde entier. Ils constituent une menace pour ce qui est de l'innocuité des produits alimentaires. A une teneur moindre, on s'inquiète davantage de la possible toxicité chronique de nombreuses mycotoxines (aflatoxines, ochratoxines, fumonisines, zéaralénone) que d'une toxicité aiguë, étant donné que certaines de ces substances ont un effet cancérigène très important et l'exposition à ces produits est largement répandue. Même si l'élimination complète des mycotoxines des aliments serait un objectif impossible à atteindre, il importe d'assurer que leur teneur ne constitue pas une menace pour la santé. Ces dernières années, toute une variété de méthodes interdépendantes ont été mises au point pour évaluer les dangers, déterminer l'exposition et définir les risques associés. Ces méthodes doivent être transparentes afin que les dangers et la nécessité d'une gestion des risques et d'une intervention soient clairs. L'évaluation des risques fournit une base scientifique qui permet de prendre des décisions judicieuses visant à protéger le consommateur, à un coût abordable, et permet d'examiner, d'analyser et d'harmoniser les politiques au niveau international. Étant donné qu'il existe des différences dans les effets biologiques et dans les données disponibles, on ne dispose pas à l'heure actuelle d'une méthode unique pouvant être utilisée pour tous les problèmes concernant les mycotoxines, et c'est pourquoi une approche au cas par cas est nécessaire.

### El análisis de riesgos de micotoxinas en los suministros alimentarios

Las micotoxinas son metabolitos fúngicos que están presentes en una gran parte de los suministros alimentarios mundiales, y pueden representar una amenaza potencial para la inocuidad de los alimentos. La posible toxicidad crónica de muchas micotoxinas (aflatoxinas, ochratoxinas, fumonisinas, zearalenona) en dosis inferiores suele suscitar mayor preocupación que la toxicidad aguda, dado que algunas de esas sustancias son carcinógenos muy poderosos y la exposición a ellas es muy amplia. Aunque sería imposible eliminar por completo las micotoxinas de los alimentos, es importante asegurarse de que sus niveles en los alimentos no representen una amenaza para la salud. En los últimos años se han elaborado varios enfoques relacionados entre sí para evaluar los peligros vinculados a la exposición a micotoxinas y determinar los riesgos asociados. Es necesario que este proceso sea transparente a la hora de declarar los peligros y la necesidad de una gestión de los mismos y de una intervención. La evaluación de riesgos proporciona el fundamento y los conceptos científicos necesarios para adoptar decisiones normativas acertadas que protejan al público con un costo asequible, y permitan asimismo un debate, una supervisión y una armonización internacional. Teniendo en cuenta las diferencias de los efectos biológicos y los datos disponibles, no hay en la actualidad un único enfoque que pueda aplicarse a todos los problemas relacionados con las micotoxinas, por lo que es necesario examinar cada caso por separado. ♦