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EVALUATION OF CERTAIN MYCOTOXINS IN FOOD

Fifty-sixth report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization
Geneva

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations

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Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Safety evaluation of certain mycotoxins in food. WHO Food Additives Series, No. 47, 2001; FAO Food and Nutrition Paper, No. 74, 2001.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme on Chemical Safety (IPCS).

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

Contents

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 6 to 15 February 2001. The meeting was opened by Mrs A. Kern, Executive Director, Sustainable Development and Healthy Environments, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Mrs Kern noted that this was the first meeting of the Committee that had been convened to consider only contaminants, which reflected the increasing attention being given to food contaminants by the Codex Committee on Food Additives and Contaminants and the increasing concern among consumers worldwide about the potential risks associated with their intake.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been fifty-five previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the fifty-fifth meeting (Annex 1, reference *149*), of priorities established by the Codex Committee on Food Additives and Contaminants, and of the recommendation of the Third Joint FAO/WHO/UNEP International Conference on Mycotoxins that FAO and WHO should consider convening a meeting of the Expert Committee devoted specifically to risk assessment of mycotoxins as soon as the requisite databases can be compiled (*2*).

The tasks before the Committee were:

— to elaborate further principles for evaluating contaminants (section 2); and
— to evaluate certain mycotoxins that may be present as contaminants in food (section 3).

2.1 Analytical methods

Use of validated analytical methods is essential to ensure that the results of surveys provide a reliable assessment of intake. Official methods will have usually been validated for analytical performance in collaborative studies, in which characteristics such as accuracy, precision, specificity and practicality have been tested. A number of international organizations are involved in the validation of analytical methods, including AOAC International, the International Organization for Standardization and its European equivalent, the European

Committee for Standardization, and the International Union of Pure and Applied Chemistry. Methods of analysis are accepted by these organizations only after they have been validated within their harmonized protocol for the conduct of collaborative studies.

Use of official validated methods is, however, no guarantee of accurate results. Furthermore, it may not always be possible to use an official method, either because it is not suitable for a particular toxin–matrix combination, because some reagents and instruments are not available, or because it is not cost-effective or practical.

Whenever possible, laboratories that supply analytical data that are used by the Committee should have been accredited by a recognized body to ensure that they are applying a system of analytical quality assurance. Such a system should include, when possible, systematic use of reference materials or certified reference materials and regular participation in inter-laboratory comparison studies. Certified reference materials, which contain certified amounts of the substance of interest, exist for a number of the mycotoxins evaluated by the Committee at its present meeting, namely aflatoxin M_1, ochratoxin A and deoxynivalenol.[1] Certified reference materials are relatively expensive and supplies are limited. It is therefore advisable for laboratories to develop their own reference materials for routine use, the toxin content of which should be established on the basis of the certified reference materials.

Participation in inter-laboratory comparisons, such as proficiency testing schemes, is becoming increasingly important as part of the analytical quality assurance measures that a laboratory must undertake to demonstrate acceptable performance. Various national and international organizations conduct such studies, in which samples are distributed to participants and the analytical results are assessed by the organizers. A number of proficiency testing schemes for mycotoxins exist at the international level, including those organized in the European Union by the Community Reference Laboratory for Milk and Milk Products, in the United Kingdom by the Central Science Laboratory (the Food Analysis Performance Assessment Scheme), and in the USA by the American Oil Chemists' Society.

Regardless of whether accredited methods are used to produce data, laboratories should undertake internal analytical quality assurance measures such as:

[1] Such reference materials may be obtained, for example, from the European Commission Joint Research Centre, Institute for Reference Materials and Measurements, Geel, Belgium.

— intra-laboratory validation of standard operating protocols;
— use of tests for recovery;
— checking the identity and concentrations of standard solutions for calibration; and
— use of tests to confirm the identity of mycotoxins detected in samples.

In the studies evaluated by the Committee at its present meeting, it was usually clear which analytical method had been used; however, much less information was available about analytical quality assurance. For future evaluations, surveillance data should be accompanied by information on the method of analysis used and its validation. In addition, individual, rather than pooled, surveillance data should be reported.

Specifically, the Committee recommended that:

(a) Surveillance data be accompanied by a clear description of the analytical method used and an indication of whether it has been formally validated.
(b) Limits of detection and quantification should be provided, with the definitions used to derive them.
(c) Recoveries determined using "spiked" samples or reference materials should be given with analytical results; the levels of spiking should be defined, and it should be specified whether the analytical data reported were corrected for recovery.
(d) An estimate of the uncertainty of measurement should be given, derived from measurements of repeatability or by calculation.[1]
(e) The source of the standard solution(s) for calibration should be provided, the procedure used to verify its (their) identity and concentration should be described, and the method of preparation of the solution(s) should be given.
(f) There should be an indication whether the laboratory that reported the results was accredited and, if so, for which analyte–matrix combinations.
(g) There should be an indication whether the laboratory that reported the results took part in inter-laboratory comparisons and, if so, for which analyte–matrix combinations.

2.2 Sampling

In order for the results of surveys to be meaningful, representative samples must be collected from carefully selected sources of food (e.g.

[1] Calculations can be done according to the guidelines published by Eurachem: *Quantifying uncertainty in analytical measurement*, 2nd ed.(*3*).

batches or lots, marketplaces and farm shops), which, in turn, should be representative of clearly defined locations (e.g. country or region within a country). These requirements apply throughout the survey. If, for example, the levels of mycotoxin contamination are likely to vary at different times and in different agroclimatic regions, it is essential that representative sources of food be carefully selected from each region. Once a source has been selected, it is equally important that samples be collected using a clearly defined sampling plan designed to give a reasonably representative sample. Although sampling variability is unavoidable, the precision of the sampling plan must be clearly defined and considered acceptable by those responsible for interpreting the results of the survey. If the samples are too small, a wide range of estimated levels of contamination with mycotoxins will be obtained for a given source, and there will be a strong probability that the concentrations will be significantly lower than the true value. It is equally important that a sufficient number of samples be collected from each source to ensure that occasional highly contaminated samples are included.

Most studies of sampling have focused on the development of sampling plans for regulatory purposes, and little work has been done to address the need for specific sampling plans for surveys. Similarly, little or no information was available on the efficacy of sampling plans for the determination of the mycotoxins evaluated by the Committee at its present meeting. Consequently, authoritative recommendations could not be made about the sampling procedures to be used in surveying the concentrations of these toxins in foods. Most of the data that were used for risk characterization at the present meeting were based on sampling protocols of unknown efficacy in a variety of unprocessed, processed, imported and locally produced foods.

Further studies on sampling variability are urgently required so that practicable, economically feasible sampling plans can be developed for convenient, accurate determination of mycotoxins in foods, thus improving the quality of future risk characterizations.

2.3 Data on food consumption

In its assessments of the risks associated with exposure to specific contaminants in food, the Committee determines the total dietary intake of the contaminants at the international level. For this purpose, it uses the regional diets of the WHO Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme (GEMS/Food) (*4*), which approximate the average consumption of commodities in five defined regions, and are based on

FAO food balance sheets. While data from the food balance sheets tend to result in overestimates of consumption by about 15% (*5*), use of the GEMS/Food regional diets may sometimes result in underestimates of the mean consumption of specific commodities because regional consumption is calculated by averaging data from selected countries in each region. The Committee noted that GEMS/Food is developing an additional 13 regional diets (*6*), which it considered would be more representative of the consumption patterns in different countries.

Most of the values for consumption of food commodities included in the GEMS/Food regional diets are for raw agricultural commodities. The effects of processing, such as milling of cereals and baking of bread, should be taken into account in assessing intake, as processing of raw agricultural commodities may alter the levels of contamination in the final products.

A consumer of a single food item at the 95th percentile of the distribution of consumption might have approximately three times the estimated mean intake calculated for that food, and the intake by a consumer of all foods at that level might be about twice the mean (*7*).

The Committee suggested that data from national food balance sheets or, preferably, from national food consumption surveys, should be used in order to obtain more accurate assessments of intake at the national level. In addition, individual data on levels of contaminants in foods as consumed, such as those obtained from total diet studies, provide the best estimates of intake of contaminants by national populations and by subgroups at risk.

2.4 Availability of data and other issues related to dietary intake

The Committee is occasionally asked by the Codex Committee on Food Additives and Contaminants to estimate the relative health risks associated with specific proposed maximum limits for a particular contaminant. In the past, the Committee has usually had access to pooled data, which are useful for estimating mean intakes. The most commonly used method for estimating intake is to combine data on mean food consumption with weighted mean levels of contamination. While this method provides an estimate of the mean intake of a contaminant at the international level, a probabilistic (stochastic) model is necessary to address relative risks.

Where the data submitted to the Committee were insufficient to calculate the weighted mean intake of foods contaminated with mycotoxins in each GEMS/Food regional diet, the weighted mean intake

based on all the available data was estimated. When there was clear evidence that particular toxinogenic fungi and their associated toxins did not occur in domestic or imported commodities in a particular region, intake for that region was not estimated. This approach allowed the identification of potential risks in relevant regions, with the aim of encouraging surveys of all relevant commodities in those regions.

In view of the complex nature of assessments of individual dietary intake and to permit analysis of particular situations, probabilistic approaches are starting to be applied at the national level. In these approaches, various values can be introduced to ensure the representativeness of all possible outcomes (5). Algorithms are used to sample the probability distributions of the input variables randomly. One commonly used sampling technique, the Monte Carlo technique, involves taking values at random from the range of the probability distribution(s). An alternative sampling technique, the Latin hypercube technique, results in an accurate representation of the input distribution and requires fewer iterations. Use of such techniques makes it possible to take into account various permutations of food consumption and contaminant concentrations and to calculate the probability distributions of both the likelihood and the magnitude of dietary intake.

Food consumption and concentrations of chemicals in food can be represented by probability distributions and sampled accordingly. A value for dietary intake can be calculated from the sample values. When this process is repeated many times, a distribution of the probability of dietary intake of chemicals in food can be obtained. The method can also be used to examine the concentrations of a chemical in various foods or to evaluate exposure from various sources. By its nature, probabilistic modelling takes account of the possibility that not all of the foods chosen will contain the chemical in question.

For a probabilistic assessment, the input variables must be described by frequency distributions. Such distributions have an important influence on the outcome of a simulation, and an assessment might be erroneous if an inappropriate distribution is used for an input variable. Use of histograms of the frequency of input distributions based on actual data, rather than distribution functions fitted to the data, can reduce such error, provided the data are sufficient. This technique ensures that none of the individual values used in a simulation is outside the range of the original data. Sensitivity analysis, assessment of the effects of correlations of food consumption pat-

terns, and other techniques can improve the results of probabilistic modelling (*8*).

Data on the concentrations of individual contaminants in food commodities are needed in order to construct distribution curves that allow detailed assessment of intake and its impact on health risks. However, because the distribution curves for contaminants are highly skewed, the potential effect on health of any proposed maximum level that lies at the extreme end of the distribution curve would be limited. The data must be of suitable quality (*9*). To facilitate global cooperation in risk analysis, such data should be submitted according to the protocol developed by GEMS/Food (*10*). The protocol for submission of pooled and individual data on contaminants is being updated to include a description of the sampling method and the performance characteristics of the analytical method used, as described in sections 2.1 and 2.2 of this report. However, data may be submitted in other formats.

2.5 Prevention and control

The prevention and control of mycotoxin formation depend to a large extent on the commodity and fungus of concern, but some general principles apply. Approaches can be used before harvest, immediately after harvest, or during storage. A draft code of practice for preharvest and postharvest control of mycotoxin formation, including suggestions for management systems based on the principles for the application of the Hazard Analysis and Critical Control Points (HACCP) system, has been proposed by the Codex Committee on Food Additives and Contaminants (*11*). The main approaches for preharvest prevention of mycotoxin formation include appropriate agricultural practices, most aspects of which are covered in the Codex draft code of practice and in the report of the Third Joint FAO/WHO/UNEP International Conference on Mycotoxins (*2*). Another approach is to breed plants for resistance to the fungus of concern. Several studies have been conducted on breeding cereal crops for resistance to infection by *Fusarium* spp., with limited practical results. Success has been achieved with crops genetically modified to resist penetration by insects, resulting in a reduction in contamination of maize with fumonisins. Biological control has been of some use against infection by certain *Fusarium* spp., but not particularly those that produce mycotoxins. Competitive exclusion, by the introduction of non-toxinogenic strains in the field, has been used with some success against *Aspergillus flavus* for reduction of aflatoxin B_1 formation in groundnuts and cottonseed. This approach may be useful for other applications.

The main postharvest strategy involves drying commodities, keeping them dry (below a water activity (a_w)[1] of 0.70) and, in addition, cleaning grains and removing the dockage. This and other aspects are covered in the Codex draft code of practice (*11*).

A variety of approaches to control are possible during storage, including use of antifungal chemicals. Various physical means, such as aeration, cooling, hermetic storage and modified atmospheres, have been used effectively to reduce insect and fungal growth in stored grains in some countries, thereby controlling mycotoxin formation. Irradiation with gamma-rays, which is used for insect control, is unsuitable for fungal control since the doses required are greater than those permitted for use in grains. Addition of natural products extracted from medicinal plants has been used successfully on a laboratory scale against a variety of fungi. Addition of biological control agents such as bacteria and yeasts has shown some promise. Use of an integrated approach, combining low levels of more than one control agent, may contribute to fungal control and to reducing contamination by mycotoxins.

The physical and chemical strategies for reducing mycotoxin concentrations in affected commodities include:

— ammoniation, for reduction of the aflatoxin concentrations in feeds;
— processing (see below);
— adsorption onto inert materials; and
— colour sorting, with rejection of discoloured grains and nuts containing mycotoxins.

3. Specific mycotoxins

The Committee evaluated six mycotoxins for the first time (fumonisins B_1, B_2 and B_3, deoxynivalenol and T-2 and HT-2 toxins) and re-evaluated two mycotoxins (aflatoxin M_1 and ochratoxin A).

3.1 Aflatoxin M_1

Aflatoxins may be produced by three species of *Aspergillus* — *A. flavus*, *A. parasiticus* and the rare *A. nomius* — which contaminate plants and

[1] Defined as $a_w = P/P_o$
where:
P = partial pressure of water above the sample
P_o = vapour pressure of pure water at the same temperature.
Water activity is a measure of the "availability" of the water in the sample and not the water content.

plant products. *A. flavus* produces aflatoxins B_1 and B_2, while *A. parasiticus* and *A. nomius* also produce aflatoxins G_1 and G_2. Aflatoxins M_1 and M_2 are the hydroxylated metabolites of aflatoxins B_1 and B_2 and may be found in milk or milk products obtained from livestock that have ingested contaminated feed. The main sources of aflatoxins in animal feeds are groundnut meal, maize and cottonseed meal.

The aflatoxins were evaluated by the Committee at its thirty-first, forty-sixth and forty-ninth meetings (Annex 1, references *77*, *122* and *131*). At its forty-ninth meeting, the Committee considered estimates of the carcinogenic potency of aflatoxins and the potential risks associated with their intake. At that meeting, the Committee reviewed a wide range of studies, conducted in both animals and humans, that provided qualitative and quantitative information on the hepatocarcinogenicity of aflatoxins. The Committee evaluated the potency of these contaminants, linked those potencies to intake estimates and discussed the potential impact of hypothetical standards on the overall risk for certain populations. The Committee noted that aflatoxin B_1 is the most potent carcinogen of the aflatoxins and that most of the available toxicological data relate to aflatoxin B_1. The carcinogenic potency of aflatoxin M_1 is approximately one order of magnitude less than that of aflatoxin B_1. The Committee also noted that the carcinogenic potency of aflatoxin B_1 is substantially higher in carriers of hepatitis B virus (about 0.3 cases per year/100 000 people per ng of aflatoxin B_1/kg of body weight per day), as determined by the presence in serum of the hepatitis B surface antigen ($HBsAg^+$ individuals), than in $HBsAg^-$ individuals (about 0.01 cases per year/100 000 people per ng of aflatoxin B_1/kg of body weight per day). Thus, reduction of the intake of aflatoxins in populations with a high prevalence of $HBsAg^+$ individuals would result in a greater reduction in liver cancer rates than reduction of the intake of aflatoxins in populations with a low prevalence of $HBsAg^+$ individuals. The Committee further noted that vaccination against hepatitis B virus would reduce the number of carriers of the virus, which might reduce the carcinogenic potency of the aflatoxins in vaccinated populations and consequently their risk for liver cancer.

At its forty-ninth meeting, the Committee analysed the effects of applying hypothetical standards for contamination of food with aflatoxin B_1 (10 and 20 µg/kg) and concluded that reducing the standard from 20 µg/kg to 10 µg/kg would not result in any observable difference in the rates of liver cancer.

The present evaluation was conducted in response to a request by the Codex Committee on Food Additives and Contaminants at its Thirty-second Session (*12*) for the Committee to "examine exposure