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RESEARCH ARTICLE

Harmonize approaches to analysis and risk assessment of mycotoxins in foodstuffs

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Abstract

The mycotoxins are fungal metabolites, found in most foods offered in the world. They represent a potential threat to food safety. Chronic toxic effects are possible at low levels of mycotoxins and are more serious problem than acute toxic effects, due to carcinogenic properties and prevalence of mycotoxins in such levels.

Since complete removal of mycotoxins from food is not possible, it is necessary to take steps towards the assessment and management of the risk to the health of humans and animals. To assess the possible dangers, scientists developed different scientific approaches and extrapolation models. Their purpose is to achieve uniform scientific criteria for evaluation of available data and harmonization of legislative decisions to reach the general principle of EU food safety "from the farm to the fork".

Introduction

A number of cereals and other crops are susceptible to the action of the microscopic fungi, both on the field, and during the storage, as well. They are able to produce mycotoxins such as secondary metabolites by the metabolism. The levels of the different kinds of mycotoxins in foods can vary widely and differ significantly in different calendar years. These fluctuations depend on many reasons such as adverse climatic conditions, further to fungal invasion and growth.

The mycotoxins are a highly varied group of chemical substances. When they are present in food, those may become causes of acute and/or chronic adverse health effects in animals and humans and may affect many target organs and systems, particularly liver, kidneys and nervous, endocrine and immune systems. The low levels of exposure can cause the occurrence of chronic effects. The International Agency for Research on Cancer (International Agency for Research in Cancer, IARC, 1993) classified several kinds of mycotoxins as carcinogenic or potentially carcinogenic to humans.

There are geographical and climatic differences in the occurrence of the mycotoxins, but the exposure is spread around all over the world and much of the foods and feeds are somewhat "contaminated". In some areas, where the high levels can cause problems associated with adverse health effects, it is necessary to perform monitoring for mycotoxins content in foods and feeds (Figure 1). According to data from 2011, the pollution with aflatoxins, zearalenon, deoxynivalenol, fumonisins and/or ochratoxin A was 27 %, 40% , 59% , 51 % and 27 % of the total analyzed 4327 samples collected worldwide (Mycotoxin Survey Program, 2011).

Although it is not possible these toxic substances be removed completely from the offered foods, the risk analysis based on scientific knowledge makes it possible to determine the levels (tolerances, guide values and

maximum residue levels) that are less likely harmful to health. This step will help harmonization of the laws and crop procedures for the mycotoxins control, and will facilitate international food trade.

It has been done considerable amount of efforts, already, to assess the health risks, arising from some of these chemicals. In terms of exposure and severity of chronic diseases (especially cancer), the mycotoxins pose a higher risk than anthropogenic pollutants, pesticides and food additives (Figure 2 and Table 1) (ToxiMet & ITL, 2012).

Furthermore, it is necessary to think about of the combined effects caused by the action of several mycotoxins simultaneously.

It is a general principle of EU food safety to use an integrated approach "from the farm to the fork", which includes the protection of human health and animal health (Regulation (EC) 178/2002 of the European Parliament and of the Council).

RISK ANALYSIS

The development of application of risk analysis on issues related to mycotoxins was not sufficient during the meetings on mycotoxins conducted by Food and Agriculture Organization (FAO), the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) in Bangkok in 1987 and in Nairobi in 1997. The lack of unified approach between the members had led to various guidelines and regulations regarding mycotoxins.

Risk analysis approaches have made a great progress over the next decade, for all chemicals that are dangerous for food safety. International organizations such as WHO and FAO took the leading role, especially through the Codex Alimentarius Commission (CAC), as well as the Joint Expert Committee on Food Additives (JECFA) of the International Agricultural Research Centers. Important was the role of the Organization for Economic Co-operation and Development (OECD) and the International Life Sciences Institute (ILSI), and several national agencies (IPCS, 1990; IARC; JECFA, 1996; CAC, 1998).

Essential meaning for the harmonization of the legislation is the adoption of common approaches and common terminology. At present time, a framework of risk analysis, similar to the proposed by FAO/WHO, (1995) is being used to deal with problems associated with the mycotoxins.

According to this framework, the risk analysis consists of three parts:

- risk assessment,
- risk management and
- risk communication.

Each of these main areas concurs with the others. Such approach is based on the scientific principles related to human and animal health, including comparisons with other risks (as part of risk communication) and reflects the social and economic factors (as part of risk management). The aim is to achieve practical decisions: guidance on maximum residue levels, methodological guidelines for prevention (Hazard Analysis and Critical Control Point (HACCP)) or a combination of the both. In the best case, such guidelines are acceptable to the both – producers and consumers.

The improvement of detection methods and the use of biomarkers made possible to obtain new data on toxicology, epidemiology and human exposure to mycotoxins, thus updated the assessment of IARC and the national agencies.

The scientific assessments are the basis for recommendations regarding the international regulation of mycotoxins (Ochratoxin, Patulin, Zearalenone) made by the Codex Committee on Food Additives and Contaminants (CAC, 1999) and European Union (EU).

Several factors hamper the harmonized approach. One of them relates to the conflict between national and commercial interests. Interests of the producing countries do not necessarily match those of the recipient countries and the presence of mycotoxins in food can lead to trade barriers unless all of them uniform on the approach to reach safe levels and are convinced it is in their own interest. Other limiting factors relate to data interpretation and analysis, and differences in patterns of dietary intake between the parties.

RISK ASSESSMENT

The risk assessment includes a full toxicological evaluation, epidemiological assessment, exposure assessment and risk characterization (ToxiMet & ITL - seeding new ground in food safety testing, 2012), but risk management of mycotoxins usually requires an action before all of this information is available.

EFSA provides a way for scientific decisions and risk assessments for the purposes of risk management in the EU and achieves:

• Evaluations of the toxicity of mycotoxins on humans and animals, based on all available toxicological information;
• Assessments of humans and animals exposure, using available data, based on the monitoring in the Member States;
• Investigation of the exposure of certain populations, such as infants and children and people in needs of specific diet;
• Investigation of the exposure of different animal species, such as producing animals, horses, fish, pets;
• Scientific recommendations for mycotoxins database for risk assessment.

The model for risk assessment is described in the scientific statements of EFSA regarding mycotoxins in food and feeds. From 2010 the agency has prepared risk assessments for the following mycotoxins (EFSA Journal, 2010; EFSA Journal, 2011; EFSA Journal, 2012):

- zearalenone (2010, 2011)
- T-2/HT-2 toxins (2010, 2011), nivalenol (2010), diacetoxyscirpenol
- Moniliformin (2010), beauvericin, enniatins (2010)
- Ergot alkaloids (2012)
- Alternaria toxins (2011)
- Citrinin (2012)
- Sterigmatocystin, phomopsins (2012)

Four step process to risk assessment of mycotoxins.

There are two basic scientific terms in risk assessment - "hazard" and "risk".

The term "hazard" is defined as the 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.

The term "risk" is defined as the expected probability of adverse health effects in humans, because of their exposure to biological, chemical or physical agent in food.

The process of risk assessment includes the following steps:

Hazard identification - use of all available data to establish that a substance apparently has the ability to cause an adverse effect;

Characterization of danger (relationship dose-response) - assessment of the relationship between the dose or/and level of exposure to the incidence or severity of the effect;

Exposure assessment - evaluation of the dose or level of a chemical substance in the environment, to which a variety of individuals, populations or ecosystems are exposed;

Risk characterization - assessment of the frequency and severity of adverse effects that can occur in a population or ecosystem caused by an actual or projected exposure.

Hazard identification - Many economically important mycotoxins have carcinogenic properties that affect several organs. They may also cause an effects on the organism development, including birth defects, disturbance in the immune system, and some also exhibit hormonal activity or neurotoxicity. In addition, there are adverse effects in the gastrointestinal tract, inflammation of the skin and hematological reactions.

Usually these studies empirically determine the so called threshold value of "no-observed-adverse-effect level" (NOAEL).

Some mycotoxins have two carcinogenic properties - property to initiate and property to promote the carcinogenesis. The proof of these two properties is evident in the pathology of tumors and the results of genetic toxicity tests. It is assumed that there is no certain threshold for this process.

Other mycotoxins seem to have mostly tumor-promoting effects, suggesting that there is a certain threshold for this effect.

In risk characterization, these two types of carcinogenic mycotoxin groups are treated differently and this affects the way of determining the safe levels. However, it is not always possible to distinguish clearly the two groups of carcinogens. The mycotoxins have a wide range of toxicological effects and can affect many different cellular processes. This variety of biological effects requires carrying out an assessment in each case and may require different techniques for extrapolation (in phase "Characterization of danger").

Mycotoxins are widespread and this is one of the reasons for the development of mycotoxicosis both in humans and in animals (ergotism, liver cancer, yellow rice disease, alimentary toxic aleukia (ATA), turkey-X-disease). Therefore, the risk assessment includes also information from epidemiological studies of exposed people.

The process of risk assessment involves determining the following toxicological reference points:

- **Acute reference dose (ARfD)** - for substances with a threshold of toxicity, where relevant accidental exposure (**i.e**. marine biotoxins);
- **Acceptable daily intake (ADI)** - to avoid substances with a threshold of toxicity, where chronic exposure is important (food additives);
- **Tolerable daily intake (TDI)** - for substances with a threshold of toxicity, where chronic exposure is important (certain mycotoxins).

When these reference points are not exceeded, the risk is considered as "insignificant."

Characterization of danger

Characterization of the danger is the extrapolation phase in the risk assessment. Its purpose is to produce predictable risk characterization for humans, based on animal studies (species extrapolation) in low exposure (extrapolation from high to low dose), as described by Boermans HJ and Maxwell C.K., 2007 in Figure 3.

The reference point for hazard characterization is the assessment of the "safe dose" as a temporary acceptable daily intake (PTDI-provisional tolerable daily intake) or its equivalent.

The term "acceptable" indicates that in general mycotoxins do not serve an useful purpose to people. Affordable (Acceptable) daily intake (TDI-Tolerable daily intake) represents an estimate of the amount of unintended substances in water, air, food or drink that can be adopted to day along the entire lifetime without an appreciable health risk. This reference value is suitable for many mycotoxins, with a threshold of toxicity. (P) TDIs are determined on the basis of knowledge of the mechanism and mode of action only when it is likely to be a threshold toxicity dose-response relationship. Critical effects have to be identified. They are NOAELs for each study. In the absence of other information as the basis for determining the TDI used the lowest NOAEL. To establish the value of TDI to humans, it is common extrapolation from animals to humans is to divide NOAEL safety factor of 100 (the default). This takes into account a factor of 10 for interspecies differences and other factors internal 10 different species variations (in this case, take into account differences between individuals). When significant irreversible impacts for which thresholds are established (as is the case for non-genotoxic carcinogens) or insufficient data can add additional uncertainty factor. Sometimes the definition of (P) TDI is postponed until sufficient data become available. Alternatively, and as a temporary measure, is sometimes used approach to determine the margin of safety as the temporary risk assessment for fumonisins.

For genotoxic carcinogens, there is no threshold dose by default, in which the impact, such as the occurrence of carcinogenic processes will not happen, and usually not determined TDI.

Carcinogens without threshold toxicity values are not permitted in food. When these chemicals cannot be completely avoided (as in the case of certain mycotoxins), a variety of approaches have to be used. Mathematical models are used, most of which is presumed that the effects of low doses are linear, to extrapolate the possibility of side effects at lower doses.

Dose corresponding to the level of risk 10^{-5} or 10^{-6} has been evaluated in some legislations, as representing a negligible risk. According to the others, the most appropriate method for regulating genotoxic carcinogens or even genotoxic agents (patulin) that the carcinogenic potential is not proven, is to determine the levels are "acceptable lowest possible point" is (ALAR-"as low as is reasonably achievable") or as low as technologically achievable (Tasheva-Petkova and Christova-Bagdassarian, 2014).

Alternative regulation may be based on biological factors such as mode of action and the dietary burden, which is certified by the severity of the resulting injury. This information can be combined with assessment of tumor potential in magnitude as TD05. Dividing a TD05 uncertainty factor of 5000 was obtained a value which is equivalent to the level of risk of 1:100 000 and the thus obtained values to safe levels are similar to those obtained using the linearized model of low doses (Kuiper-Goodman T., 1990 , 1991, 1996, 1998) . This approach can be used for both genotoxicity and for non - genotoxic agents, which is particularly useful when the mode of operation is insufficiently understood, namely - with and without - limit, any example of the ochratoxin A) (Kuiper- Goodman,

T. 1996). The estimation "safe dose" can also be prepared from the corresponding epidemiological studies. For example, such studies are available on aflatoxins.

Another conception is the use of Benchmark dose (BMD) (Figure 6). This approach finds applications in both threshold and non-threshold compounds. BMD index is defined as a dose that corresponds to a given change in adverse reaction in comparison with the response at the non-exposed subjects and lower 95 % confidence limit, called indicator of dose level (BMDL). BMDL modeled for 10% extra risk above the critical impact. The approach is an alternative to using for many years in a dose - response NOAEL- approach.

BMDL10 = 95% lower confidence limit of BMD for an additional 10% risk of critical effect (JS Wheeler, S.Chou, 2002).

The efforts should be aimed at creating international harmonization in solving the problem with mycotoxins. Despite the difficulties in defining, TDI can be regarded as an inherent property of mycotoxins, which takes into account both the activity of the measured effects and biological factors, severity, relevance and importance of the consequences for people.

Exposure assessment

Currently, there are reliable and validated analytical methods for only a few mycotoxins. There are improved processes associated with the development of specific antibodies for use in enzyme-linked immune-sorbent assays (ELISAs) and with the use of an immune-affinity column purification of the sample. The main issues in the analysis arise from the fact that the distribution of mycotoxins is not homogeneous in food, which requires an adequate sampling.

The exposure to mycotoxins depends on the level of these substances in various foods and the intake of these foods. There may be major national and regional differences in food intake, so that the exposure estimates are specific to each country and this creates difficulties in harmonization. Data from several years of monitoring of mycotoxins in food products causing anxiety usually provide input levels. There are possible changes in the levels of mycotoxins in the actually consumed foods by including information on the production and processing (industrial or domestic). Exposure assessment can be based on the average intake of the overall population, of value at the 90th percentile of the general population, or to evaluate only those persons who actually consume the food. This can explore different age groups or targets, depending on the scenario of the study (acute intake compared with chronic intake). The exposure varies depending on the age. Small children, in general, have a much higher percentage (relative to body weight) of products such as milk (up to seven times) and peanut oil (four times), which may contain aflatoxins and their metabolites. Sometimes exposure is based on the measurement of biomarkers in humans (aflatoxins, Ochratoxin A) and receptions can be calculated based on pharmacokinetic interactions.

It is also necessary to pay attention to the potential risks to human health arising from the presence of mycotoxins in foodstuffs of animal origin. At high levels in feed, mycotoxins can cause illness or death of livestock animals by developing toxicosis. Animal studies were conducted only on the main mycotoxins and more information is needed about the bioavailability of the parent compound and its metabolites, including those related metabolites (conjugates, proteins) in humans. At lower levels in the food mycotoxins may not show visible effect on the animals, but their residues and related substances can move up the food chain. This indirect intake of mycotoxins and related substances resulting from the consumption of foods of animal origin may constitute a danger to human health. It was found, recently, that the risk for the people associated with the indirect exposure of food products of animal origin is generally slightly lower than that of the direct exposure caused by direct consumption from cereals and other foods that may contain mycotoxins (Kuiper-Goodman T., 1998-2008).

The exposure tends to be lower, in a well-developed market economies where mixing commodity with different origin is common practice, but usually has a greater duration of time. In some low developed economy areas, it may appear high exposure with a shorter duration sometimes. The knowledge is limited about differences in the long-term risks associated with these two types of the exposure. It was recently introduced the term probable exposure estimations" that help to visualize the distribution of exposures in a variety of scenarios. An international decision is needed to select the appropriate parameters of the probability distribution.

Risk Characterization

Risk characterization is the qualitative and/or quantitative evaluation, including accompanying uncertainty of the severity and likelihood of occurrence or absence of known or potential adverse health effects on exposed populations. It is based on hazard identification, hazard characterization and exposure assessment. Risk characterization may also be the establishment of daily exposure where the risk is negligible throughout life (exposure should be below TDI or another measure of safe dose). The latter definition can be more relevant by incorporating and uncertainties. For substances, without TDI, the safety margin between human exposure and side effects in animal models, can serve as an indicator of the likelihood of disease in humans and that can be used to manage the risk. This is the case in the evaluation of fumonisins (Kuiper-Goodman, T. 1996).

Along with the general population, the risk characterization should also be considered for those groups that are most vulnerable to exposure, such as children (due to their lower body weight), and other groups for which there may be differences in bioavailability, the general metabolism or genetic predisposition, and the elderly people as well. In this regard, it should be checked and further refine the adequacy of the tenfold safety factor used to eliminate differences in sensitivity between individuals in humans resulting from human variability. Detailed risk assessments have been carried out for only a few mycotoxins (aflatoxins, deoxynivalenol, ochratoxin A, zearalenone, fumonisin) (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, 2012) and these estimates are periodically reviewed in the light of new information for both exposure and in basic toxicology, and better understanding of the mechanism of action (Tasheva-Petkova and Christova-Bagdassarian, 2014)

RISK MANAGEMENT

In terms of mycotoxins, there are a variety of options for managing the risk that help to ensure food safety. They range from the prevention of mold presence and the establishment of regulatory constraints in order to redirect the foodstuffs to alternative uses. All these features are associated with huge economic costs.

The establishment of maximum residue limits for mycotoxins is a difficulty to harmonization in the field of trade. In over 100 different countries, there are different regulations. In Europe for example, 39 countries have certain regulations (99% of the region's population). In the EU is adopted harmonized limits for aflatoxins, ochratoxin A, patulin, DON, zearalenone, fumonisin, T-2/HT-2, ergot alkaloids (ergot alkaloids) and other mycotoxins. Moreover, the EU has introduced limits for aflatoxin B_1 in feeds. There are guidance documents for the values in feeds for ochratoxin A and F toxins some of the EU.

Figure 5 presents FAO data about the existing regulations for common mycotoxins in 75 countries to 2011 (FAO, 2003, 2004).

Usually MRLs are based on scientific assessments. These values shall not be exceeded in trade commodities trade, but the levels of mycotoxins slightly above these levels are usually tolerated by accident. The highest percentage of incidence of mycotoxins is those cases are with levels well below the MRL.

The exports of commodities is an ongoing process, so it is not possible to estimate the permissible levels based on the average weighted values of the actual levels, adjusted for several commodities or to revise the permissible levels for different products based on annual data. In the final risk assessment, mycotoxins exposure assessment can be based on actual residue levels (not MRL) as a worst-case scenario. The concern of regulators is if higher levels for MRL are allowed, that would become an acceptable level for the industry and that would lead to increased exposure, therefore mixing of is not allowed.

Other factors also affect the regulations of mycotoxins by determining the TDI (stage assessment of the hazards) and the availability of methods for sampling and analysis of mycotoxins.

In the USA there have been developed and validated methods for approximately 45 mycotoxins according the AOAC International (Association of Official Analytical Chemists).

In CEN (European Standardization Committee), the European equivalent of ISO, based on performance criteria, usually established on inter laboratory tests, there have been standardized 12 methods for mycotoxins. CEN criteria reflected in the analytical methods, ensuring the requirements of the formal EU legislation on mycotoxins in food and feed. For the purposes of risk management in the Member States of the EU in 2010 published a guidance

document for competent authorities commenting monitoring compliance with the legislation on aflatoxins for the official control of the EU (Regulation (EC) 165/2010 of 26 February 2010 amending Regulation (EC) 1881/2006 setting maximum levels for certain contaminants in foodstuffs as regarding aflatoxins).

It is necessary to pay attention to potentially dangerous synergistic effects on animals from the presence of more than one mycotoxin in feed. Given the ubiquity of mycotoxins in the world, it is necessary to develop an effective program for risk management, which would be crucial to reduce costs and economic losses in farms associated with the risk of contamination (Alexander J. et all ., 2012)

CONCLUSIONS

Mycotoxins present in significantly high levels in the diet and can become causes of acute and/or chronic adverse health effects in animals and humans. There is a variety of rules relating to mycotoxins, but many of them are not based on steady scientific assessment. In recent years, the aim is to move towards harmonization of the legislation. The endpoint is to achieve optimization of the regulations that would be able to ensure the safety of people and at the same time would not become barrier to the free trade and marketing. An integrated approach "from the farm to fork" is a general principle of EU food safety, including both protection of human health and animal health. Risk management based on scientific approaches in evaluations is aimed to ensure food safety.

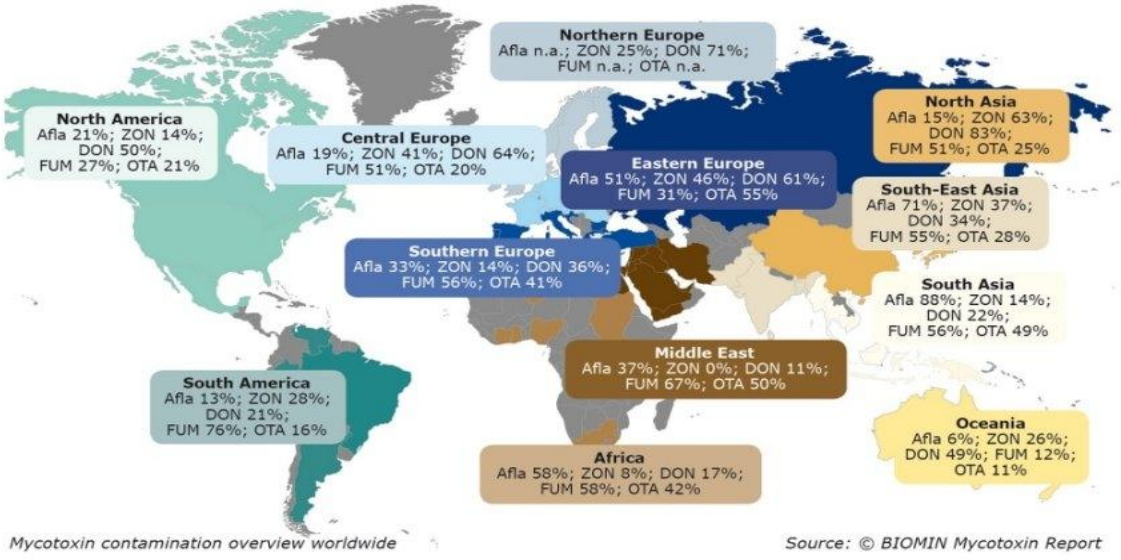

Figure 1. Distribution of mycotoxins-world map (Mycotoxin Survey Program, 2011)

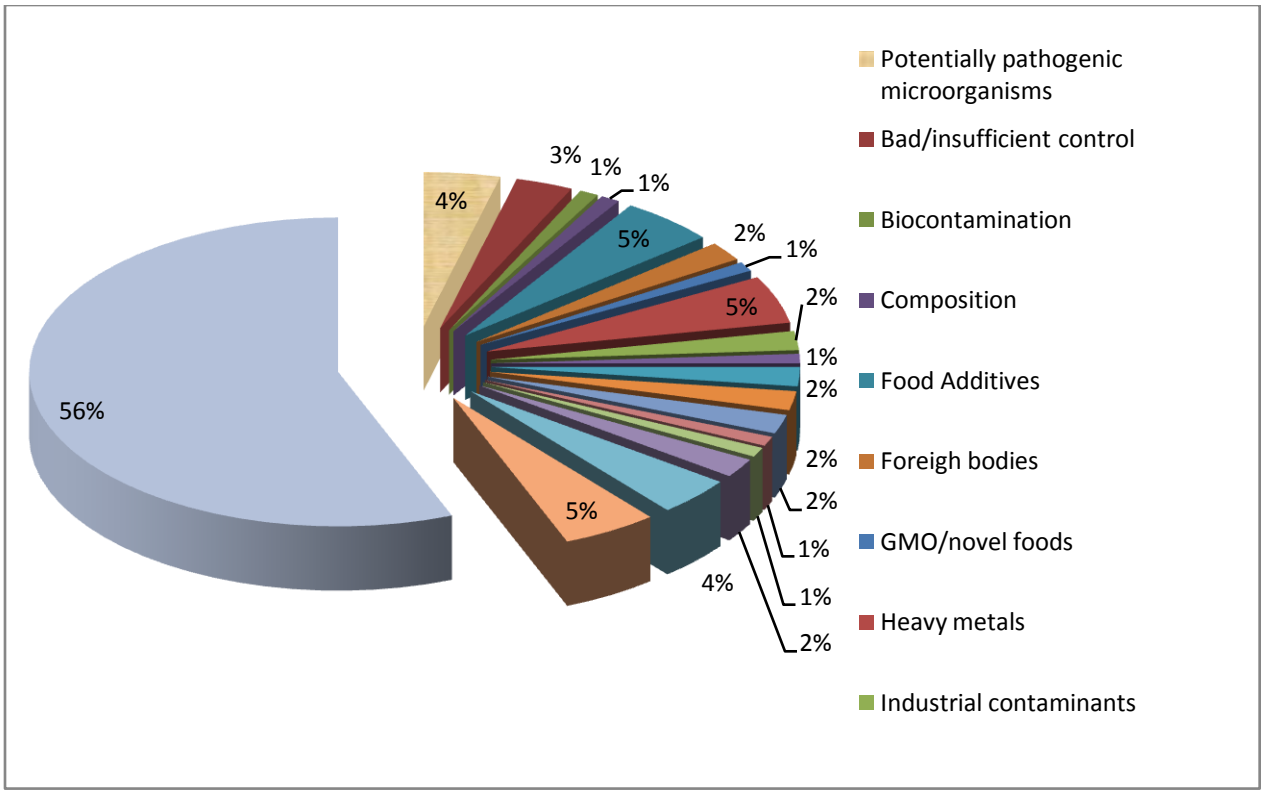

Figure 2. Mycotoxins-share in terms of all pollutants (Toxymet, 2012)

Table 1. Rating of the health risks of foods (Source: Kuiper-Goodman, 1998.)

Acute Risk	Chronic Risk
HIGH	
Microbiological	Mycotoxins
Phycotoxins	Anthropogenic contaminants
Some phytotoxins	Some phytotoxins
Mycotoxins	Unbalance diet
Anthropogenic contaminants	Phycotoxins
Food additives	Microbiological
Pesticide residues	Food additives
	Pesticide residues
LOW	

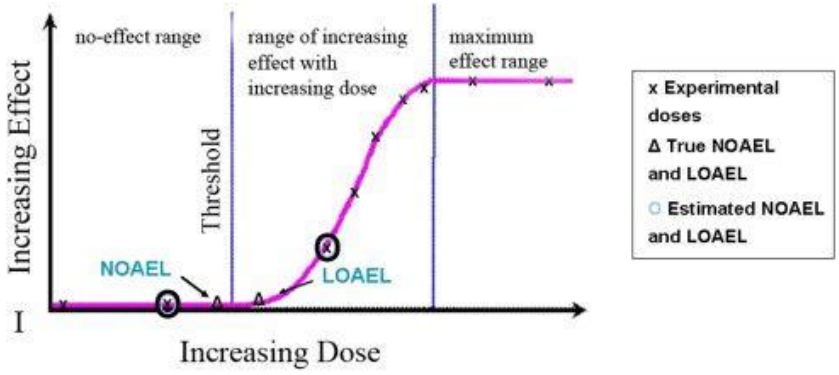

Figure 3. Illustration of the calculation of the NOAEL and LOAEL, using dependence "dose-response" (Boermans HJ, Maxwell CK, 2007)

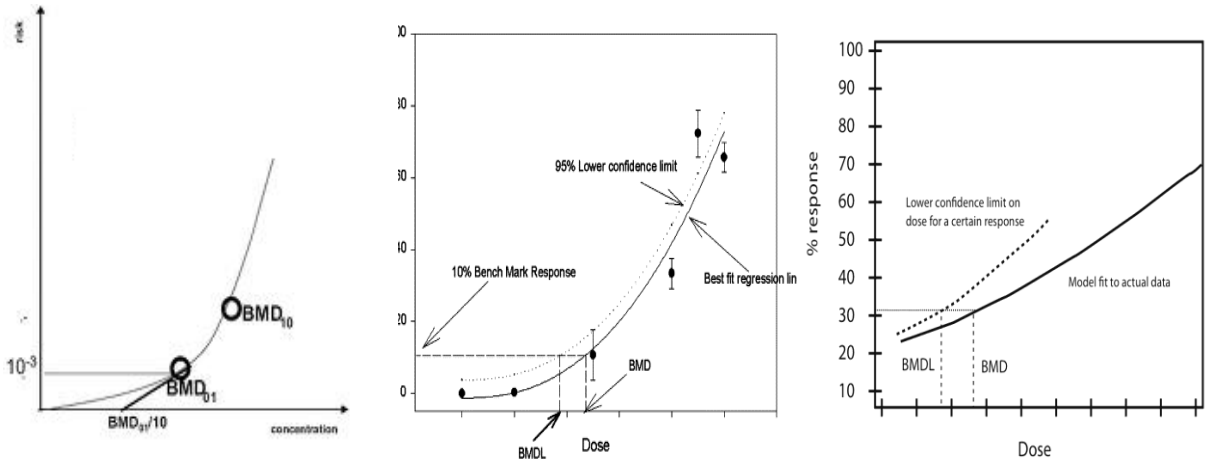

Figure 4.Benchmark dose (BMD) (J.S. Wheeler, S.Chou, 2002; FAO, 2004; EFSA, 2013)

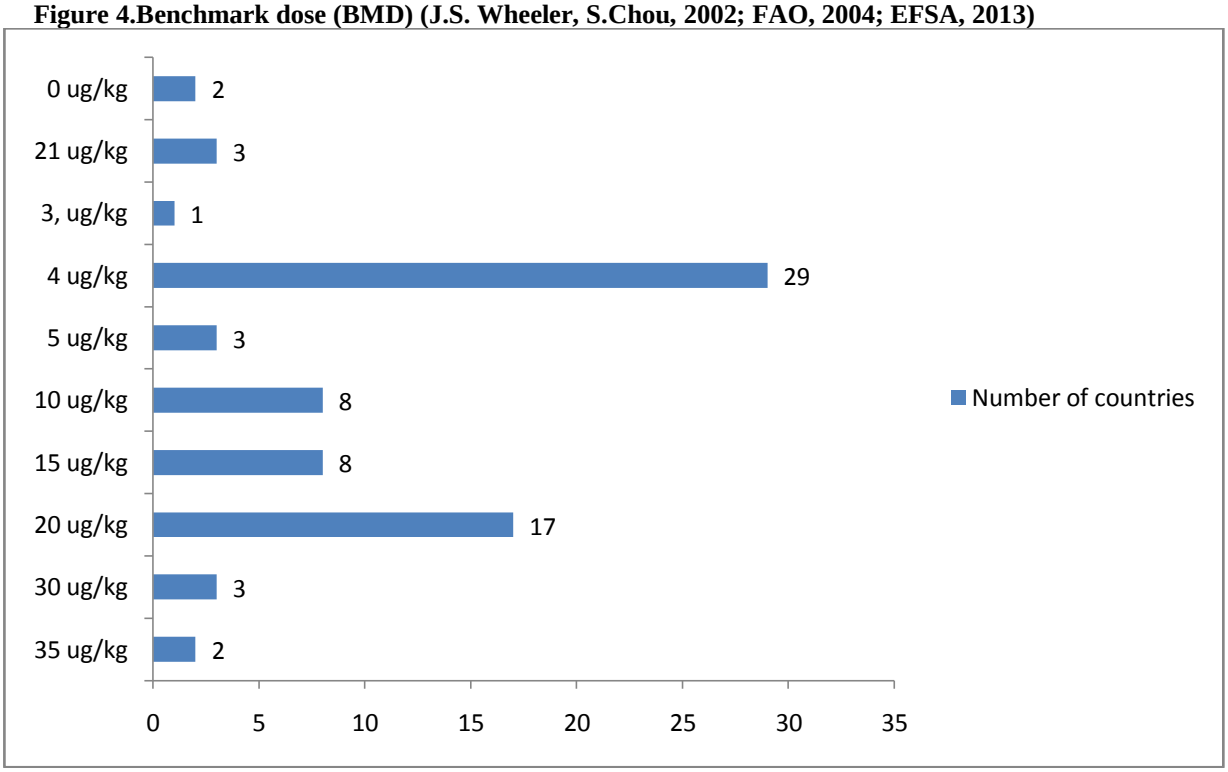

Figure 5. Regulations for common mycotoxins in 75 countries; 2011 (FAO Worldwide regulations for mycotoxins in food and feed in 2003, Food and Agricultural Organization of the United Nations, Rome, 2004)

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