SPECIAL GUEST EDITOR SECTION

Food and Feed Safety Assessment: The Importance of Proper Sampling

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The general principles for safety and nutritional evaluation of foods and feed and the potential health risks associated with hazardous compounds are described as developed by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) and further elaborated in the European Union-funded project Safe Foods. We underline the crucial role of sampling in foods/feed safety assessment. High quality sampling should always be applied to ensure the use of adequate and representative samples as test materials for hazard identification, toxicological and nutritional characterization of identified hazards, as well as for estimating quantitative and reliable exposure levels of foods/feed or related compounds of concern for humans and animals. The importance of representative sampling is emphasized through examples of risk analyses in different areas of foods/feed production. The Theory of Sampling (TOS) is recognized as the only framework within which to ensure accuracy and precision of all sampling steps involved in the field-to-fork continuum, which is crucial to monitor foods and feed safety. Therefore, TOS must be integrated in the well-established FAO/WHO risk assessment approach in order to guarantee a transparent and correct frame for the risk assessment and decision making process.

Traditional foods and feed are considered safe and nutritious for humans and animals, even though they may contain natural toxins and/or antinutrients. The presumed safety and nutritional value of traditional foods and feed is primarily based on extensive experience and long history of use under well-known conditions of preparation and storage. Therefore, systematic testing of traditional foods and feed is regularly not done unless specific potential risks of consumption by humans and/or animals are identified, as in the case of foods/feed irradiated for preservation purposes.

Worldwide intensification of agricultural production has put great pressure on basic quality and safety characteristics of food and feed products. Wide-scale use of fertilizers, pesticides, growth promoting agents, and veterinary drugs may leave residues in edible products, and the presence of environmental contaminants in foods/feed may pose possible health risks to consumers and husbandry animals (1). In addition, pathogenic microorganisms, viruses, and mutant proteins (prions) have caused serious outbreaks of human/animal illnesses (2). Continuing attention is needed to safeguard the agricultural production chain from current and newly appearing health threats. This is a demanding challenge given the complexity of agricultural production systems and globalization of trade in agricultural produce.

The development of new food/feed production and breeding technologies using recombinant DNA/RNA technologies also demands our attention given the fundamentally new characteristics of derived foods and feed and the still very limited experience in evaluating their potential impact on human/animal health and the environment.

Food and feed materials are routinely sampled for a wide range of objectives, which can be broadly categorized into few main areas: risk analysis, compliance with regulatory requirements, post-market monitoring, surveillance, and manufacturing process control. Those involved with safety assessment establish daily requirements for nutrients in food and feed as well as safety ranges for toxic substances that may be present in foods and feed. Those involved with regulatory enforcement, compliance, and post-market monitoring are a diverse and large group that ensures fulfillment of legal requirements at the many different levels of the food and feed production chains. In this paper we focus on food and feed safety assessment, and we describe the general principles for risk analysis of foods and feed with respect to health and nutritional impact on humans/animals, as developed by the Food and Agriculture Organization/World Health Organization (3) and further elaborated in the European Union funded project Safe Foods (4). We emphasize the important role of sampling to ensure representative test materials for hazard identification, hazard characterization, and exposure assessment, and we enrich the FAO/WHO safety assessment approach for foods and feed integrating into it the Theory of Sampling (TOS), necessary to ensure representativeness and fit-for-purpose sampling procedures.

A reliable analysis of potential health risks for humans/animals consuming foods/feed can only be made when realistic exposure scenarios and well-defined estimations of exposure levels are in place. Various types of substances that are present in the

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different food/feed matrixes and commodities, raw or semi-processed, pose challenges to develop appropriate sampling strategies and analytical detection methods. Both sampling and analytical errors affect the reliability of any final risk estimation, but much more attention has been devoted to the development and improvement of analytical methods over the last decades, as compared to the development of appropriate sampling plans.

Analytical results are of low value, no matter the quality of the method used, if the sampling process is not representative of the entire field-to-aliquot pathway. Over the last six decades, the TOS has developed a complete theory of heterogeneity, sampling procedures, and sampling equipment assessment, the importance of which was first recognized in the mining and geological sectors, but has since transgressed nearly all boundaries of science, technology, and industry (5, 6). For the last 10–15 years the universality of TOS principles has been proven thoroughly, demonstrating that all sampling processes irrespective of the nature of their target lots need to be structurally correct in order to ensure a sufficient degree of accuracy and unbiased, representative precision (7). This also applies to the assessment of foods and feed safety, including food/feed contaminants, additives, naturally occurring toxins/antinutrients, or contaminating microorganisms, and whole foods/feed derived from genetically modified plants/animals.

Current Approaches for Risk Analysis of Foods, Feed, and Associated Hazards

Risk analysis is a systematic approach to reach conclusions on the safety and nutritional value of foods, feed, and associated hazards for humans or animals. This comprises three key elements: risk assessment, risk management, and risk communication (3). In the context of risk analysis a hazard is defined as the intrinsic potential of a food/feed or agent to cause adverse health effects in humans/animals or the environment. Risk is defined as the likelihood that under particular conditions of exposure, a hazard will represent a real threat to human or animal health. Risk is thus a function of hazard and exposure.

Risk assessment is a science-driven process, comprised of identification of hazard(s) or potential risks; toxicological/nutritional characterization of the identified hazard(s); evaluation of exposure to food/feed or associated substances by humans or animals; and overall characterization of the identified risk(s) regarding their impact on humans/animals and the environment. The main objective of risk assessment is to characterize the nature and severity of the identified risk(s) and to provide information whether safe threshold levels for consumers or animals can be established, and if these levels have been exceeded.

Hazard identification.—Aims at the identification of biological, microbiological, chemical, or physical agents, present in a particular food and feed, which may be capable of causing adverse health effects in exposed humans/animals.

Hazard characterization.—Establishes the nature and severity of the adverse health effect(s) in humans/animals. Studies on a possible dose-response relationship are carried out to identify exposure levels at which no adverse effects are observed (No Adverse Effect Level). Studies are generally performed with laboratory animals and/or target animals, or with in vitro systems (isolated cells or organs of animals) or in silico (computer-based simulations), but in certain cases human studies may also provide useful information.

Exposure assessment.—A crucial part of the risk assessment process, aimed at estimating the likely intake/exposure of humans and animals to the food and feed under study.

Risk characterization.—The challenging overall evaluation and estimation of the probability of occurrence of potential adverse health and nutritional effects in a given population, or subpopulation, as exposed under certain conditions. Attention is paid to constraints of the experimental systems and their predictive power, for instance, extrapolation of data from laboratory test animals to humans, and identified uncertainties.

Risk management.—The process of weighing risk management options for decision-making regarding the release of foods/feed and constituents on the market. Maximum permissible levels for specific substances or the obligation of labeling products that contain allergens may need to be established. Appropriate monitoring plans may need to be organized once a product has been released on the market, in order to confirm the conclusions of the risk assessment (Post-Market-Monitoring).

Socioeconomic aspects should also be considered, including: acceptable levels of protection for humans and/or animals or the environment are acceptable; identified benefits that can be balanced against potential risks of the product or technology; potential impact of measures on sustainability, (international) trade, and respect for fair trade practices and animal welfare principles.

Risk communication.—An interactive exchange of information and opinions throughout the risk analysis process in which all interested stakeholders participate, including risk assessors and risk managers from government, industry, the academic community and, most importantly, representatives of consumer organizations. Public acceptance of the proposed risk mitigation measures or socioeconomic consequences of the introduction of new foods/feed or specific constituents is an important topic of debate.

The risk analysis elements are complementary and should be carried out in an integrated manner. A functional separation between risk assessment and management should be kept in order to guarantee an independent and objective science-based risk assessment. While this is not a waterproof separation, it is meant to stimulate and practice active interaction among the different interested parties in the risk analysis process and subsequent enforcement and monitoring activities. Risk assessors, risk managers, food/feed producers, monitoring and surveillance experts should closely interact to verify whether risk mitigation measures, if needed, are feasible and would effectively minimize and control identified risks.

Further Improvements of the Risk Analysis Model

Recently the risk analysis model for foods and feed as developed by FAO/WHO and summarized above, has been further elaborated in the EU-funded project Safe Foods with respect to the introduction of state-of-the art methods to be used for risk assessment, enhancement of transparency, openness, and accountability of the risk analysis process (4). In this project, specific attention was paid to a coherent scientific analysis of health and environmental risk-benefits, as well as to an analysis of impacts on economics, and social and ethical aspects. In the improved model a special evaluation phase is proposed where all

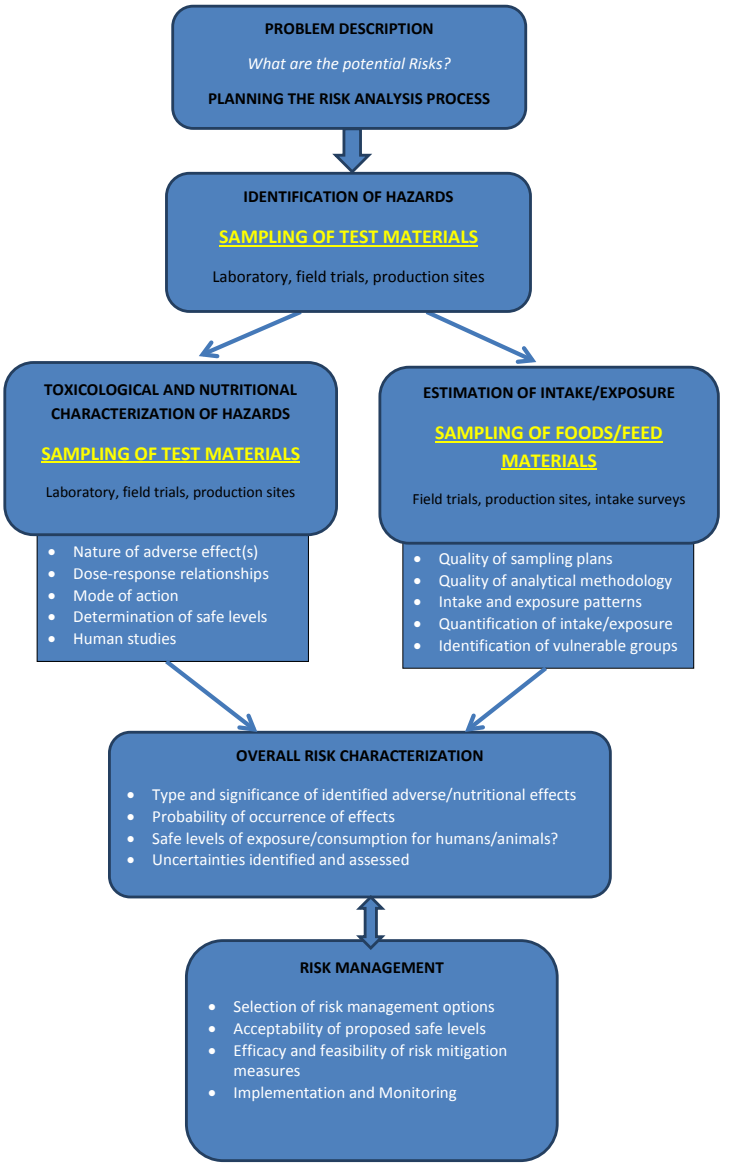

Figure 1. The role of sampling in the risk analysis process for foods and feed.

available information from the risk-benefit assessment process is evaluated, i.e., acceptability and distribution of risks, costs, and benefits. During this transparent evaluation phase in which interested stakeholders may participate, possible differences in views on the results of the scientific assessment may be identified. These should be considered when final decisions are made by the responsible risk manager(s).

The risk assessment approach for foods/feedborne hazards as described above is originally designed for evaluating chemical risks, but can also be used for safety assessment of food/feed related safety and nutritional issues. Extensive experience with the safety evaluation of foods/feed and associated compounds of interest has been built up over the last five decades. The results are reliable and robust and no misjudgments on safety have been recorded so far. The approach can also be applied with flexibility, on a case-by-case basis, to food/feed nutrient substances, chemical contaminants, or microbial contaminants, as well as for the safety assessment of foods/feed derived from genetically modified organisms.

Central to this approach is the sampling necessary to collect the test materials for hazard identification and characterization and for estimating exposure levels for humans and animals. Here we further improve this approach and explicitly describe the relevance of proper sampling for foods/feed safety assessment.

The Explicit Role of Sampling in the Risk Analysis Process

A central issue common to the safety assessment of foods, feed and foodborne hazards is the nature of the sampling process. This should be carried out to provide adequate and representative samples as test materials for hazard identification and characterization of materials to be used for estimating exposure levels for humans and animals. The quality of sampling is critical, since inadequate sampling plans will compromise the

reliability of the results and impact the risk assessment. Among the great difficulties for designing reliable and representative sampling approaches are the great diversity in food and feed sources, kinds and degrees of food contaminations, and different types of intentional food/feed alterations.

Figure 1 illustrates explicitly the central role of sampling in the Risk Analysis Process. Sampling is necessary for:

(**a**) The identification of hazards in a given food/feed. Normally, this first step focuses on the identification of differences among samples of foods/feed under assessment in comparison to an appropriate control. Clearly, if the samples are not representative of the entire food/feed decision unit for which inferences are to be made (8), the identification of potential risks cannot be reliable.

(**b**) The qualitative and/or quantitative characterization of the identified hazard(s). This second step focuses on the characterization of the potential toxicological and/or nutritional effects of the identified differences in samples of the food/feed under assessment. The main objective of the risk assessment is to characterize the nature and severity of the identified risk(s), to provide information whether safe threshold levels for consumers or animals can be established, and to determine whether nutritional benefits can be attributed to food/feed specific substance under assessment. If the sampling is not representative, the characterization of the identified hazards or potential benefits cannot be proved to be reliable.

(**c**) The assessment of the exposure to an identified and characterized hazard. Correct estimates of human/animal exposure to foods/feed and related compounds are only possible if the sampling plans provide accurate data, representative of the entire lot or decision unit for which inferences are to be made. Exposure assessment is a crucial part of the risk assessment process. If no exposure occurs to an identified hazard, it will not constitute an actual risk to humans and/or animals. The aim of the exposure assessment is to quantify the likely exposure of humans and animals to the food and feed or specific compounds under study, and to characterize the frequency and duration of exposure. For example, specific segments of the population may be particularly sensitive, e.g., allergic people, the elderly, or infants, and should be clearly identified. Groups of the population with an expected high exposure to compounds or foods/feed should also be considered regarding established safety limits or recommended consumption levels. The selection of individuals of the human or animal population with specific predispositions is of vital importance for estimating actual exposure levels. This needs further development of appropriate sampling strategies capable of ensuring representativeness of population exposure patterns, which can only be achieved with the specific support of experts from different scientific backgrounds, such as toxicology, medical sciences, nutrition, and analytical chemistry.

Analyses of average (median) and maximum/minimum levels of foods and feed or compounds of interest should be made only on representative estimates, taking into account natural variation, in order to obtain reliable quantitative estimates of the expected intake. Probabilistic methods are normally used to determine ranges of plausible intake values (9–11). The state of processing of a food item determines to a great extent the actual intake by humans/animals.

Unfortunately, little attention is normally paid to sampling issues during the risk assessment process. Efficient sampling means to ensure a high degree of confidence in the estimation of (true) mean concentrations and concentrations ranges, taking into account the unavoidable degree of heterogeneity intrinsic to any food and feed commodity. This reduces the possibilities of either misestimating actual exposure values for humans and animals or, worse, underestimating the risks for consumers to exceed tolerable intake levels. This is also important in the case of foods and feed with nutritional benefits, where under- or over-estimating intake levels may lead to nutritional or deficiency problems. This plays a critical role in the surveillance of foods and feeds with unintentional contaminants or intentional adulterations, due to their often low concentration and highly heterogeneous distribution.

To date, most efforts have been devoted to the reduction of errors in the analytical methodology, without dedicating sufficient attention to the reduction of sampling methodology errors. It has been demonstrated, however, that both equally influence the overall uncertainty of any analytical result, and very often the total sampling errors dominate (12, 13). As a direct consequence of the focused concerted efforts to minimize analytical errors only, very often sampling errors are of a much larger magnitude than analytical errors. Minkkinen et al. (14) provide a poignant example. Devoting resources to the reduction of sampling errors will have a great impact on the accuracy of true mean and associated variability. This should become a priority in order to ensure accuracy and precision of food and feed commodity surveys. The selection of sampling plans along the food/feed chain strongly affects conclusions regarding consumers' risks and producers' interests. From a food and feed safety assessment perspective, minimizing consumers' risk must be the priority, and any error in the estimation of such risk should be avoided or at least minimized.

Papers in this Special Section describe the scientific process for obtaining representative samples to perform a reliable safety assessment of foods and feed commodities. A specific discussion is presented on the possible consequences of inaccurate sampling, such as sampling that relies on stringent unverified distribution assumptions (15). A number of factors must be taken into account when defining sampling protocols. Among these, especially when large-scale testing and monitoring programs are conceived to assess the safety of foods and feed products, is the degree of risks that regulators are prepared to accept for the consumers (which defines the complementary producer risk). Once this is defined, sampling protocols can be designed accordingly, so that sampling survey costs can be minimized without compromising result reliability beyond a certain level, i.e., the accepted consumer risk. Obviously, the smaller the acceptable risk level, the larger the demand on the sampling plan. Unfortunately, such a simple and logical approach has not been adopted in food and feed safety assessment because of economic limitations, resources, and time restrictions, and most importantly a lack of adequate training in representative sampling. A thorough, reasoned critique of this state of affairs is presented by Esbensen et al. (16, 17).

It remains necessary to assess sampling challenges and identify the deficiencies in the current practices. What has served as an acceptable basis for the development of sampling protocols for nutrient concentrations above trace concentrations, e.g., >1%, are likely not adequate to protect consumers from isolated microbiological contamination, mycotoxin contamination, monitor pesticide residues, or intentional adulteration. Lower

analyte concentrations and high distributional heterogeneity greatly increase the sampling challenge in this concentration realm, but the principles necessary for representative sampling are identical. Indeed, the challenge is precisely linked to the possibility of properly characterizing on a case-by-case basis the heterogeneity patterns and correctly taking them into account to ensure fit-for-purpose sampling strategies. The TOS provides such a frame because it calibrates the sampling strategy to the specific heterogeneity characteristics, as further explained in this Special Section.

The identification of a systematic sampling approach applicable to the many diverse scenarios, decision units, target materials, and target analytes present in the food and feed area is greatly needed in order to guarantee fit-for-purpose representativity. Proper sampling, i.e., documentable representative sampling is a fundamental criterion for reliable safety assessment and decision making (7). Such a systematic sampling approach only exists within the frame of the TOS, because all the elements to be taken into account to ensure representativity under any conditions are fully described. More specifically, TOS allows estimating the variability remaining after all sources of sampling bias have been removed, i.e., the variability intrinsic to the specific material under investigation (7). From a food and feed safety perspective, this constitutes the level of unavoidable risk associated to any given survey, which may or may not be acceptable. If not acceptable, it can be reduced by collecting more primary samples, as discussed by Esbensen (7) and in this Special Section. No other sampling framework allows objective quantifying the risk as a direct function of the specific heterogeneity properties of the test material. On the contrary, all other sampling frameworks rely on specific distributional assumptions, do not characterize heterogeneity patterns stemming from the specific properties of the test material, and do not provide an estimation of the risk associated with sampling surveys (15). For these reasons we consider that TOS provides a complete frame to ensure accuracy and precision of all sampling steps involved in any given scenario, from the primary sampling all the way to the subsequent secondary sampling steps involved in the field-to-fork continuum necessary to monitor foods and feed safety. Therefore we explicitly recognize the central role of sampling in foods and feed safety assessment (Figure 1) and integrate in the well-established risk assessment approach the TOS in order to guarantee a transparent and correct frame for safety decision making process.

Examples of Risk Analysis to Demonstrate the Importance of Sampling

A few illustrative examples of risk analyses scenarios with diverging purposes are provided to highlight how representative sampling is a critical factor common to all.

Risk Assessment of Nutrients in Foods/Feed

The increased use of fortified foods, food supplements, and functional foods may result in a higher intake of nutrient substances by humans. This may be of concern regarding intake levels sufficiently high to induce adverse effects.

In contrast to contaminants, nutrients are essential for human/animal health and have their positive nutritional effects within specific concentration ranges governed by homeostatic mechanisms. Adverse health effects may occur due to over consumption or may lead to deficiency symptoms in case of under consumption. Therefore upper intake levels of nutrients from food sources by humans/animals not inducing adverse health effects and minimal required intake levels should be identified in order to avoid nutrient deficiencies. Such intake levels vary substantially and may be specific for subpopulations of various age/sex/life stage and nutritional status. Proper sampling methods to be applied in various stages of production and processing of these foods are needed in order to correctly determine actual intake levels of nutrients by humans/animals and compare these with the established upper safety limits and minimal required intake levels.

Risk Assessment of Microbiological Contamination of Foods/Feed

An increased spread of pathogens in the food production chain is noticed, presumably due to globalization of trade and migration of people (18). New pathogenic microorganisms have been detected and characterized, as well as an increase in antibiotic-resistant bacteria, presumably due to massive use of antibiotics for human therapy. Ingestion of pathogens or their toxins may induce a variety of diseases in humans/animals, ranging from acute illness such as diarrhea to chronic diseases and death. Specific guidance for risk assessment of microbial food and feed contamination has been developed (19).

One of the main issues for risk assessment of microbial contamination is the dynamics of microbiological growth, survival, and the (rapid) transfer of microorganisms throughout the food production chain in many types of foods, raw or processed, and further spread in the environment. Exposure assessment is of critical importance for the risk assessment, and the definition of suitable sampling plans that take into account the specific distributional characteristics of microbial populations and of their spreading dynamics are of utmost importance to allow an effective safety evaluation of food and feed commodities.

Risk Assessment of Genetically Modified (GM) Plants and Derived Food/Feed

The development of new food/feed production and breeding technologies using recombinant DNA/RNA technologies demand our attention given the fundamentally new characteristics of derived foods/feed and our still very limited experience in evaluating their potential impact on human/animal health and the environment. Within this context, sampling plays an imperative role, as discussed by Esbensen et al. (20).

The risk assessment strategy for GM plants and derived food and feed regarding possible risks for human/animal consumption of these products, is a comparative approach, i.e., comparing the characteristics of GM plants and derived food and feed with those of their respective non-GM counterparts which have gained a history of safe use for humans/animals (21–23). The objective of the comparison is to identify possible differences between the GM plant and the traditional non-GM counterpart which are subsequently assessed regarding their toxicological/nutritional impact. Detailed information is requested on the molecular aspects of the genetic modification

and the properties of the GM plant; comparative analysis of the phenotypic/agronomic characteristics and of the composition of the GM plant and its comparator; toxicological assessment of newly expressed protein(s) and of relevant change(s) in the GM plant resulting from the genetic modification; assessment of potential allergenicity of the novel protein(s) and of the whole food derived from the GM plant; and the nutritional characteristics of the GM plant-derived products which include a detailed intake/exposure assessment of the GM plant-derived food/feed.

The comparative analysis of the phenotypic/agronomic and compositional properties of GM plants and their non-GM comparators should be based on materials produced in properly designed field trials of different scale, performed under different agricultural and environmental conditions (24–26). This endeavor is impossible if not based on appropriate sampling strategies, and protocols are essential for the production of representative test materials needed for the exposure assessment.

Environmental Risk Assessment of Genetically Modified Plants

The environmental risk assessment (ERA) of GM plants is carried out on a case-by-case basis, following a step-by-step assessment approach and focusing on specific areas of concern: persistence and invasiveness of the GM plant, or its compatible relatives, including plant-to-plant gene transfer; plant-to-microorganism gene transfer; interaction of the GM plant with target organisms and nontarget organisms; impact of the specific cultivation, management, and harvesting techniques; effects on biogeochemical processes; and effects on human and animal health (26, 27).

A correct ERA can be ensured only if field trials to produce the test materials are properly designed and the sampling methods to collect them are representative and fit-for-purpose with respect to the issues listed above, in order to ensure accuracy and precision of environmental GM plant testing surveys.

Conclusions

The risk analysis model, developed by FAO and WHO, was originally designed for the safety assessment of chemical compounds, but is also considered suitable for the assessment of potential food safety risks, which can be of very different nature and origin. The approach is internationally well accepted and used for safety assessment of food/feed related issues. Experience over the last 5 decades has indicated that the risk analysis procedure is reliable and no misjudgments have been recorded regarding their safety.

The FAO/WHO risk analysis model has been further elaborated in the EU-funded project Safe Foods, paying specific attention to a coherent scientific analysis of health and environmental risk-benefits, as well as to an analysis of impacts on economics, social, and ethical aspects. In the improved model a special evaluation phase is proposed where all available information from the risk-benefit assessment process is evaluated, i.e., acceptability and distribution of risks, costs, and benefits. All interested stakeholders are invited to participate to this transparent evaluation phase to identify possible differences in views on the results of the scientific assessment, which should be considered when final decisions are made by the responsible risk manager(s).

The improved FAO/WHO risk analysis approach is sufficiently flexible to deal with questions regarding safety of foods/feed contaminated with residues of chemical nature, microbes, or other living materials (viruses and prions), or fortified with nutrients. Foods/feed derived from GM plants or food producing animals, containing new substances or with altered compositions, can also be assessed regarding their safety and nutritional value for humans and animals.

Central to this approach, is that sampling is necessary to collect the relevant test materials for hazard identification, characterization, and estimating exposure levels for humans and animals. Safety assessment must always ensure global adherence to principles of representative sampling to guarantee the same level of consumer, animal, and environmental protections. To achieve this, all professionals involved in safety and nutritional assessment and management of foods and feed must consider sampling a prerequisite equally important as the analytical methodology to ensure reliability of final results. We point to the TOS as the only available framework to control and minimize all relevant sampling errors along the foods and feed industrial chain(s), providing a scientifically solid, transparent, and representative frame for risk assessment and safety decision making processes.

We also recommend an intensive exchange of information and cooperation among those involved in the food/feed production chain (farmers, food/feed producers, analytical chemists, toxicologists, microbiologists, and nutritionists) in order to ensure representative-powered sampling plans, accurate analytical detection methods, and science-based risk analyses of foods/feed and related safety/nutritional issues. Proper sampling is essential before any other framework linked to food and feed safety assessment can be considered, including regulatory, scientific, administrative and managerial, and starting with the proper establishment of decision units for which inferences are to be made.

The objective of this special issue is to establish the necessary and sufficient competence regarding representative sampling for food and feed safety purposes; hopefully it will provide to the reader the required comprehensive overview for this task. Certainly this is only a beginning. Further work is needed to explore in more detail the specific interaction between TOS and the alternative frameworks within which TOS exists. This will be treated separately in the near future.

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