**Organisation and implementation of training activities on principles and methods of risk assessment in the food chain under the "Better Training for Safer Food" initiative.**

***Course 5 - Risk assessment in biotechnology***

***SYLLABUS***

|  |  |
| --- | --- |
| A. BACKGROUND |  |
| B. KEY ISSUES |  |
| C. CONTENTS OF THE TRAINING COURSE |  |
| TOPIC 1 INTRODUCTION TO THE RISK ASSESSMENT IN GMOs |  |
| *1.1 Introduction to risk assessment in GMOs and derived food and feed products* |  |
| *1.2 Overview of techniques for genetically modifying organisms* |  |
| *1.4 Introduction into the four basic steps of risk assessment* |  |
| TOPIC 2 HAZARD IDENTIFICATION |  |
| *2.1 Molecular characterization and Comparative analysis* |  |
| *2.1.1 Molecular characterization: genetic elements and their biological functions* |  |
| *2.1.2 Comparative analysis* |  |
| *2.1.3 EFSA guidance for selection of comparators* |  |
| *2.2 Toxicity and allergenicity assessments* |  |
| *2.3 Animal Feeding studies* |  |
| TOPIC 3 HAZARD CHARACTERIZATION |  |
| *3.1 Intended modifications vs. unintended effects* |  |
| *3.2 Implementing nutritional assessments of food/feed products derived from GM plants* |  |
| TOPIC 4 ASSESSMENT OF EXPOSURE TO CONSUMERS |  |
| *4.1 Methodologies for assessing the exposure of GM food/feed products to consumers* |  |
| TOPIC 5 RISK CHARACTERIZATION AND MANAGEMENT |  |
| *5.1 Implementing risk characterization* |  |
| *5.2 Risk management*  |  |
| TOPIC 6 POST-MARKETING MONITORING (PMM) |  |
| *6.1 Evaluating predictions made in risk assessments* |  |
| TOPIC 7 GM FOOD AND FEED FROM MICROORGANISMS, ANIMALS, AND INSECTS  |  |
| *7.1 GM microorganisms, animals and insects for food/feed purposes* |  |
| TOPIC 8 ENVIRONMENTAL RISK ASSESSMENT (ERA) OF GMOs  |  |
| *8.1 Purpose of environmental risk assessments* |  |
| *8.2 The seven areas of concern* |  |
| *8.4 The interplay between EU regulations on GMO and on pesticides*  |  |
| TOPIC 9 POST-MARKETING ENVIRONMENTAL MONITORING (PMEM) |  |
| *9.1 Ensuring continued safety – Monitoring the impact of GM plants in agroecosystems* |  |
| *9.2 Reporting PMEM results* |  |
| TOPIC 10 GMOs MADE BY NEW TECHNOLOGIES – CHALLENGES FOR REGULATIONS |  |
| *10.1 Implications of Synthetic biology for environmental risk assessments* |  |
| *10.2 “Omics”-technologies for risk assessments – implications for risk assessments*  |  |
| TOPIC 11 RISK COMMUNICATION |  |
| *11.1 An introduction to risk communication strategies* |  |

**A. BACKGROUND**

Genetically modified plants and their products are common constituents of food and feed consumed in Europe and other parts of the world. While only a few countries of the European Union (EU) have adopted the cultivation of GM plants (i.e. currently exclusively maize cultivars with the event MON810), a significant proportion of GM feed is imported from South America, especially Brazil, into the EU. Beyond plants, GM organisms contributing to food and feed supply include microorganisms and possibly, with an increasing trend, also animals and insects. Before such products reach the market, and after their approval, their potential adverse effects on human and animal health as well as on the environment must be assessed and evaluated. EU regulation for pre-marketing risk assessments of GM for food and feed use, for import, processing and cultivation are in place and functional.

The legal procedures and risk assessment strategies implemented by the EU differ from those of other countries, like USA or Canada. For many years and until today, the usefulness of the EU procedures is controversially debated between different stakeholders (e.g., GM producers vs. NGOs). Furthermore, increasing international familiarity with some GM plants as well as more precise genetic modification methods on the one side, and increasing molecular complexity of new genetic modifications on the other side, are challenging the currently implemented procedures and ask for updated regulations and guidance for risk assessments.

The overall objective of this course is to provide knowledge about the general and applied risk assessment procedures required for genetically modified organisms and products made by molecular nucleic acid modifying techniques. Legal backgrounds and relevant guidance documents will be presented, addressing the fundamental steps for risk assessment, including data requirements and their statistical treatments. Going through the different key topics for risk assessment step-by-step during the course, the participants will increase their knowledge and gain familiarity with the procedures as they are required for assessing GMO and their products in the EU. Examples of recent opinions of the European Food Safety Authority (EFSA) on the risk assessment of GMO will be analysed. The participants obtain an up-to-date view on the issues related to new molecular plant breeding technologies and new tools for risk assessments.

Five scientific experts with first-hand experience in GMO risk assessment as conducted by the EU will act as tutors in this Course 5. They represent the different topics which are introduced by lectures. Following the experts’ presentations, knowledge about the specific topics will be intensified and exercised in interactive sessions and guided discussions, also utilizing a set of five GM case studies. The participants will also gain an understanding about current and future developments of GMO and how those will challenge current regulations and may require adjustments of new regulations. Finally, participants will learn with a lecture and role plays about the principles of risk communication which are an essential part of risk analyses and risk management in the field of food/feed safety.

**B. KEY ISSUES**

Key issues that have been taken in consideration for the preparation of the program and training materials are:

* Structured four steps approach in risk assessment for genetically modified organisms: Hazard Identification, Hazard characterization, Exposure assessment, Risk characterization
* Principles and methods of hazard identification and characterization when applied to whole food/feed
* identification of newly inserted genes and gene products
* toxicity and allergenicity assessment
* nutritional assessments
* feeding studies
* intended vs. unintended effects
* Uncertainty and variability
* Weight-of-evidence approach
* Risk mitigation
* Post-market monitoring
* Environmental risk assessment (ERA) of GMOs
* Post-market environmental monitoring
* New molecular breeding techniques (RNAi, CRISPR/Cas) and their challenges for risk assessments
* Synthetic biology
* GM plants, microorganisms, animals (vertebrates) and insects
* Omics as a new toolbox in risk assessment
* Risk communication

**C. CONTENTS OF THE TRAINING COURSE**

**TOPIC 1 INTRODUCTION TO THE RISK ASSESSMENT IN GMOs**

***1.1 Introduction to risk assessment in GMOs and derived food and feed products***

**Module Description**

* Risk analysis principle on food safety according to the Codex Alimentarius and its implementation in the EU legal framework [Reg. EC 178/2002, etc.]: division of competences between RA and risk management
* How to deal with the outcome of the risk assessment (RA) of GMOs according to the EU and international legal framework? [Directive 2001/18/EC; Reg. (EC) 1829/2003; EFSA guidance documents on RA of food and feed from GM plant and on the environmental risk assessment of GM plant]
* Risk analysis of GMOs as an implementation of Precautionary Principle
* Overview on GM plants and analysis of recent relevant EFSA opinions on the matter: identifying issues unique to their risk assessment

**Key concepts, information and messages for this module**

Risk analysis has three major components: risk assessment, risk management and risk communication. These components interact with each other, though the actors involved tend to be well separated by legal provisions, especially in Europe. Regarding the risk assessment of GMOs, contained uses and deliberate releases into the environment - for research and for the placing on the market - follow different norms and procedures. Altogether, the European directives and regulations on the deliberate release of GMOs in the environment should be regarded as an expression of the precautionary principle, as an inspiring principle of the European environmental law. The precautionary principle aims at dealing with scientific uncertainties, as raised by emerging technologies like molecular breeding techniques, and organizes feedback loops between risk management and risk assessment, via surveillance and post-market monitoring plans. In Europe, harmonization of risk assessment was ensured by the creation of the European Food Safety Authority, which works in cooperation with the Competent Authorities of Member States, in a complex and still evolving scheme which will be described.

***1.2 Overview of techniques for genetically modifying organisms***

**Module Description**

* Introduction to molecular breeding techniques (trans- and cisgenesis, gene stacking, gene editing and gene drive, synthetic biology)
* Genetic transformation methods
* Plants genetically modified in their nucleus or in plastids
* Controlling the expression of transgenes and the location of transgene products in the plant

**Key concepts, information and messages for this module**

GM organisms can be generated with different techniques. Most GM plants under cultivation are produced by inserting different genes cloned from other organisms into the plant chromosome. Different techniques can be used to achieve this transfer and such techniques may impact risk assessment, e.g. by the left-over of antibiotic resistance genes of rudimentary DNA sequences with identity of bacteria. Depending on the technique actually used for the genetic modification, the organism will be regulated as a GMO in the sense of the EU law or not. Participants will gain knowledge about the different techniques and how this may affect the data requirements for risk assessment of the corresponding organisms.

***1.4 Introduction into the four basic steps of risk assessment***

**Module Description**

* Risk assessment is the scientific evaluation of known or potential adverse health effects in consequence of human exposure to foodborne hazards. The process consists of the following steps:
(1) Hazard identification: identification of known or potential health effects connected with an agent
(2) Hazard characterization: qualitative and/or quantitative evaluation of the adverse effects associated with agents, which may be present in food and a dose-response assessment if the data is obtainable
(3) Exposure assessment: qualitative and/or quantitative evaluation of the degree of intake likely to occur
(4) Risk characterization: integration of hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely to occur in a given population.
* The risk assessment of GM food/feed is characterized by an assessment of a whole food or of a component thereof relative to the appropriate conventional counterpart taking into account both intended and unintended effects, identifying new or altered hazards, identifying changes in key nutrients relevant to human health.

**Key concepts, information and messages for this module**

The risk analysis process for GM food/feed is consistent with the Codex Working Principles for Risk Analysis. Risk assessment aims to identify whether a hazard, nutritional or other safety concern is present, and if present, to collect information on its nature and severity. The risk assessment includes a comparison between the GM food/feed and its conventional counterpart focusing on determination of similarities and differences (comparative approach). If a new or changed hazard, nutritional or other safety concern is recognized, the risk associated with is characterized to decide its relevance to human health.

**QUESTIONS AND ANSWERS: TOPIC 1**

***Question 1: What are the usual steps and time frames regarding authorization procedures (especially in the food and feed sector)?***

Please refer to the EFSA web site <https://ec.europa.eu/food/plant/gmo/authorisation/decision_making_process_en>

describing the procedure with indications of time line. It is worth noting that ‘stop-the-clock’ mechanisms are used when new questions are sent to the applicant, giving them extra-time for generating data and answering the questions.

***Question 2: Comparative analysis : in the difference between GMOs and non GMOs do we take into account also the interaction between new proteins and the proteins already present?***

This question aims at having more details on the approach used for the comparative assessment of new proteins. This evaluation is performed taking into consideration the interaction of the new protein with the metabolic pathways of the plant. Furthermore, more detailed on these aspects  is provided by the relevant presentations 2.1.2 on Comparative assessment, Toxicity and allergenicity assessments and Nutritional assessments of food/feed products derived from GM plants.

**TOPIC 2 HAZARD IDENTIFICATION**

***2.1 Molecular characterization and comparative approach***

2.1.1 Molecular characterization: genetic elements and their biological functions

**Module description**

* Providing data on the structure and expression of the insert(s) and on the stability of the intended trait(s) in order to assess whether genetic modification raises any issues regarding the potential for producing new toxins or allergens

**Key concepts, information and messages for this module**

The participants will learn what kind of information is legally required on the genetic modification, and how applicants include such information into dossiers submitted to EFSA. They will gain the skill to distinguish complete from incomplete information. Starting from well-established cases on transgenic organisms, the participants will evaluate whether and how the data requirements should be adapted to more recent molecular techniques of DNA modification, like gene editing with CRISPR/Cas9.

2.1.2 Comparative analysis

**Module description**

Performing a comparative analysis

* Rationale of the comparative risk assessment strategy
* Overview of the biology of the plant (compositional, agronomic and phenotypic characteristics)
* The tests of difference and equivalence between a GM plant and a non-GM reference variety (comparator)
* Their practical implementation through field trials in appropriate receiving environments

**Key concepts, information and messages for this module**

Comparative analysis is a fundamental aspect for GMO risk assessment as conducted to date in the EU. Information will be provided on the data requirements and their rational. Also participants will learn about the importance of statistical tools and methods to evaluate the quality of data.

2.1.3 EFSA guidance for selection of comparators

**Module description**

* Criteria for the selection of receiving environments and of comparator(s) [introducing relevant EFSA guidance]

**Key concepts, information and messages for this module**

The rational of the comparative approach departs from the assumption that conventional plants have a history of safe use. Beside the introduction of the new trait(s), it is paramount to assess whether the modified plant behave like conventional plants under a range of receiving environments (sites, environmental conditions, management practices) as representative as possible of those conditions in which the GM plant is likely to be introduced and cultivated.

***2.2 Toxicity and allergenicity assessments***

**Module Description**

* Introduction to methodology of toxicity and potential allergenicity assessment
* Assessing potential toxicity/allergenicity of gene products and/or of the whole GM plant and derived food/feed
* Introduction to OECD principle for a toxicology study and to EFSA guidance updating and complementing an allergenicity assessment:

Experiments to support the toxicity assessment should consider:

* the newly expressed proteins
* new constituents other than proteins
* altered levels of food and feed constituents
* Assessment of the whole food and/or feed derived from GM plants.
* Experiments to support the allergenicity assessment should consider:
* allergenicity of the newly expressed protein
* allergenicity of the whole GM plant
* possible adjuvant activity
* Non-IgE-mediated adverse immune reactions to foods

**Key concepts, information and messages for this module**

The purpose of performing toxicological studies, using either experimental animals and/or in vitro systems, is to characterise any hazard linked to their presence and to determine exposure levels that do not result in adverse effects to humans and animals. The used approach is similar to the one applied for testing chemicals in foods. The EFSA Guidance Document (EFSA Journal 9(5):2150) provides information requirements, testing strategies for whole foods like GM plants, derived food, and feed.

The needs for toxicological testing are based on the outcomes of the molecular and comparative analyses.

In line with EFSA guidelines and the Codex *ad hoc* Intergovernmental Task Force on Foods Derived from Biotechnology, an integrated, case-by-case approach, i.e. so called weight-of-evidence approach, is used in the assessment of possible allergenicity.

***2.3 Animal Feeding studies***

**Module Description**

* According to the EU legislation the potential impact of any changes resulting from the expression of introduced genes or any other type of genetic modification shall be assessed;
* Relevant toxicity data may be obtained from in vivo, in vitro and/or in silico studies.
* The purpose of animal feeding studies is:

(1) To demonstrate that the intended effect(s) of the genetic modification of the GM animal and derived food or feed has no adverse effects on human and animal health upon consumption;

(2) To demonstrate the absence of unintended effect(s) of the genetic modification(s) on human and animal health upon consumption.

* Experiments to support the assessment should consider:

(1) The presence of newly expressed proteins;

(2) The potential presence of other new constituents;

(3) The possible changes in the levels of natural constituents;

(4) The impact of changes in composition due to the genetic modification.

**Key concepts, information and messages for this module**

In the EFSA Guidance Document (EFSA Journal 9(5): 2150) toxicity tests are not considered necessary in case of history of safe use of the newly expressed compound(s). However, 90-day feeding studies have become a compulsory requirement according to the EC implementing regulation No 503/2013.

Toxicity testing should be conducted according to internationally agreed protocols and test methods and apply quality assurance systems in compliance with the principles of Directive 2004/10/EC.

The risk assessment of the GM food/feed is primarily based on molecular characterisation, comparative phenotypic and compositional analysis. When these types of analyses cannot rule out uncertainties about the comparative food/feed safety with the conventional counterpart, a 90-day rodent feeding trial should be carried out according to the principles of internationally agreed guidelines.

**QUESTIONS AND ANSWERS: TOPIC 2**

***Question 1: When EFSA experts issue some new regulations it is based on scietific publications or it is based on something else?***

EFSA experts never issue new regulations! At best they can issue recommandations for the implementation of existing rules. All the work of expertds is strictlky based on peer-reviewed scientific literature.

***Question 2: EFSA guidance document: what are the general criteria in terms of uncertainty and how to manage it?***

A general criterion adopted by EFSA for risk assessment is to firstly distinguish between uncertainties that reflect natural variations in biological parameters (e.g. different susceptibility to a toxicant in a population), and possible differences in responses between species (e.g. extrapolation of the experimental resuts). Estimation of uncertainties in experimental data should be handled by proper statistical analyses (see EFSA Scientific Committee, 2018
<https://doi.org/10.2903/j.efsa.2018.5123>).

Any absence of data essential for the risk assessment should be indicated and it should be made clear how this has been taken into account. A peer review by experts employing scientific judgement, can be considered as a form of quality control. In cases where scientific information is insufficient, inconclusive or uncertain, opinions can be issued accordingly and further recommendations to risk managers are necessary.

**TOPIC 3 HAZARD CHARACTERIZATION**

***3.1 Intended modifications vs. unintended effects***

**Module Description**

The module further describes the tests of difference/equivalence introduced above and how lack of equivalence and/or differences between a GM plant and its comparator is analysed so as to assess potential impact on human and animal health:

* Intended alterations fulfilling the objective of the modification vs unintended effects;
* Concepts of biological relevance, uncertainty analysis and weight-of-evidence to support the identification of unintended effects.

**Key concepts, information and messages for this module**

Given the diversity of receiving environments and their potential interactions with the GM plant, differences between the GM plant and its comparator, observed differences might not be biologically relevant. Several guidance documents have been developed to help assessors identify those differences that deserve further analysis.

***3.2 Implementing nutritional assessments of food/feed products derived from GM plants***

**Module Description**

* Evaluating potential alterations in the total diet for the consumers/animals due to the introduction of food/feed derived from GM plants. The nutritional assessment should consider:
* The composition of the food with regard to the levels of nutrients and anti-nutrients;
* The bioavailability and biological efficacy of nutrients in the food taking into account the potential influences of transport, storage and expected treatment of the foods;
* The anticipated dietary intake of the food and resulting nutritional impact.

**Key concepts, information and messages for this module**

The nutritional evaluation should demonstrate that the introduction of food and feed derived from a GM plant into the market is not nutritionally disadvantageous to humans and animals, respectively. The nutritional assessment should indicate:

* if the food and feed is nutritionally equivalent to its comparator, taking into account natural variation;
* if the identified changes have an impact on the anticipated intake of the food and feed;
* if the unintended effects of the genetic modification, either identified during hazard identification or during the preceding molecular, compositional and phenotypic analyses, have affected the nutritional value of the food and feed;

In case of GM plants containing stacked events, it should be tested if there are changes in nutritional value due to additive, synergistic or antagonistic effects of the gene products.

In the case of GM plants modified with traits enhancing nutritional performance, (e.g. higher level of an essential amino acid or a vitamin), an appropriate control diet with similar nutrient profile should be formulated using a non-GM control supplemented with the specific nutrient as present in the GM plant.

**TOPIC 4 ASSESSMENT OF EXPOSURE TO CONSUMERS**

***4.1 Methodologies for assessing the exposure of GM food/feed products to consumers***

**Module Description**

The estimation of dietary exposure requires two types of data: occurrence or concentration data that provides information on the amount of a compound/s present in different food commodities, and consumption data that informs on the intake of these food commodities. By combining these two types of data and considering the body weight of the subjects, dietary exposure is estimated. In the frame of the authorisation of GM crops, the focus is put on how both the available concentration and consumption data should be used to estimate dietary exposure by:

* Estimating the average and maximum dietary intake level (use of international Food consumptions databases and EFSA Comprehensive European food consumption database);
* Anticipating influences by processing the food and feed;
* Identifying particular groups of population with an expected high exposure;
* Evaluating intended function and level of use (e.g. raw, cooked, etc.).

**Key concepts, information and messages for this module**

According to EC implementing regulation No 503/2013 an estimate of the expected intake is an essential element in the risk assessment of GM plants and derived food and feed. Data to support the assessment should consider the intended function, the dietary role, and the expected level of use of the food and feed derived from the GM plant. Estimations of dietary exposure (chronic and acute) should cover average and high consumers across all the different age classes and special population groups for which consumption data are available. In addition, the new statement on Animal dietary exposure in the risk assessment of feed derived from GM plants is introduced. The statement is aimed at facilitating the reporting of the information that applicants need to provide on expected animal dietary exposure to newly expressed proteins and to increase harmonisation of the application dossiers to be assessed by the EFSA GMO Panel.

The use of the EFSA consumption database to estimate dietary exposure to GM foods will allow a direct linking between the consumption data and the concentration values reported for the different GM food constituents in raw primary commodities.

**TOPIC 5 RISK CHARACTERIZATION AND MANAGEMENT**

***5.1 Implementing risk characterization***

**Module Description**

* Integrative manner vs case-by-case basis, considering also other factors (e.g. receiving environments and cultivation practices affecting food and feed quality)
* Key concepts and approaches of uncertainty analyses
* Overview on the uncertainty analysis framework as proposed by EFSA
* How to move from a qualitative to a more quantitative risk characterization: role of modelling

**Key concepts, information and messages for this module**

The previous steps of the risk assessment allow conclusions on the likelihood of additional adverse effects against human and animal health and the environment, as compared to corresponding non GM organisms. These additional adverse effects might depend on the receiving environments and managing practices, it is paramount to assess and frame this variability. Identified risks and their variability prompt the definition of suitable risk management practices, which include risk mitigation and risk monitoring. In addition, uncertainties exist at different steps of the risk assessment and these should be identified as far as possible (see Guidance on Uncertainty in EFSA Scientific Assessments) and the analyses may indicate and prompt to specific research needs and motivating the general surveillance GM organisms and the derived products.

***5.2 Risk management***

**Module Description**

* The concept of risk management measures
* Acceptable and inacceptable risk levels
* How to upscale effects (long-term, landscape) observed of small scale (field trails) and role of modelling
* Mitigation of risk using specific risk management strategies (e.g. containment, monitoring) and precautionary approach

**Key concepts, information and messages for this module**

The actual impact of differences measured between a GM plant and its comparator depend on the receiving environment in which the GM plant is introduced. The given effect of a toxin on non-target organisms as measured in a lab experiment may result in no harm at all in a given receiving environment (if populations can easily recover) or lead to detrimental effects in other cases. This highlights the need to develop a more quantitative approach of risk assessment on the one hand but also means that risk management might mitigate some identified risks. Examples are given for managing risks for human and animal health as well as for the environment, the latter connected to the cultivation of GM plants in agroecosystems

**TOPIC 6 POST-MARKETING MONITORING (PMM)**

***6.1 Evaluating predictions made in risk assessments***

**Module Description**

* Unintended side effects of the product and the need for their detection
* The need of a case-by-case post-marketing monitoring (e.g. foods with altered nutritional composition and modified nutritional value and/or with specific health claims) to analyse whether known-effects and side-effects are as predicted or not

**Key concepts, information and messages for this module**

PMM should be required only in specific cases, and does not substitute a pre-marketing assessment, rather complements it in order to increase the probability of detecting rare unintended effects. PMM for food and feed should be designed to generate reliable and validated flow of information between the different stakeholders, which may relate consumption of food, and feed derived from GM plants to any (adverse) effect on human and animal health. As pre-market risk assessment studies cannot fully reproduce the diversity of the populations, the possibility that unpredicted side effects may occur, remains. PMM is required to assess GM food and feed with altered nutritional composition and modified nutritional value and/or with specific health claims. In particular, these products could have an impact on some individuals, such as those with certain disease states, those with particular genetic/physiological characteristics or those who consume the products at high levels. Therefore, a PMM should address the following questions: is the product use as predicted/recommended? Are known effects and side-effects as predicted? Does the product induce unexpected side effects?

**TOPIC 7 BEYOND PLANTS: GM FOOD AND FEED FROM MICROORGANISMS AND INSECTS**

***7.1 GM microorganisms, animals and insects for food/feed purposes***

**Module description**

* Importance of GM microorganisms and their products for food/feed processing and as supplements
* Short introduction to the current possible future importance of GM animals, including farm animals, insects and fish
* Introduction to EFSA guidance documents dealing with GM microorganism and animals (including fish and insects)

**Key concepts, information and messages for this module**

While the focus of this course is on plants as food and feed sources, this topic introduces to the other GM organisms, which are used for food and feed purposes. GM microorganisms and their products are important food and feed additives, including vitamins, many different enzymes or other compounds. The risk assessment of products from GM microorganisms is described in the EFSA guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA Journal 2018;16(3):5206), except for the use of viable GM microorganisms for food and feed uses, which is described in the EFSA guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use (EFSA Journal 2011;9(6):2193) under the *Category 4*. The guidance documents are applicable to feed additives produced from genetically modified microorganisms (GMMs) for which an authorisation under Regulation (EC) No 1829/2003 is required.

EFSA has also issued guidance documents for assessing the environmental risks of GM animals, including GM fish and insects (EFSA Journal 2013;11(5):3200). The risk assessment approaches are in line with the previously developed ERA Guidance on GM plants, but considers particular hazards associated with particular properties of insects, fish and other animals as well as another diversity of receiving environments.

**TOPIC 8 ENVIRONMENTAL RISK ASSESSMENT (ERA) OF GMOs**

***8.1 Purpose of environmental risk assessments***

**Module Description**

* According to Directive 2001/18/EC that regulates the deliberate release into the environment of GMOs, they shall only be authorised for placing on the market after a scientific assessment of any risks, which they might present for human and animal health and for the environment.
* Environmental risk assessment is a science-based evaluation of complex data sets selected according to defined protection goals;
* Criteria for conducting ERA: problem formulation, hazard characterization, exposure analysis, risk assessment, risk management;
* Cross-cutting considerations: choice of comparators, receiving environment, long-term effects.

**Key concepts, information and messages for this module**

In the preparation of dossiers for authorization of the deliberate release of GMPs, seven specific areas of concern have to be addressed. The ERA should be carried out on a case-by-case basis, following a weight of evidence approach. This means that the required information may vary depending on the type of the GMPs and trait(s) concerned, their intended use(s), and the potential receiving environment(s), considering direct and indirect effects.

The EFSA guidance document provides guidance to risk assessors for assessing potential effects of GMPs to the environment, and the rationale for data requirements in order to complete a comprehensive ERA.

The overall risk assessment should express the risk(s) from deliberate release or placing on the market of the GM plant, including uncertainties. Evaluation should result in qualitative, and if possible quantitative, guidance to risk managers.

***8.2 The seven areas of concern***

**Module Description**

* Persistence and invasiveness
* Plant to micro-organisms gene transfer
* Interactions with target organisms
* Interactions with non-target organisms
* Cultivation practices
* Biogeochemical processes
* Human and animal health

**Key concepts, information and messages for this module**

For each specific area of risk, applicants are requested to provide information according to the following steps: problem formulation, hazard characterization, exposure characterization, risk characterization, risk management strategies.

Overall risk evaluation will have to characterize the possible risks, identify knowledge gaps, estimating uncertainties, suggest and quantify management strategies.

***8.4 The interplay between EU regulations on GMO and on pesticides***

**Module Description**

* Directive 2001/18/EC requires the assessment of possible immediate and/or delayed direct and indirect environmental impacts of the specific cultivation, management and harvesting techniques used for GMP. For GM herbicide tolerant (GMHT) plants this means assessing also the possible environmental impacts of the post-emergence use of the complementary herbicides.
* While GMO legislation includes the assessment of indirect effects linked to the change of herbicide regime, these are not part of ERA for pesticides, however the post-emergence use of the complementary herbicide in a GMHT crop requires a new authorisation according to the EU pesticide Regulation, because it is a new application of the herbicide;
* Change in management practices may have indirect negative or positive environmental effects.

**Key concepts, information and messages for this module**

GMHT plants will change herbicide regimes (e.g. type of herbicides and application timing) and may induce additional weed control changes to minimize weed shift. Additional environmental harm and greater adverse effects on biodiversity may result from these altered weed control systems (fewer weeds and/or weed shift). Amplification of such effects may occur in presence of acquired resistance in the GMPs or in wild relative species, which may outcross with the cultivated species.

GMHT plants facilitate the adoption of minimum tillage or no-till cultivation techniques which may lead to beneficial or detrimental environmental effects. Modelling and scenario analyses approaches can be used to assess to what extent risk management strategies may prevent adverse effects on the environment.

**TOPIC 9 POST-MARKETING ENVIRONMENTAL MONITORING (PMEM)**

***9.1 Ensuring continued safety – Monitoring the impact of GM plants in agroecosystems***

**Module Description**

* Methodology for Case-Specific Monitoring (CSM)
* Choice of comparator
* Spatial and temporal scale of CSM
* General Surveillance
* Approach and principles
* Protection goals, assessment endpoints and indicators
* Tools for General Surveillance
* On-site monitoring
* Existing monitoring networks
* Review of scientific literature

**Key concepts, information and messages for this module**

According to Directive 2001/18/EC (EC, 2001), each notification for placing on the market a genetically modified organism (GMO) shall contain a plan for monitoring. Similarly, according to Regulation (EC) 1829/2003 (EC, 2003), each application for the placing on the market of a GMO or food/feed containing or consisting of that GMO shall be accompanied by a monitoring plan for environmental effects. Monitoring can be defined as the systematic measurement of variables and processes over time and assumes that there are specific reasons to collect such data. The overall conclusions of the ERA provide the basis for PMEM plans, which focus on risks to human health and the environment (including domestic animal health) identified in the ERA and can be used to provide data on uncertainties identified in the ERA.

Risks and critical uncertainties identified during ERA should be addressed through a case specific monitoring (CSM) to check the assumptions made during the ERA and to ensure that the ERA conclusions are valid as regards the authorised use of the GMP.

Unanticipated effects can be dealt with, through general surveillance activities to determine the harm to protection goals and to resolve the causality between the detected unanticipated adverse effects, if any, and the cultivation of GMPs.

A number of newly developed protocols and models are available to support monitoring activities.

***9.2 Reporting PMEM results***

**Module Description**

* Potential use of existing monitoring networks, conceptual framework articulating CSM and GS
* Description of methods, frequency and timing for applicants’ reporting in their monitoring plan;
* Procedures to be adopted if unanticipated adverse effects have been detected.

**Key concepts, information and messages for this module**

During the ex-ante ERA, mitigation measures might be proposed to reduce identified risks below an acceptable level. Case-specific monitoring aims at checking whether the identified risks have been actually controlled. In addition, general surveillance is needed to detect possible effects on the environment which were not detected during the initial risk assessment. It may concern:

* Effects that are only expressed during large-scale deployment and over time;
* Indirect effects that may pop up due to the changing environmental conditions of agroecosystems, such as climate change or management practices.

As there is no hypothesis to test and as agroecosystems evolve continuously with changes in practices, cropping systems or land use, general surveillance cannot be restricted to the specific GM stressor and all possible stressors and their potential interactions should be considered, which requires adequate methods and resources. Exploiting existing environmental monitoring networks and linking agricultural practices with global impacts may help but give rise to many methodological challenges (Scientific Opinion on the use of existing environmental surveillance networks to support the post-market environmental monitoring of genetically modified plants EFSA Journal 2014;12(11):3883).

**TOPIC 10 GMOs MADE BY NEW TECHNOLOGIES – CHALLENGES FOR REGULATIONS**

***10.1 Implications of Synthetic biology for environmental risk assessments***

**Module Description**

* What is Synthetic Biology?
* ERA of microorganisms made by Synthetic biology
* Xenobiology
* ERA of plants made by Synthetic biology

**Key concepts, information and messages for this module**

Will GM organisms (microorganisms or plants) produced by Synthetic Biology require modifications of current risk assessment procedures as implemented in the EC? Are there new hazards and risks associated with organisms made by Synthetic Biology, reaching the EU market in the future? In 2019 EFSA has started, on request of the EC, working groups which prepared two documents on the environmental risks and their assessments of organisms produced by synthetic biology, which may reach the marked in the (near) future. At the time of this Course 5 in May 2020, these documents should be under public consultation, thus accessible for discussion.

***10.2 "Omics”-technologies and molecular techniques to deal with unintended effects***

**Module Description**

* Application of ‘Omics’ and high-throughput sequencing technologies in support of risk assessment
* Tackling unintended effects due to the insertion of new pieces of DNA
* Tackling the need of selection markers during the genetic transformation

**Key concepts, information and messages for this module**

So-called ‘omic’ and high-throughput sequencing technologies allow the high-throughput characterization of the molecular characteristics of cells and organisms, but their usefulness in risk assessment is subject to debates. In order to reduce or to avoid unintended effect of the genetic modification, strategies for the site-specific integration of foreign DNA, as well as for the removal of undesired DNA (e.g. selection markers) in the final organism have been developed.

**TOPIC 11 RISK COMMUNICATION**

***11.1 An introduction to risk communication strategies***

**Module Description**

* Definition of risk communication
* Purpose of risk communication
* Principles of good risk communication
* Communication strategies in case of crisis situations
* Best practice to communicate uncertainties
* The importance of the risk perception in handling hazards
* Different types of communication “styles” adjusted to target audience
* Stakeholders, their core business and their language
* Communication levels – written, discussions, interviews

**Key concepts, information and messages for this module**

The exchange of information and opinions concerning risk and risk-related factors among risk assessors, risk managers, consumers and other interested parties is an essential element of a full risk analysis. Its main objective is to increase understanding among various food safety stakeholders regarding the rationale behind the decisions taken to assess hazards and manage food safety risks, and to help people to make more informed judgements about the food safety hazards and risks they face in their lives (EFSA, 2017. ISBN 978-92-9199-778-7;doi: 10.2805/119491). Risk communication also informs about risk management decisions, e.g. hygienic measures or other containment strategies, and thereby may strongly affect their efficacy. According to a joint statement of the WHO and FAO (2016; Risk communication applied to food safety handbook. ISBN 978-92-5-109313-9) decision makers Decision-makers and risk managers within governments have an obligation (1) to ensure effective risk communication with interested parties when developing scientific and technical analyses; (2) to involve the public and other stakeholders when appropriate in the risk analysis process; (3) to understand and respond to the factors driving public concerns about health risks as well as technical risk assessments.

Further reference is made to recent documents/guidelines issued by EFSA:

* *Engagement Toolkit - Methods, tips and best practices to design effective participatory processes (March 2021)*
* *Catalogue of Communication Tools and Dissemination Guidelines: benchmarking current practice in EU and Member State bodies (March 2021)*
* *Best practice for crisis communicators - How to communicate during food or feed safety incidents (2023)*