GMSAFOOD

GM POST-MARKET MONITORING

the conference

REPORT

March 6-8, 2012: Medical University of Vienna, Austria

GMSAFOOD Conference Report

Content

Introduction

On March 6-8th, the European Commission FP7-funded GMSAFOOD consortium announced significant results regarding the safety of GM foods based on genetically modified (GM) crops, to members of the press, as part of a three day conference to disseminate the results of over three years of research by Austrian, Australian, Norwegian, Irish, and Hungarian scientists.

One study, conducted at the Medical University Vienna (MUW), refutes the findings of a 2005 study by Prescott et al., which initiated extensive controversy with the claim that field peas modified to inhibit alpha-amylase induce an allergic response in mice. After the 2005 study, development of the GM pea was immediately abandoned. The incident is regularly cited by those on both sides of the GM debate as an example of either the inherent dangers of genetically modified foods or the effectiveness of pre-market studies in identifying potential risk factors. The latest findings by MUW call for a re-evaluation of both positions. One of the consortium's most important contributions is its proposal for a novel approach to post-market monitoring. Despite the 114,507 hectares of biotech crops planted in the EU in 2011 (www.isaaa.org), there is currently no adequate system in place for monitoring the effects of GMOs on animal and human health once a crop has been approved for market, with current emphasis placed almost entirely on pre-market testing. Given the inadequacy of a traditional epidemiological approach to monitoring GMOs in the marketplace, the consortium proposes a "clustering and neural network"-type machine-learning framework to identify potential biomarkers capable of detecting unforeseen health risks. Such biomarkers could also be useful in predicting immune responses of multiple species to future genetically modified organisms. These methods, coupled with meta-analysis of data within a prospective public repository, would significantly complement pre-market testing procedures currently in use.

Findings from GMSAFOOD research teams presented at the GMSAFOOD conference at the Medical University of Vienna, Austria 6-8 March 2012, included:

- The production of alpha amylase inhibitor peas, cowpeas, chickpeas for insect protection (Australia)
- Pig feeding studies (Ireland)
- Salmon feeding trials (Norway)
- Investigation of human immune response to potential allergens in GM peas using human-SCID mice (Austria)
- Food chain studies where rats were fed pork and fish which had been raised on Bt-corn (Norway)
- Epitope mapping and antibody determinations (Hungary)

The conference included invited Keynote speakers Sandy Lawrie, Gerard Barry, Helmut Gaugitsch, Yves Bertheau, Gerhard Flachowsky, Richard Goodman, Alan Kristal and Anne Constable who spoke on aspects of food and feed safety, biotechnology, and post market surveillance.

In addition to lectures, there was a panel discussion and small group interactive sessions that generated a lot of intense discussion between all participants.

Sugar Coated Proteins in Certain Foods

TJ Higgins of CSIRO in Australia described the development of three GM legumes (pea, chickpea and cowpea). They contain a gene from the common bean (Phaseolus vulgaris) for alpha-amylase inhibitor (AAI) to protect peas in the field from pea weevil and the harvested grain of chickpea and cowpea from larvae of cowpea weevil, an extremely important pest in many developing countries in Africa and Asia. The AAI protein is sugar-coated slightly differently in the three transgenic species (Pisum sativum, Cicer arietinum and Vigna unguiculata), with variants of the four asparagine-linked glycans (consisting mostly of the sugars mannose with minor amounts of xylose and fucose). A close examination of the glycans on several Phaseolus varieties such as Tendergreen, Red Kidney, Pinto and Cannellini led to the conclusion that there is just as much variation in the glycans of different beans as there is in the different AAI transgenics, pea, chickpea anwd cowpea. Photo shows GM peas protected against the pea weevil whereas the non-transgenic pea is severely damaged.

Australian team

From left to right: Andy Moore, Stephanie Gollasch, Lisa Molvig, Carlos Popelka, TJ Higgins

CSIRO

Short, Medium & Long-term Studies in Pigs fed GM Feed

Bt maize caused no adverse effects on growth performance of pigs following short- (31 days), medium-term (110 days) feeding trials. A trans-generational study found that feeding Bt maize to sows during gestation and lactation resulted in offspring with improved lifetime growth performance, even though no differences in the birth weight of piglets was observed. Organ structure and function of pigs fed Bt maize as well those of the offspring at birth from sows fed Bt maize was normal. Based on the parameters investigated, feeding of Bt maize to pigs of different ages and for extended periods of time is safe. Alpha-amylase inhibitor (AAI) peas compared with the isogenic parent line and an Irish-grown commercial field pea variety had no effects on growth performance or organ weight. Some changes in haematological parameters were found between pigs fed the isogenic and AAI peas, however, no differences were found between AAI peas and commercial field peas. This highlights the importance of correctly interpreting data on GM ingredients. Even a comparison between two conventional varieties of any feed ingredient is likely to yield differences in some parameters of interest. Therefore, it is important that feeding trials investigating the safety of GM ingredients should also include a comparison to other conventional varieties of the same feed ingredient.

No allergenic responses to Bt maize were found in pigs. The Bt toxin and cry1Ab transgene were not found outside of the intestinal tract.
Feeding alpha amylase inhibitor peas had no effect on pig health.

Irish team

From left to right: Stefan Buzoianu, Paul Ross, Mary Rea, Peadar Lawlor, Gillian Gardiner, Maria Walsh

Atlantic salmon, zebrafish and the food chain

GMOs in diets for Atlantic salmon

NVH reported on a series of feeding trials with Bt maize and its isogenic counterpart conducted on Atlantic salmon. Both healthy fish and fish which were sensitized by dietary inclusion of soybean meal (immune stimulated), were used at various stages of development in studies lasting up to 5 months. The effects of Bt maize on intestinal functions indicated somewhat less efficient feed utilization and lower body fat deposition. Potentiation of cellular stress in the intestine of fish consuming Bt maize and soybean meal was observed, but Bt maize effects did not differ between healthy and sensitized fish. No detectable systemic health effects were observed. Antibodies to Cry1Ab protein were not detected. Major health effects were not observed in Atlantic salmon fed Bt maize but longer term trials may be useful to ensure long term safety. The results of a transgenerational trial on zebrafish as a potential model for various fish species was also reported. No adverse effects on growth performance of parents or offspring, nor on reproductive performance of the parents or behavior of the offspring in Zebrafish studies were reported. An experiment with AAI peas in the diet for Atlantic salmon showed no change in growth performance.

GMOs in the Food Chain

The results of a 90-day feeding trial with weanling brown Norway rats were presented. The rats were fed diets with Bt maize and flesh from Atlantic salmon and pigs fed Bt maize or diets with the isogenic counterpart. The rats were evaluated for effects on feed utilization, growth performance, general health status, organ morphology, digestive enzyme capacities, stress and immune responses. The observed responses related to Bt maize indicated increase in feed intake and protein deposition and in body and heart weight, decrease in stomach and colon compared to responses related to the isogenic maize. For other observations no differences were seen. The conclusion was that Bt-maize effects may be transferred through food chain but the values of all measurements were within normal ranges suggesting no long term health concerns.

Norwegian team

From left to right: Åshild Krogdahl, Anne Marie Bakke, Gunn Østby, Elin Christine Valen, Ellen Elisabeth Koren Hage

Are mice a good model for testing GMO allergenicity?

The MUW team reported on the transgenic expression of AAI protein in peas, cowpeas and chickpeas, which leads to the synthesis of altered glycosylated forms of AAI. They found that there was no correlation between different glycosylation patterns and immunogenicity. It was not possible to predict whether a transgenic protein would be more immunogenic due to the differential posttranslational processing in the new host plant. Natural variation of glycosylation occurs in both native beans and AAI peas and these glycosylation differences do not distinguish between GM and non-GM forms of the proteins. Moreover, while allergenicity to AAI may be linked to changes in glycosylation, there was no evidence that it was linked specifically to GMOs. In feeding experiments, they found that all peas, Tendergreen and Pinto beans induced allergic responses to AAI. Antibodies to AAI developed whether mice were fed peas or beans, including peas not containing AAI. Upon further study, they observed that non-transgenic and GM peas induced AAI antibody responses that are cross-reactive with antibodies generated against pea lectin. This cross-reactivity could be misleading. In other studies, severe combined immunodeficiency (SCID) mice lacking functional T and B cells were reconstituted with human peripheral blood mononuclear cells to create an in vivo model to study human disease. They transferred cells from healthy individuals and legume allergic patients having antibody titres against AAI. The hu-SCID mice developed allergic asthma upon feeding with AAI peas and Tendergreen beans and challenge with pure AAI. Healthy and allergic patients could not be distinguished with these models. Lastly, mice were fed peas during pre-existing allergic asthma to an unrelated egg allergen. No change in egg allergic disease was observed indicating that pea feeding did not worsen allergic responses to unrelated allergens.

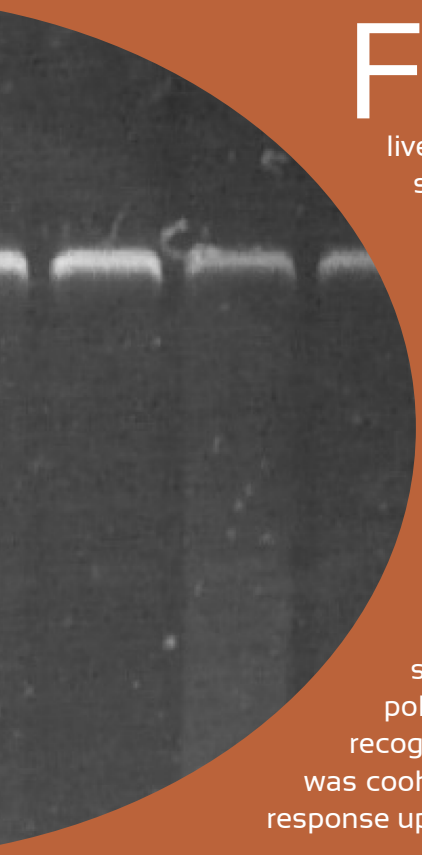
Bt maize fed to mice at the time of the first episode of allergic asthma and during asthma attacks with egg white protein, ovalbumin were unaffected. The mice did not develop more severe allergic disease when fed GM maize compared to normal mouse food and non-GM maize. These results indicate that there is no increase in allergenicity to other unrelated allergens upon eating Bt maize.

Austrian team

Michelle Epstein, Szivlia Steiner, Daniela Reiner (left), and Rui Lee (right)

MEDIZINISCHE UNIVERSITÄT WIEN

Tracking antibodies, proteins and transgenes



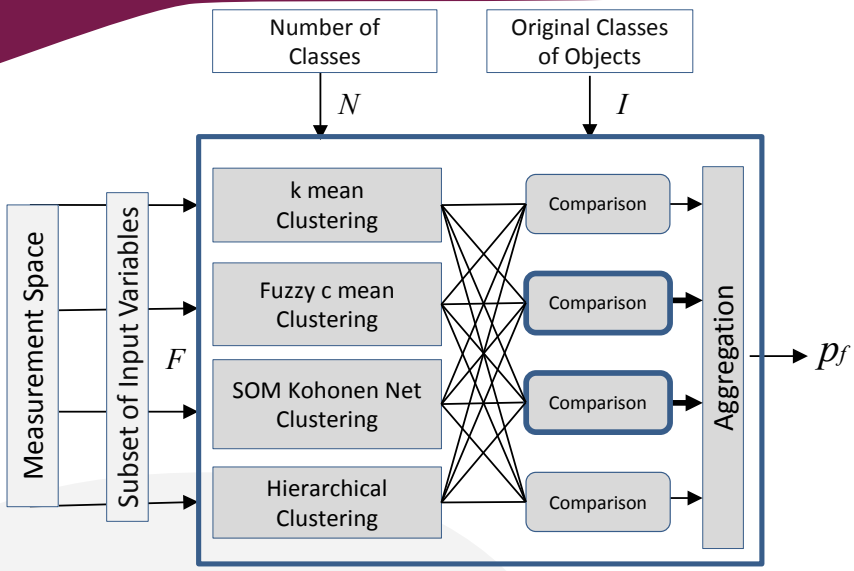
Feeding pigs of GM (MON810) maize for short and medium term experiments revealed that the fate of the transgenic DNA and protein in the GM maize-fed pigs was limited to the gastrointestinal digesta and was not found in the kidneys, liver, spleen, muscle, heart or blood. Feeding on Bt maize did not induce Cry1Ab specific IgG and IgA antibody responses. Fish feeding of Bt maize in short and medium term experiments did not reveal Cry1Ab protein concentrations in the plasma and did not induce specific antibodies (immunoglobulin M) against Cry1Ab.

Patients with a history of gastrointestinal, skin and respiratory symptoms in response to legumes were compared with healthy controls without allergy. Patients included in the study had clinical symptoms after legume exposure, positive allergen specific IgE-RAST prick or patch test, and elimination diet and repeated legume food challenges. Patient sera were positive for antibodies against AAI from pea and beans. AAI was identified on SDS PAGE gels and could separate allergic patients from healthy controls on western blots. Positive sera cross-reacted with 2-DE separated and deglycosylated AAI showing that the IgE reactivity was against polypeptides from pea or bean proteins and not carbohydrates. There is IgE recognition against deglycosylated AAI that were lost when testing after seedmeal was cooked, illustrating that the potential allergenic protein does not induce an allergic response upon cooking.

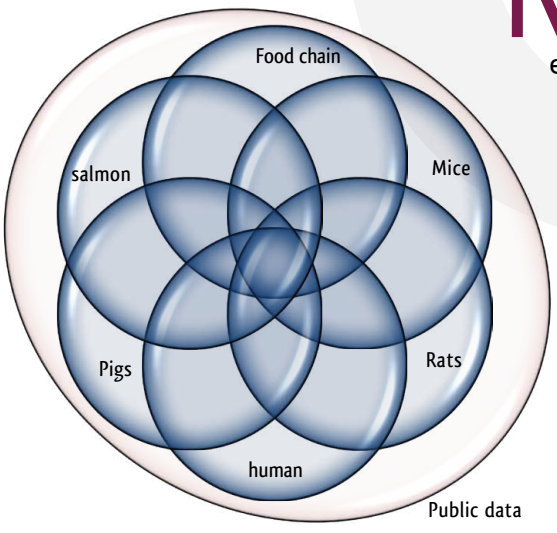
Hungarian team

From left to right:
Molnár Mihályné, Jánosi Anna, Szabó Erika, Ujhelyi Gabriella, Jánosi Anna, Gelencsér Éva, Kissné Valentin Éva, Rimányi Lívia, Molnár Mihályné, Szamos Jenő, Maczó Anita, Sólyom Katalin, Nagy András

Biomarkers for Post Market Monitoring by Machine Learning



Karin Pröll from Medical Informatics and Bioinformatics at the Upper Austrian University of Applied Sciences in Hagenberg, Austria, and Michelle Epstein from the Medical University of Vienna, Austria presented results from machine learning analyses. The method focused on the scoring function specification and feature selection by combining unsupervised learning with supervised cross validation. A one dimensional Kohonen SOM (Self-Organizing Map) is used to perform a clustering of object data for a chosen subset of input features and given number of clusters. The resulting object clusters are compared with the predefined original object classes and a matching factor is calculated (see figure). This score is used as criterion function for heuristic sequential feature selection Additionally, the significance of an individual feature for recognition of original classes or composed groups of original classes is calculated based on this matching factor. The results are compared and aggregated with the result of sequential feature selection to find a final sensitive feature space. The method was applied to different feeding experiments of fish, pigs, rats and mice. The approach is seen in the scheme above.



Venn Diagram illustrating Machine Learning analysis exemplified with GMSAFOOD datasets from vastly different datasets across species and used to arrive at common and/ or independent biomarkers. Publicly available datasets can be included in this analysis.

Michelle Epstein from the Medical University of Vienna presented results derived from mouse Bt maize feeding studies. She showed how parameters from experiments done under different conditions can be compared together with the machine learning approach illustrated above. This example was used to show how such analysis can compare parameters within individual experiments but also between disparate experiments. Importantly, analysis of datasets within experiments found potential classifiers not found in traditional statistical analysis and comparisons between experiments done under different conditions that cannot be statistically analysed may find robust classifiers e.g. predictive biomarkers.

The conclusions of this talk were that GMO safety and other aspects of food safety can be assessed using a multitude of datasets derived from animals and humans. These datasets can be evaluated with machine learning for post market monitoring. This approach is important because data from experiments across species can be compared. The consortium is recommending to the EC to store all GMO-specific data in public databases available to all researchers. These data would be incorporated into hierarchial mathematical models that could be used to identify biomarkers useful for post market monitoring.

Invited Keynote Speakers

Sandy Lawrie
UK Food Standard Agency, UK

Gerard Barry
International Rice Research Institute, Philippines

Helmut Gaugitsch
Environment Agency Austria, Austria

Yves Bertheau
INRA, France

Gerhard Flachowsky
Friedrich-Loeffler-Institute, Germany

Richard Goodman
University of Nebraska-Lincoln, USA

Alan Kristal
Fred Hutchinson Cancer Center, USA

Anne Constable
Nestlé Research Institute, Switzerland

GM food and feed: EU legislation and post-market monitoring

Sandy Lawrie
UK Food Standard Agency, Novel Foods Unit

Sandy Lawrie focused on the legislation on GM food and feed, what the legislation says about post-market monitoring, how it works in other areas of EU legislation and what is the current thinking on the PMM and the safety of GM food and feed. Genetically modified (GM) foods and other types of novel foods can only be marketed in the European Union if they have passed a rigorous safety assessment. GM foods may only be authorised (and re-authorized) for marketing if they are judged not to present a risk to health, not to mislead consumers and not to be of less nutritional value than the foods they are intended to replace. Validated detection methods must also be available. The current procedures for evaluation and authorisation of GM foods are laid down in Regulation (EC) 1829/2003 on GM food and feed. The Directive 2001/18/EC on deliberate release of GMOs provides the definition of "GM", sets out criteria for environmental aspects, framework for regulating crop trials (at national level) and for non-food crops. Legislation is kept under review. Two evaluation reports were published by Commission in 2011 (1829/2003: GM food and feed; 2001/18: deliberate release). No legislative changes are being proposed. The commission seeks to improve implementation of existing legislation. Regulation 1829/2003 refers to post-market monitoring in relation to the application for authorisation, the EFSA opinion, the authorisation decision. In the case of GMOs, monitoring concerning environmental effects is compulsory and it is necessary to introduce, where appropriate and on the basis of the conclusions of the risk assessment for the use of GM foods and feeds. Where post-market monitoring has been imposed on the authorisation-holder, the authorisation-holder shall ensure that it is carried out and shall submit reports to the Commission in accordance with the terms of the authorisation related (e.g. usage, exposure and beneficial or adverse effects on consumer). Results of post-market monitoring can help refine risk assessment and/or risk management. Examples were conducted how the regulation works in other areas as pesticides, food additives and novel foods. Current Draft Commission Regulation on requirements for applicants is based on latest EFSA guidance on GM food/feed from GM plants and includes an article (Regulation 1829/2003, article 5(3)) that would clarify how applicants should address post-market monitoring. According to this new regulation, the application shall be accompanied, where appropriate, by a proposal for post-market monitoring regarding the use of food for human consumption.

Experience and future of GM crop products

Gerard Barry
International Rice Research Institute, Los Banos, Laguna, Philippines

Gerard Barry provided an overview of GM crop adoption. He described current products and how they affected policy and research and development as well as what's coming next. There are 11 current crops in commercial production and the area over which they are grown are summarized at ISAAA www.isaaa.org and Brief 43. In 2011 nearly 17 million farmers (mostly developing countries) grew GM crops with an end-product value of US$160 billion. Farmers chose GMOs predominantly because of increased yield and decreased input costs and more time available for other farm practices. In the Philippines the yield of maize increased from 2 tonnes per hectare to over 2.6 in the 6 year period following the introduction of GM maize in 2003. India grows GM cotton and has moved from being a net cotton importer to being the world's top exporter and cotton farm income increased by US $2.5 billion in 2010. New GM crops in the pipeline (http://ipts.jrc.ec.europa.eu/publications/) come from multinational companies but are increasingly coming from national research institutions especially in China, India, Brazil, South Africa and the Philippines. They will involve strategic national collaborations in China, India and Brazil and will involve indigenous companies. The traits in the pipeline include nitrogen and water use efficient plants, sugarcane with enhanced bio-fuel conversion rates, climate adapted crops, virus resistant beans, omega 3 fatty acids in oilseeds, other nutritional improvements include mono-unsaturated fatty acids, enhanced folate and beta carotene and high lysine cereals. In 2009 China approved the release of pest resistant rice and a phosphorus efficient maize intended for animal feed. These approvals were noteworthy because they were the first approvals for grain in China.

International guidance on risk assessment of GMOs

Helmut Gaugitsch
Environment Agency Austria

Helmut Gaugitsch provided information about the Draft Guidance on Risk Assessment of LMOs. The Cartagena Protocol on Biosafety deals with risk assessment for the intentional release of a living modified organism (LMO, more generally known as GMOs) whether in field trials or for commercialisation after a transboundary movement and import. The Ad Hoc Technical Expert Group (AHTEG) on risk assessment and risk management was established in 2008 and will develop a "road map" providing guidance on specific aspects of risk assessment. This 28 person expert committee has been working for 4 years and has obtained input from an extensive network of risk assessors, decision makers and stakeholders. The roadmap is intended to build on and complement Annex III of the Protocol. It will describe the planning phase of the risk assessment taking into account uncertainty and contains 5 steps in the conduct of the assessment. It will also contain a flowchart which is intended to provide a simple visual representation of the roadmap. In conducting the risk assessment, five steps are envisaged, namely; Step 1: Identification of potential adverse effects, Step 2: Evaluation of the likelihood, Step 3: Evaluation of the consequences, Step 4: Estimation of the overall risk, Step 5: Recommendation whether risks are acceptable or manageable, any risk management strategies. Each of these steps has an average of six sub-headings each with their own guidance. The roadmap is only part I of a two part guidance. Part II: Specific Types of LMOs and Traits, LM plants with stacked genes or traits, LM plants with tolerance to abiotic stress, LM Mosquitoes. There is also Further Guidance (since AHTEG – 3): LM Trees, Monitoring of LMOs released into the environment, The next meeting of AHTEG is in June 2012 for a finalization of tasks. A Report and Decision is expected at COPMOP-6 in India by October 2012. More information is available at http://bch.cbd.int/protocol/. There was a lively Q&A largely focused on how the AHTEG guidances propose to harmonize with existing national biosafety laws and legislation. There were several queries about the appropriateness of the huge complexity being introduced by Part I and II and whether any thought had been given to the consequences of such a burden, especially for developing countries.

Invited Keynote Speakers

GMOs status in France

Yves Bertheau
INRA
France

Yves Bertheau, INRA, France presented an overview of the French regulatory framework concerning GMOs. He detailed the interactions between stakeholders, government, NGOs and the general public in relation to GMOs since the latter were introduced in France. GMO acceptance in France has decreased over the last decade and culminated with a ban on GM maize cultivation in 2007 and destruction of experimental plots cultivated with GMOs in 2010-2011. In February 2012, France requested a ban on GM MON810 maize cultivation in the EU and no commercial GMO cultivation is expected in France in 2012. A post-market monitoring framework dedicated to GMOs is not yet in place in France, however, use and improvement of existing frameworks for this purpose is being considered at the moment. In this context, France and the European Union would benefit from a global post-market monitoring database to include information on all GMOs present on the market.

Feed from transgenic plants in animal nutrition

Gerhard Flachowsky
Institute of Animal Nutrition, Friedrich-Loeffler-Institute, EFSA GMO safety committee
Germany

Gerhard Flachowsky discussed a future, in which there will be competition for arable land use for phytogenic biomass production of feed/food, fuel, fibre and other industrial materials, as well as for settlement and natural conservation areas because of the growing population and limited natural resources. Plants with high and stable yields, low in undesirable substances, robust against biotic and abiotic stressors and requiring low external inputs (Low Input Varieties) should be the main aims of plant breeding. Traditional breeding and plant biotechnology could complement one another. Currently, we are in the initial phase of this breeding technology. The cultivation of genetically modified plants (GMPs) increased from 1.7 (1996) to about 160 Mio. ha (2011; more than 10% of all arable land throughout the world). Most modified plants are soybean, maize, cotton and rapeseed, and mainly possess an increased tolerance to herbicides and a higher resistance against insects. Nutritional and safety assessment studies with feed/food made from such modified plants are one of the most important prerequisites for public acceptance. In many countries e.g. Australia, China, EU, India, USA, special guidelines for assessment exist. The first step in the nutritional and safety assessment is compositional analysis, including accounting for the newly expressed proteins and other new constituents, by comparison with conventional counterparts. Then, in vitro studies as well as 28 and 90-day feeding studies with rodents comprise the next steps. Between 60 and 80% of the harvested biomass from GMPs are consumed by food producing animals and thus, feeding studies with target animals are important for nutritional assessment. More than 150 studies with food producing animals have been done with first generation GMPs which do not have substantial changes in composition. No unintended biologically relevant effects in composition, nutrition and safety were registered in feeding experiments including long term and multi-generation studies. More animal groups fed with commercial varieties should be included in the studies to assess the biological range of the data. Other experimental designs for nutritional and safety assessments are recommended for GMPs with output traits or with substantial changes in composition such as "Golden rice"; crops with lower phytate or higher amino acid concentration; oilseeds with other fatty acid patterns, etc.. Transgenic DNA and newly expressed proteins in GM-crops should show similar properties during processing (e.g. silage making, oil extraction) and in animals (effects of digestive enzymes) as "native" plant-DNA and proteins. For additional references, please contact: gerhard.flachowsky@t-online.de

Evaluating the potential allergenicity of GMOs intended for food use

Richard Goodman
University of Nebraska, Lincoln

Richard Goodman presented a detailed description of the allergenicity assessment of GMOs intended for food use, as outlined by CODEX (2003) and the EFSA requirements (including those of 2011). The bioinformatics comparison of AAI with AllergenOnline.org identified modest alignment (34% identity overall and ~43% identity to an 80 amino acid alignment) with a minor IgE binding protein, peanut agglutinin that was identified as a possible minor allergen of peanut. Serum IgE binding test results using 34 peanut allergic subjects demonstrated a lack of cross reactivity between AAI and peanut agglutinin. However, AAI and phytohemaglutinin (PHA), a major glycoprotein of beans, were bound by IgE from a few peanut subjects who do not claim allergy to beans. Competitive inhibition demonstrated the IgE binding was restricted to the complex asparagine linked glycans of both AAI and PHA. 'These glycans are known as cross-reactive carbohydrate determinants (CCD) and have been demonstrated by others to be ineffective epitopes for IgE cross-linking on mast cells. When the same sera were used to sensitize basophils in culture followed by exposure to AAI, navy bean or peanut, it is clear that IgE biding to AAI of pea was unable to induce activation of the basophils. The data demonstrates a lack of risk of allergy for those who have peanut allergy or IgE binding to the CCDs. The data support the long history of safe use of common beans (green beans, the source of the AAI, as well as kidney, navy and pinto beans). The conclusion was that the GM legumes transformed with AAI would not present a risk of allergy for consumers.

The limits of epidemiology for food post market monitoring surveillance; lessons from olestra post marketing surveillance study

Alan Kristal
Fred Hutchinson Cancer Center, Seattle, USA

Proctor & Gamble was required to carry out a post-market surveillance (PMS) of their products containing olestra when it was approved for commercial release by the FDA in 1996. The two areas of concern were identified during extensive pre-market assessments: decreased absorption of dietary carotenoids and vitamins D, E and K when foods with these nutrients were consumed with olestra-containing products; and gastrointestinal symptoms of diarrhea and cramping. The post-market surveillance was conducted to monitor: 1) adoption and use of olestra-containing foods; 2) changes in general food consumption patterns, especially related to savory snacks and the co-consumption of olestra-containing foods with fruits and vegetables; and 3) changes in nutritional status. Concerns about gastrointestinal effects were evaluated in randomized clinical trials, which demonstrated that ad-libitum consumption of olestra-containing snacks had effects no larger than those seen during pre-marketing studies. PMS consisted of: annual random digit dial surveys; annual cross-sectional studies measuring serum carotenoids and fat-soluble vitamins; and a cohort study of heavy olestra users carotenoids and vitamins. The study began in 1996 in the first large test market (sentinel site) and then in 3 large cities (national sites) following nationwide release. In the sentinel study, olestra consumption was associated with modest weight loss and significantly reduced serum lipid levels, and had no significant effects on serum carotenoid or micronutrient levels. Sale of olestra-containing foods was poor, and Proctor & Gamble stopped PMS in 2000. Results in the national sites differed from those in the sentinel site: there were no associations of olestra with weight or serum lipids, and there were small but statistically significant associations of olestra use with decreased serum carotenoids.

Invited Keynote Speakers

Post market monitoring of novel foods - an ILSI Europe expert group opinion

Anne Constable
Nestlé Research Institute, Lausanne, Switzerland

Anne Constable presented a paper on the Application of Post-market Monitoring (PMM) to Novel foods (Hepburn et al 2008, Food and Chemical Toxicology 46: 9-33). This paper had been developed by an expert group set up by the ILSI Novel Foods Task Force, in order to derive guidance as to in which situations the application of PMM might be warranted. The notion of history of safe use as used in novel food safety assessment, and the totality of data which may be required in order to perform an adequate pre-market assessment of a novel food was presented. Subsequent risk assessment informs on risk management decisions, the aim being to ensure foods are safe for intended uses. There is no mandatory requirement to perform formal PMM for foods. Case studies were presented to highlight possibilities and limitations of PMM schemes for foods. Available methodologies and data sources for investigating food consumption and health status, with requirements for generating data for a valid PMM, were discussed. PMM may have a role as a complement to, but not as a replacement for, a comprehensive pre-market safety assessment. Its major use may be to confirm that product use (e.g. intake, consumption patterns) is as predicted in the pre-market assessment. PMM might also be appropriate to provide reassurance that effects observed in the pre-market assessment occur with no greater frequency or intensity in the post-market phase than anticipated; and to investigate the significance of any adverse effects reported by consumers after market-launch. However PMM is insufficiently powerful to test the hypothesis that any effects seen in the pre-market assessment are absent in the post-market phase. Any PMM programme must be a hypothesis-driven scientific exercise. Requirements for a PMM would include sufficient power to ensure statistically valid interpretation, clearly defined study parameters and timelines, adequate traceability and reliable assessment of intake of the food/ingredient, appropriate expertise to carry out and evaluate the studies, and should be a transparent process. Current methodologies place limitations on what PMM can achieve. PMM should only be used when triggered by specific evidence-based questions.

Small Group Sessions

Interactive small group theme discussions were organised at the conference to enable participants to address speakers and other participants on specific subjects



Biotechnology: the making of new GMOs
TJ Higgins and Gerard Barry



GMOs in animal feeds
Peadar Lawlor and Gerhard Flachowsky



Post market monitoring of novel foods and GMOs
Alan Kristal



Allergenicity risk in GMOs in humans
Richard Goodman & Heimo Breiteneder



GMOs and human nutrition
Ashild Krogdahl & Candan Gurakan



GMO safety and Post market monitoring Panel Discussion

Armin Spök began by introducing all the Panelists. He declared that one cannot consider Post Market Monitoring (PMM) in isolation because it must be considered within the context of GM risk assessment. Before any GM food or feed is marketed, it must follow a risk assessment procedure, as described at the International level by the Codex Alimentarius guidelines (2003). PMM are then implemented at the National and EC level and should: 1. Take into account unintended and intended effects, and 2. Identify any changes relevant to human health.

The first question focused on **why PMM schemes were added to GM legislation.** Helmut Gaugitsch responded by saying that PMM was related to risk assessment. He said that EC member states wanted a case-specific PMM to complement risk assessment. The idea was that PMM would confirm the conclusions from the original risk assessment and that 'general surveillance' would address problems that were not predicted by risk assessment.

The chair asked for **comments on monitoring of GM feeds.** In response, Richard Goodman proposed that PMM for food is an evolving science. He recalled his participation at the 2001 Codex Alimentarius meetings when the guidelines for food safety and allergenicity were generated. Originally, there were concerns about gene technology but that GMOs now have good history of safety. Any PMM must be based on hypotheses that can be addressed. For example, a nutritionally improved product would need PMM for 2 reasons, 1. To assess effectiveness and 2. A possible inadvertent secondary metabolite that may have toxic effects. However, he emphasized that pre-market risk assessment would be able to detect these possibilities. He remarked that there was never an intent to consider general PMM for all GMOs for all aspects of food safety. He noted that conventional breeding may lead to exchange of large sets of genes, or parts of chromosomes or gene breakages induced by radiation and other types of mutagenesis and that these cases do not undergo PMM. T.J. Higgins added that conventional breeding can be between within the species, across species or even across genera. For example, a commonly used feed cereal, Triticale was derived from a cross between rye and wheat.

The chair stated that PMM of novel foods may be a potential model for GMOs. He asked for **comments on PMM in novel foods and food safety in the last 3 decades.** Gerard Barry said there is a lot of PMM in nutrition. He gave an example of iodine deficiency in some countries as a result of reduced use of iodized salt but this and other PMM are hypothesis driven. That is, it is clear what effects are being sought and measured. Alan Kristal mentioned the melamine adulteration of milk in China and recent infectious contamination of fresh vegetables. His point was that these scares are always acute and that they affect a certain number of people that makes the occurrence unusual and it triggers an investigation.

The surveillance systems for these unusual

GMO safety and post market monitoring panel discussion
From left to right: Alan Kristal, Peadar Lawlor, T.J. Higgins, Richard Goodman, Armin Spoek, Helmut Gaugitsch, Ashild Krogdahl, Yves Bertheau, Gerard Barry, Gerhard Flachowsky

events are well established especially for clusters in time and space. The most complex example that he could think of is mad cow disease. It took a long time to identify the contaminant and that it affected humans. He posed a crucial question; **can surveillance be maintained for unintended effects?** Especially, for those in which the effects are not acute and rapid and if they are vague, e.g. cancer, diabetes or cardiovascular risks. His answer was that he thought that it would never be possible to detect such risks. Gerhard Flachowsky confirmed that the BSE crisis, Foot and Mouth disease, and other problems with animals were addressed quickly and mentioned that EFSA was established to deal with food safety.

Peadar Lawlor added that the fullout from dioxin contamination crisis in Ireland was reduced due to the routine measurement of dioxins in insects. As a result, the monitoring identified dioxin contamination in pig meat early before extensive damage was done to the market.

Several incidents and scares in the last decades have led to an increased perception of food safety and changes in food safety regulation. The chair asked for **opinions on hypothesis-driven and an untargeted general surveillance in relation to food.** Alan Kristal, reiterated that a hypothesis driven approach is a clearly justifiable scientific method while untargeted general surveillance is problematic because it is not possible to identify unknown risks. Richard Goodman used food allergy as an example suggesting that some untargeted PMM approaches are successful. The labelling of foods for peanuts is an important safety approach handled by industry. Alan Kristal again voiced that there are only two approaches, one is hypothesis driven from reverse reporting or is hypothesis driven to begin with. He proposed that non-targeted general surveillance is not justified. Helmut Gaugitsch pointed out that there are predicted and unpredicted effects but that predicted risks are more important than the unpredicted risks because there is no hypothesis for unpredicted risks e.g. colony collapse disorder. It is important to identify the adverse event and backtrack it to the incident. Ashild Krogdahl supported this notion and pointed out that Norway has a lot of surveillance programs for adverse effects of food. Backtracking is important for finding causes there too. Historical data is important for finding certain factors. Yves Bertheau talked about case-specific monitoring and about traceability and sanitary issues. In China, the reduction in pesticide use in GM cotton led to increased insect attack on trees. It was an unexpected effect of GM cotton. There are always unexpected, unpredicted effects and thus, there has to be general surveillance. There is no mandatory requirement for PMM by EFSA although there is a recommendation for case-by-case consideration. Gerhard Flachowsky described the EFSA guidelines. Both risk assessment and risk management are important and if there are problems without clear answers, EFSA recommends that the EC conduct PMM.

Armin Spök asked whether anyone **can anticipate which GMOs should be tested by PMM?** Richard Goodman suggested that a low allergenicity peanut would have to be followed by PMM. Alan Kristal suggested that the PMM could be managed if it addresses the following: "Is the product being used the way that you thought it would be used, in the amount that you thought that it would be used, by the people you thought would use it". If you go beyond this and ask whether there is a health consequence related to its use then it becomes enormously difficult.

Armin Spök proposed that there is a distinction between effectiveness and safety. Gerard Barry remarked that effectiveness monitoring functions well for dietary supplements, fortifications, and others that are not necessarily GMOs. Ashild Krogdahl suggested that it is important to assure the general population that their food is safe. PMM would be helpful for the general population. Gerard Barry pointed out that the adverse event reporting works.

What would you consider the **remaining challenges and limitations for PMM?** Richard Goodman pointed out how difficult it is to deal with the food supply and the safety of a new commodity. For example, Kiwi fruit was introduced into the USA for 11 years before it was shown to be allergenic for some people. Exposure is almost impossible to follow. Peadar Lawlor mentioned that

veterinarians or animal nutritionists can do PMM on farms although it is hard to follow all feed ingredients because diets for animals are formulated on a least cost basis and their ingredients content is likely to vary greatly even in the short term. For this reason, a GM feed ingredient may be present in an animal diet this week but not the next. He suggested that there was a need for new methods to detect adverse events. Yves Bertheau suggested that using the Internet more broadly for following adverse following the introduction of new foods could be useful. A major hurdle is that the costs of PMM are extraordinary and it is not clear **who should bear the costs for PMM**. Gerard Barry mentioned that there is a survey of food / dietary intake every 5 years in the Philippines and that the government bears the costs. Richard Goodman pointed out that it is the consumer who will pay and that general surveillance is too expensive and should be restricted.

In conclusion, Gerard Barry reiterated that PMM on fortified foodstuffs is in place for effectiveness but is hypothesis driven. Ashild Krogdahl thought that it is necessary for more surveillance on emerging risks because she could not see how to identify emerging risks if there is no surveillance in place. Helmut Gaugitsch suggested that the approaches to environment monitoring and food safety monitoring could learn from each other. Richard Goodman reiterated that the focus on risk assessment should be on the next generation of GMOs because the first generation of GMOs are as safe as conventional products and suggested to focus on robust pre-market risk assessment. TJ Higgins said that there are 300,000 higher plants and 80,000 are edible and pointed out that our discussion was addressing about 10 GM plants. Peadar Lawlor said that safety is important and our regulators should ensure the food supply is safe but this has to principally come from pre- market assessment. Alan Kristal concluded by pointing out that money should not be wasted on PMM unless it is justified. You need a reason to do PMM.

Some impressions from the GMSAFOOD Conference

In the autumn last year Michelle Epstein ask me to participate in the "GMO-Safety and Post-Market Monitoring (PMM)" conference in Vienna, organized by the Medical University of Vienna, and to review the topic feeds from GM crops in animal nutrition. I was absolutely surprised about this meeting and my invitation because of different reasons like, that the organisation of such a meeting was being done by a Medical University and that the organisation of the meeting was being done in Austria, which is known for its critical attitude to GMOs and because the of the other invitations to speakers with different thinking about GMOs. Later I learnt what the background of the conference was and I agreed to review the current knowledge on GM-feed from the perspective of animal nutrition. The participation in the meeting was a large gain for me for many reasons including some presentations with very interesting results from the studies in the research project of the 7th-EU-framework. Especially interesting were the studies in pigs, salmon and rodents. Additional talks such as the fate of DNA and newly expressed proteins, sugar coated proteins in legumes and biomarker search strategy were also interesting to me. The organisation of the meeting was excellent. There was sufficient time for discussion with interested participants and for scientific talks. There was a small group discussion session with various themes and a GMO-safety and post market monitoring panel discussion, which were open for all interested in such topics. The press conference was also open for all interested in the topics. There was a broad spectrum of participants including scientists, administrators, NGO´s, industry, etc. and interesting science-based and disciplined discussion between them all. The well-organised social events especially the „Welcome-reception" in the Institute Francais and the „Heurigen dinner" in a typical Viennese Winery were enjoyable. All in all, the meeting had a kind atmosphere between participants from 16 countries. During the by-programme, there was ample opportunity for fruitful talks and discussions with scientists, well-known from the scientific literature. Most presentations were characterized by a high scientific level starting with an excellent review about the present stage of GMO-research, cultivation and future crops, followed by many detailed reports about GM-products in the food chain, evaluating the potential allergenicity of GMOs intended food use, EU and international guidance of risk assessment and post-market monitoring of GM food and feed. The Panel discussion summarized important results of the conference and came to the conclusion that the risk assessment is the most important aspect of GMO-safety assessment. Presently, there seems to be no need for PMM with GMO of the first generation in the food chain (GMcrops with input traits). Finally, it is a real pleasure for me to thank Michelle Epstein very much and her international team for the excellent organisation of the GMSAFOOD Conference and to wish her much scientific success and yield in her future work.

Gerhard Flachowsky
Institute of Animal Nutrition,
Braunschweig, Germany

This experience in olestra PMS informs plans for post-marketing surveillance of GM foods in several ways. First, epidemiological studies with health-related outcomes are expensive: the olestra PMS cost over US $27 million. Second, rigorous PMS requires a study design that addresses specific hypotheses: these should be based on what is known from pre-market studies. Third, there are many challenges to PMS which include accurate and unbiased assessments of exposures and outcomes, as well as inherent limitations in observational epidemiological research related to measurement error, selection bias and confounding. The design of these studies does not follow standardized procedures used to test the safety of pharmaceuticals, and there is an important role of judgment in the analysis and interpretation of data. Fourth, PMS cannot address rare or unanticipated outcomes, such as changes in cancer or cardiovascular disease risk. When not specified a-priori, differences between exposed and not-exposed persons cannot be distinguished from chance.

Alan Kristal
Seattle, USA

www.GMSAFOODproject.eu

For further information please contact:

secretariat@gmsafoodproject.eu

Peadar Lawlor
Teagasc, Irish Agriculture and Food Development Authority, Pig Development Department, Animal & Grassland Research & Innovation Centre,
Moorepark, Fermoy, Co.Cork, Ireland
Phone: +353 25 42217
Fax: +353 25 42340
Email: peadar.lawlor@teagasc.ie

Åshild Krogdahl
Norwegian School of Veterinary Medicine
Gut and Health Group of the Aquaculture Protein Centre
P.O. Box 8146 Dep,
NO-0033 Oslo, Norway
Phone: +47 22964534
Fax.: +47 22597310
Emil: ashild.krogdahl@nvh.no

TJ Higgins
CSIRO Plant Industry
Clunies Ross St, Black Mountain
Canberra ACT 2601 Australia
Phone: +61 2 6246 5001
Fax: +61 2 6246 5000
Email: Tj.Higgins@csiro.au

Éva Gelencsér
Central Food Research Institute
Department of Food Safety
H-1022 Budapest, Herman Ottó út 15.
Phone: +36 1 225 3342
Fax: +36 1 225 3342
Email: e.gelencser@cfri.hu

Michelle Epstein
Medical University of Vienna
Department of Dermatology, DIAID, Experimental Allergy
Währinger Gürtel 18-20, Room 4P9.02,
A1090, Vienna, Austria
Phone: +431 40160 63012
Fax: +431 40160 963012
Email: michelle.epstein@meduniwien.ac.at

Thank you

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