







Science Strategy

2012 - 2016

Committed to ensuring that Europe's food is safe

efsa
European Food Safety Authority

Science Strategy

OF THE EUROPEAN FOOD SAFETY AUTHORITY FOR

2012 - 2016

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1 Executive Summary

Since its inception in 2002, EFSA's scientific advice has been central to European decision-making on the protection of the consumer against threats in the food chain. In the intervening years, the Authority's operating context has evolved considerably, driven by, for example, scientific and technological advancement and the changing legislative framework and, as the organisation has matured, its scientific capacity has developed considerably. These evolutions are reflected in EFSA's scientific work programme where in recent years the emphasis has increased towards the evaluation of regulated products and where the assessment of environmental risk and risk-benefit and the post-market monitoring of authorised products are more prominent.

This strategy has been guided by and will complement EFSA's corporate *Strategic Plan 2009-2013*. It has been built through a process of extensive consultation, internally with EFSA's Scientific Committee, Advisory Forum, Management Board and staff and its various stakeholders.

It begins by stating its vision, taking stock of what has been achieved in its first ten years of existence and then explores the drivers for progress and change: the evolving European policy context; the nature and volume of EFSA's workload and, briefly, the economic context, with the prospect of a stable budgetary situation for the duration of the strategy and the possibility of EFSA receiving fees for some of its work. In this manner, the strategy identifies the key challenges and future demands on the organisation.

Next the document lays out how EFSA will continue to support the European food safety system over the next five years and meet the demands that are placed upon it. The document explains why EFSA has selected certain strategic priorities and how it plans to make the best possible use of the resources at its disposal.

In the coming five years, EFSA's scientific activities will focus on four key strategic objectives:

- further develop excellence of EFSA's scientific advice;
- optimise the use of risk assessment capacity in the EU;
- develop and harmonise methodologies and approaches to assess risks associated with the food chain;
- strengthen the scientific basis for risk assessment and risk monitoring.

This ambitious strategy will ensure that EFSA can continue to support the European food safety system in the coming years through up-to-date, science-based risk assessments. In so doing, it contributes to improving the health and welfare of humans and animals as well as plant health. Through its contribution, EFSA fulfils not only its mission to protect consumers but also provides food operators with a regulatory environment which is not only demanding but also predictable. This fosters technological innovation, thereby supporting sustainable growth.

To practically support the implementation of these objectives, a number of key initiatives are proposed, one of which is to enhance the contribution of EFSA staff to support the scientific work of the EFSA Scientific Committee and Scientific Panels.

The strategy will remain a "live document" that will be regularly reviewed to adjust the strategic direction in line with changes in the working environment. Progress in implementation will be assessed annually against EFSA's corporate key performance indicators and any remedial actions will be included in the multi-annual work programme and annual management plans of the Authority.

2 Vision for EFSA's Scientific Work

EFSA is recognised as providing Europe with the best scientific advice that enables timely decision-making to protect consumers from food-related risks and support healthy dietary choices as well as improve animal health and welfare and plant health.

The Founding Regulation[1] of the European Food Safety Authority (EFSA) defines the principles of risk analysis, putting these in the European context and giving the responsibility for independent risk assessment at a European level to EFSA[2]. The Authority's overall mission is two-fold: to deliver independent, high-quality and timely scientific advice on risks in the food chain from farm to fork in an integrated manner and to communicate on those risks in an open manner to all interested parties and the public at large. The present document concerns the core task of delivering scientific advice whereas the communication of this advice is addressed in EFSA's *Communications Strategy 2010-2013*[3].

This document sets out how EFSA aims to further strengthen its scientific work in line with its mission through 2016. It does so by taking stock of what has been achieved thus far, identifying the key challenges, describing what the main goals are and how it aims to achieve these goals.

EFSA has developed this strategy over the past year through workshops with its staff, discussions with the Scientific Committee, Management Board and Advisory Forum, input from other stakeholders and through a public consultation. An external study was commissioned to identify with EFSA's stakeholders, including the Commission, scientific experts and national authorities, the key issues the Authority must address to develop its future scientific direction[4]. The issues raised in these discussions have been incorporated into the development of the strategy.

01. Regulation EC No 178/2002 of the European Parliament and of the Council on 28 January 2002, laying down the General Principles and requirements of food law, establishing a European Food Safety Authority and laying down procedures in matters of food safety. Official Journal L 31, 1.2.2002, p.1-24.

02. Within its mandate, EFSA carries out a wide range of risk assessments, safety assessments, risk-benefit assessments and evaluations of risk assessment documents dealing with human and animal nutrition, animal health and welfare, plant health and the environment.

03. EFSA Communications Strategy 2010-2013: www.efsa.europa.eu/en/keydocs/docs/commstrategyperspective2013.pdf.

04. Support and Assistance in the Development of the European Food Safety Authority's Science Strategy 2010-2016. Author: Tony Hardy.

3 Where is EFSA Today?

Upon its creation, EFSA's initial priority was to put in place the necessary scientific infrastructure to enable it to deliver scientific opinions and advice in response to the requests it received. In this respect, the main focus was to establish the Scientific Committee and Scientific Panels, comprising independent experts selected for their expertise and experience to deliver scientific opinions. Initially, eight Scientific Panels were established but due to the evolution of the work, the number of Scientific Panels was increased to ten in 2008. Subsequently, EFSA has put in place the necessary internal scientific support, and in particular built data and information collection and analysis capabilities.

To ensure the high quality of its work, EFSA has developed guidance on methodologies for the risk assessment and the risk monitoring it undertakes. As laid down in its Founding Regulation, EFSA can initiate its own work (self-mandate). To date, EFSA has self-mandated on close to 100 occasions and this has in particular enabled it to develop fundamental approaches, methodologies and guidance documents. In particular, the Scientific Committee has developed documents to introduce general risk assessment approaches across the work of EFSA (e.g. guidance on transparency and uncertainty), on aspects of mammalian toxicology (the benchmark dose approach, the margin of exposure approach for compounds which are both genotoxic and carcinogenic) and on new or emerging areas (e.g. nanotechnology). Other areas have been principally developed by its Scientific Panels e.g. efficacy evaluation, environmental modelling and safety assessment, statistical approaches, exposure assessment methods, microbiological safety assessment, antimicrobial resistance, etc.

EFSA has begun to put in place a quality assurance system. It has established procedures for handling requests for urgent advice, initiated training on these and successfully used them on a number of occasions (e.g. melamine, dioxins, and the STEC (Shiga toxin-producing Escherichia coli) outbreaks) and has started developing processes to identify emerging risks, as foreseen in the Founding Regulation.

Since its inception, EFSA has also striven to work openly and transparently, relaying often complex scientific issues in a manner that is both accessible and useful to risk managers and other stakeholders. The Scientific Panels and the Scientific Committee have worked to ensure that scientific outputs clearly indicate what data or other information have been considered or disregarded and why, the nature and level of uncertainty, assumptions made; and any minority views that are held.

The strategic relationship of EFSA with the national food safety organisations is explicitly recognised in its Founding Regulation. Through the Advisory Forum, EFSA has established the foundation for its cooperation activities with the national food safety risk assessment and food research organisations throughout Europe. EFSA has set up Focal Points in the Member States and built nine European scientific networks (Annex 3) with its competent organisations thereby e.g. facilitating the exchange of risk assessment work. These have the objective of facilitating scientific cooperation. EFSA has established an Information Exchange Platform (IEP)[5] with the national authorities and set up a list of over 400 competent organisations in the Member States with whom it may cooperate under Article 36 of the Founding Regulation. The expenditure on grants and procurements for the outsourcing of preparatory and other support work has increased from 1 million Euros in 2007 to an expected 11 million Euros in 2012[6]. More recently, EFSA has developed cooperation with other European Union (EU) organisations, organisations in third countries and international organisations with mandates similar to EFSA's[7]. EFSA has built dialogue with its stakeholders and holds public consultations on key scientific opinions.

Since 2002, much has been achieved. EFSA has published over 2,500 scientific outputs which have been used by the European Commission, Member States and the European Parliament to underpin measures taken to protect consumers. These have had a significant impact both on regulated products, which are subject to pre-market authorisation, and on general public health issues like zoonoses or contaminants.

05. EFSA (European Food Safety Authority) 2011. Technical Report of EFSA. Information Exchange Platform-Evaluation Report. 2011:1 [59 pp.].

06. EFSA (European Food Safety Authority) 2011. Technical Report of EFSA. Follow-up to the 2009 evaluation report of EFSA's grant and science procurement schemes. 2011:1 [16 pp.].

07. EFSA's Strategic approach to international initiatives: www.efsa.europa.eu/en/keydocs/docs/intstrategy.pdf.

4 Drivers for Progress and Change

4.1 EFSA's *Strategic Plan 2009-2013* within the evolving European food policy context

EFSA's *Strategic Plan 2009-2013*[8] identified the overall vision of EFSA over this period including an assessment of how EFSA could reach its strategic goals. It assessed the external and internal challenges presented by the changing expectations and requirements of EFSA's stakeholders, advances in science and technology, workload and the types of issues faced by EFSA, particularly in relation to evolving European-level policies. It also addressed emerging issues of relevance for EFSA such as climate change and the changing demographics of the European population. Also, the overall trend in international trade has continued to rise with an increasing range and volume of imports from emerging markets of primary products, food products and ingredients[9], leading to an increased number of requests for scientific advice to be delivered by EFSA.

Since the adoption of the *Strategic Plan 2009-2013*, the EU's-policy objectives have re-emphasised the importance of innovation as a means to increase the competiveness of Europe within the framework of the EU 2020 Agenda[10]. They have also highlighted the need to ensure food security both within Europe and internationally[11], the need for environmental, social and economic sustainability, and the specific needs of the aging population[12].

08. EFSA's Strategic Plan 2009-2013: www.efsa.europa.eu/en/corporate/pub/strategicplan.htm.

09. Eurostat publication: *External and intra- European Union trade Data 2004-2009*, issued on 17 January 2011, page 20: http://epp.eurostat.ec.europa.eu/portal/page/portal/product_details/publication?p_product_code=KS-CV-10-001.

10. European Commission: *Europe 2020-a strategy for smart, sustainable and inclusive growth*: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2010:2020:FIN:EN:PDF.

4.2 Nature and volume of scientific work

In line with the scope and aims of EFSA's Founding Regulation (EC) No 178/2002, EFSA's mission relates to scientific advice and scientific and technical support for the Community's legislation and policies in all fields which have a direct or indirect impact on food and feed safety. Regulation (EC) No 178/2002 applies to all stages of production, processing and distribution of food and feed. The evolutions described above may affect the nature, fluctuation and volume of EFSA's scientific work. Since 2002, the demands on EFSA have changed and its output has substantially increased (Annex 1). The resources committed to the evaluation of regulated products have doubled over the period 2008-2010 from 20% to 40% and about two-thirds of EFSA's annual scientific outputs now relate to applications. Currently available estimates show that the regulatory workload is expected to remain high. It should be noted however that the workload associated with a question may vary considerably and therefore the number of questions alone is not sufficient to indicate the workload. This is because the nature of the work at hand depends e.g. on the extent to which new information needs to be gathered. It is reflective, though, of the growing importance of the safety evaluation of regulated products such as genetically modified organisms, pesticides, food and feed additives, food flavourings, colours and contact materials. In addition, benefit assessments are made. For example, according to the EU legislation on health claims,[13] EFSA verifies the scientific substantiation of the health claims, rather than the safety of such products.

Compared to other European agencies undertaking safety assessments, the Founding Regulation of EFSA does not provide an overall regulatory framework for the evaluation of regulated products. Rather, the regulatory processes that form the basis for EFSA's evaluation activities of regulated products are defined in a large number of sector-specific regulations with different requirements. Since 2002, these have been subject to significant changes. As a result, the volumes and content of application dossiers to be processed in a specific area have been subject to such changes that it has been challenging to plan and allocate the appropriate resources, both within EFSA and for Member State organisations that work with EFSA.

11. European Commission (2010) 672 final: *The CAP towards 2020: Meeting the food, natural resources and territorial challenges of the future*, Brussels, 18.11.2010: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52010DC0672:EN:HTML.

12. European Commission (2010) 546 final: *Europe 2020 Flagship Initiative Innovation Union*, Brussels, 6.10.2010: http://ec.europa.eu/research/innovation-union/pdf/Innovation-union-communication_en.pdf.

13. Regulation (EC) 1924/2006

At the same time as the workload on regulated products (applications) has increased, the workload in the area of public health risks has also expanded due to major mandates such as the current one on meat inspection methods which covers microbiological and chemical food safety as well as animal health and welfare aspects for various terrestrial food animal species. EFSA will thus have to ensure that, not only the work on applications, but also the generic public health orientated aspects of its work as well as its work on emerging issues are carried out effectively.

Concomitant with the increasing workload, there is a shift in the nature and complexity of the scientific advice requested. In addition, innovation in scientific knowledge has resulted not only in new food and feed products and production processes but also in new techniques and risk assessment methods which need to be developed or validated in order to be considered for use by EFSA in its risk assessment work. The agri-food sector is increasingly innovative in the way it uses novel technologies; the assessment of the risk they may carry is potentially more complex. Further to this, there is an increasing trend for risk assessments to include assessment of issues that require a marked broadening of the scientific discourse, such as environmental impacts, occupational health, post-market monitoring, risk comparisons and health benefits.

4.3 Resources

The budget allocated to EFSA is expected to remain around existing levels. As provided for in the Founding Regulation, the possible introduction of fees for the regulatory reviews EFSA carries out is currently under consideration by the European Commission. Even though it is therefore possible that EFSA would receive fees for work associated with the evaluation of regulated products, the timing and overall implications of this on EFSA's budget is not known at present.

5 Meeting the Challenges: Four Strategic Objectives

Taking into consideration the challenges raised above, EFSA has identified four key strategic objectives which will provide the focus for its scientific activities over the coming five years. These strategic objectives for 2012-2016 are:

- Further develop excellence of EFSA's scientific advice
- Optimise the use of risk assessment capacity in the EU
- Develop and harmonise methodologies and approaches to assess risks associated with the food chain
- Strengthen the scientific evidence for risk assessment and risk monitoring

5.1 Further develop excellence of EFSA's scientific advice

Scientific excellence and the other core values

It is of utmost importance that the European consumer and other stakeholders can trust the quality of the science on which risk management measures are based. This quality reflects the degree to which EFSA has successfully implemented its core values of independence, scientific excellence, responsiveness, openness and transparency. EFSA aims to forge a reputation for the quality of its scientific advice which is recognised worldwide. Recognising that quality is inherent in our core values, EFSA has decided to implement an integrated Quality Management system by 2016. This system will build on the foundations established in follow-up of the Scientific Committee recommendations[14, 15], and will be fully compatible with the ISO 9001:2008 system.

Each of EFSA's core values is important in its own right and it is essential that the right balance be struck between these potentially "competing" core values.

Scientific excellence. While EFSA aims to provide high-quality scientific advice, it is however not a research organisation. Rather it draws on work carried out in such organisations and shares their standards for scientific excellence. The basis for the excellence of EFSA's scientific advice lies in the quality of its experts and the information and the methods available to address a given topic. These elements are further discussed in Objectives 2-4 below.

For EFSA to be relevant it is essential that it is **responsive** and uses its resources judiciously. Scientific excellence may compete with responsiveness e.g. in the case where urgent advice is needed. Rapid developments in workload in new areas may challenge the core values e.g. requiring guidance documents to be developed quickly. Scientific excellence is not an absolute concept but rather excellence also has to meet the expectations of those who will use the opinion i.e. be "fit for purpose" and developed to the extent necessary to meet this aim. To increase efficiency, it will therefore be important to continue to work with risk managers to ensure that questions and responses are framed in a manner that enables EFSA to optimise its risk assessment resources and the public health relevance of the outputs.

14. EFSA (European Food Safety Authority) 2006. Transparency in risk assessment carried out by EFSA: Guidance Document on procedural aspects. EFSA Journal 2006; 353 [16 pp.].

15. EFSA (European Food Safety Authority) 2009. Scientific Opinion of EFSA. Transparency in Risk Assessments-Scientific Aspects. Guidance of the Scientific Committee on Transparency in the Scientific Aspects of Risk Assessments carried out by EFSA. Part 2: General Principles. EFSA Journal 2009; 1051 [22 pp.].

In relation to **independence,** EFSA has put in place a comprehensive system to record and evaluate the declared interests of scientific experts and to manage any conflicts of interest. In new fields where expertise may be scarce and mostly in the hands of the organisations that have a commercial interest in developing the new technology, expertise which is viewed to be independent of these interests may not be readily available. At the same time, in order not to hinder technological innovation it is crucial that EFSA has appropriate access to the necessary expertise to avoid lagging behind in its scientific excellence. EFSA is currently updating its policy on independence[16] and will continue to update and communicate its systems and procedures for ensuring the independence of its work.

Transparency. Through open and transparent ways of working, EFSA will continue to ensure that its processes and the basis for its opinions are documented and understood. On such issues as transparently demonstrating how data provided to EFSA are used and managed, as well as the mechanisms by which an opinion is developed and scientific consensus is reached, EFSA still needs to develop further, including, for example, the documentation of its preparatory work, the weight of evidence, data gaps (and assumptions made to address them), the underlying uncertainties and their potential impact on the decisions to be made.

Openness and dialogue. Further progress on the interaction between EFSA and risk managers will improve common understanding of risk assessment parameters (including benefits and limitations) and risk management goals, thereby contributing to more informed decision making.

To maintain and build trust further, EFSA will need to continue to seek ways to build meaningful dialogue with consumers and other stakeholders in order to understand and address their risk perceptions and information needs and preferences, particularly related to new or complex scientific issues. For this, EFSA aims to strengthen the dialogue with all stakeholders on processes and adherence to core values. In doing so we will strengthen engagement and consultation between risk assessors and stakeholders. EFSA will also continue to perform public consultations on scientific opinions, particularly when preparing guidance documents, and by doing so collect views from various stakeholders, risk managers and risk assessors, including the global scientific community[17]. Existing mechanisms for dialogue with applicants concerning issues related to the application assessment process will need to be reviewed to improve dialogue with applicants. To implement this, EFSA has now created and is gradually building an applications help desk function for applicant companies (as well as any other stakeholders) regarding the assessment of regulated products.

16. www.efsa.europa.eu/en/consultationsclosed/call/110707b.htm

17. www.efsa.europa.eu/en/keydocs/docs/consultationpolicy.pdf

Integrated advice

Collectively, the scope of the Scientific Panels and Scientific Committee encompasses the entire food chain (Annex 2). The assessments carried out by an individual Scientific Panel vary in scope, depending on which of the following areas of risk and/or benefit assessment they do or do not routinely cover: human, animal, plant, or environmental health. The expertise present in each panel represents what is normally needed for that panel to carry out its work in assessing risks and/or benefits. Where new developments can be anticipated, EFSA will ensure and enhance multidisciplinary membership of concerned Scientific Panels, as well as the Scientific Committee, with each triennial membership renewal, to ensure all areas of expertise that are normally needed are covered. For example, a new technology which is originally to be in the remit of only the Scientific Committee or a single Panel may later be applied by other Panels.

As identified in EFSA's *Strategic Plan 2009-2013*, it is increasingly expected that risk assessments which consider risks in a wider integrated manner will be required in order to provide risk managers with comprehensive advice on which to base their decisions. When risk assessments have required a broader range of skills than may currently exist in one single Panel, EFSA has established joint work between Scientific Panels to ensure the full range of disciplines is available to build the risk assessment. This may also require inclusion of other European agencies e.g. the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) or the European Chemicals Agency (ECHA). In this respect, the Scientific Committee is assigned a crucial role through the Founding Regulation, in being formally responsible for Scientific Opinions on what are termed in the Founding Regulation as multi-sectoral issues. EFSA may need to adapt its operating procedures in order to be better able to accommodate a growing demand on the Scientific Committee in these areas.

The Founding Regulation gives the Scientific Committee the task of general coordination to ensure the consistency of scientific procedures, in particular with regard to the adoption of working procedures, the harmonisation of working methods as well as the responsibility to provide opinions on multi-sectoral issues falling within the competence of more than one Scientific Panel and on issues which do not fall within the competence of any Scientific Panel to ensure the consistency of all the main aspects of EFSA's scientific activities i.e. general risk assessment processes, mammalian toxicology, environmental health, microbial safety assessment methods, antimicrobial resistance, efficacy, novel and emerging issues and data collection and exposure assessment. This includes the review for consistency of guidance developed by a particular Scientific Panel.

The Scientific Committee is composed of the Chairs of the Scientific Panels and six additional scientific experts who do not belong to any Scientific Panel. This contrasts with the Scientific Panels which are composed of (up to) 21 scientific experts. Due to their particular responsibilities, the Chairs already have a high workload. Therefore, with the current number of non-Panel experts being limited to six only, it is important to find new mechanisms for enhancing the capacity of the Scientific Committee to meet the responsibilities assigned to it in the Founding Regulation. To support the Scientific Committee and foster consistency across Scientific Panels in these areas, EFSA has already created task forces of EFSA staff, most often, with Panel members. This has been the case for example with environmental risk assessment methods, antimicrobial resistance and statistical methods. Other means to reinforce the Scientific Committee may need to be explored.

Scientific outputs

EFSA scientific outputs are published in the EFSA Journal on a dedicated web area of the EFSA corporate website to disseminate them among the scientific community. The EFSA Journal is an open-access online scientific journal, which is free of charge. It has an editor-in-chief and is governed by an editorial board. The EFSA Journal is already indexed in various bibliographic databases relevant to EFSA's work such as Food Science and Technology Abstracts (FSTA), CAB Abstracts, SciFinder, ISI Web of Knowledge and library catalogues. It needs to be further developed to meet requirements of other key databases such as Web of Science (Thomson Reuters) and Medline. Over time this will provide tools to compare EFSA's scientific excellence through e.g. impact indicators.

EFSA will also need to integrate into its working practices the systematic collection of feedback from those mandating EFSA's opinion in order to ensure that the delivered advice is relevant and fulfils the needs of risk managers and other stakeholders without being over-comprehensive on the one hand or over-simplified on the other.

As food and feed safety continues to be of interest to a range of differing audiences, including such stakeholders as consumers, industry, non-governmental organisations (NGOs), etc., the outputs of EFSA not only have to be appropriate for risk management needs but also convey sufficient information presented in a relevant and accessible manner for other audiences. While EFSA publishes all its findings on its website and strives for transparency in its processes, it still faces challenges in ensuring that its findings are understandable to its stakeholders, target audiences and the general public. The clarity and usability of EFSA's scientific outputs will be kept under continuous review. In particular, EFSA will strive to enhance the clarity, consistency and framing of EFSA's outputs, tailoring better communications with a focus on thematic communication tools defined in the *Communications Strategy 2010-2013*[18].

18. EFSA Communications Strategy 2010-2013: www.efsa.europa.eu/en/keydocs/docs/commstrategyperspective2013.pdf.

5.2 Optimise the use of risk assessment capacity in the EU

EFSA's scientific expertise and capacity consists of the members of the Scientific Panels and SC, the Working Groups, the Authority's own scientific staff as well as the scientists in Member State institutions working with EFSA in cooperation activities through e.g. its networks as well as other forms of cooperation through grants and contracts. For EFSA to further increase its scientific output efficiently, while tackling the complexity of the scientific tasks at hand, it has to consider the planning and prioritisation of its work and, in light of these, how to optimise the input and engagement of these various sources of expertise.

Planning and priority setting

So that all areas of EFSA's remit are addressed adequately, reviewing and balancing priorities has to be done in a structured and transparent manner taking into consideration needs for review of regulated products, other health priorities and emerging issues by developing a prioritisation framework. Using risk monitoring and risk ranking studies[19], EFSA can assist risk managers, consumers and other stakeholders to develop prioritisation tools and criteria to help support the medium- and long-term planning of the Authority's work. EFSA needs to be able to identify and evaluate emerging issues, including new technologies, which may have an impact on the safety of the European food supply. Various activities have already taken place within EFSA to build its capability to identify and evaluate emerging risks. Learning fr om this experience EFSA needs to structure this further. To this end, EFSA will further develop a proactive, integrated and focused capability to identify and evaluate emerging issues. Greater scientific cooperation with national, European, international agencies, stakeholders in the food chain and key third countries will be particularly useful in addressing the specific risks posed by increasing international trade and travel.

19. Such as the studies conducted by the Dutch National Institute of Public Health and the Environment (RIVM, 2006; cf. www.rivm.nl/bibliotheek/rapporten/270555009.pdf) and in the framework of the EUGLOREH project in 2007 (cf. www.eugloreh.it).

EFSA has striven to predict, prioritise and plan all its scientific activities efficiently over the short and medium terms in collaboration with its key risk assessment and risk management partners. As the overall volume of requests for risk assessments continues to rise, open dialogue with risk managers on the quantity (total number and its variation over time), nature and complexity of the workload is ever more vital to enable EFSA to identify whether it has appropriate resources and specific expertise available and to plan priorities appropriately. While EFSA receives requests from the European Commission, Member States and the European Parliament, overall it is the European Commission which is the source of the majority of these at approximately 90%. As the bulk of EFSA's work is in response to requests from the Commission, it has been - and continues to be - imperative that EFSA develops and agrees principles and criteria for the prioritisation of its activities in conjunction with the Commission while ensuring that the needs and demands for its advice of its other key partners (the European Parliament, Member States) are met. Such medium- and longer-term planning with the Commission services has already been instigated. It will be essential for medium- and longer-term planning to become even more comprehensive and efficient if EFSA is going to be able to accommodate fluctuations in workload and anticipate the specific expertise it needs to fulfil these demands.

Scientific experts in Scientific Panels/Scientific Committee

The Scientific Panels and the Scientific Committee are composed of independent scientific experts who are not employed by EFSA but volunteer part of their time to this task. EFSA relies on them and their employers to engage in these activities at European level.

Members of EFSA's Scientific Panels are selected on the basis of an open call for expression of interests, with the best scientists who apply being chosen while providing a balance of expertise across a given scientific sphere of activity. The opinions adopted by the Scientific Panel are the outcome of collective deliberations and decisions, each member having an equal opportunity to express his or her views. EFSA also records, where appropriate, minority views in the opinions, as well as any specific interests that have been declared in the minutes of the meetings.

While the scientific expertise that is represented in the ten Scientific Panels and the Scientific Committee is core to EFSA's activities, it is finite and in some areas overburdened. It is essential that EFSA is able to continue to attract the best external experts available, by using this key resource judiciously.

As mentioned, the number of Scientific Panels has been increased from eight to ten. The number of Scientific Panels could conceivably be further increased where new areas of work emerge that are not already covered by a Scientific Panel. However, further increase in the number of Scientific Panels increases the need for coordination so as to maintain consistency in areas covered by several Scientific Panels.

A reduction of external experts' workload related to routine activities may be an effective way to increase EFSA's attractiveness to them. Hence, meeting the growing number of requests for advice will require EFSA to focus on further building as well as better utilising the internal scientific expertise among EFSA's scientific staff and outsourcing preparatory work. This may be particularly true for work that is repetitive but can be standardised, such as well-established regulatory review processes which require substantial preparatory work. It will enable the Scientific Panels and Scientific Committee to focus more on novel and critical scientific issues, including guidance development, while assuring that the same levels of scientific excellence and independence are maintained. This will not only help EFSA to maintain its attractiveness to high-level external scientific experts but, at the same time, enable EFSA's and Member States' scientific staff to utilise to the full the breadth of their scientific knowledge and expertise.

Internal scientific expertise

EFSA has already built capacity among its own staff and established dedicated units to provide preparatory scientific support at the various stages of the scientific work: collection and analysis of data and information including literature review and exposure assessment and modelling. There is also substantial internal support in dossier evaluations and in the preparation of draft outputs. Through the streamlining of its administrative and scientific processes (e.g. efficiency of meetings), EFSA aims to increase the proportion of its scientific staff from 60% to 70%. This will increase the level of support for the work of the Scientific Committee and Scientific Panels.

There will however be a need for enhanced developmental training on risk assessment for EFSA's staff, along with external experts, including a need for greater engagement with the wider scientific community. EFSA will launch a knowledge management project to enhance working practices among EFSA's external experts and scientific staff by putting in place professional development initiatives and increasing scientific training. Specifically, EFSA will implement a tri-annual programme for sharing of best risk assessment practices between scientific staff and external experts of EFSA (2013-2015). In this, the Scientific Committee is expected to have a leading role.

Cooperation with organisations in Member States

With the resource limitations that are anticipated, it is essential that duplication of work be avoided. Coordination with organisations in the Member States, the sharing of work programmes and the use of joint initiatives will have to be continually improved in order to make the best use of available capacity and resources throughout Europe.

Through the implementation of the EFSA *Strategy on Cooperation and Networking with Member States*[20], grants and contracts have been put in place with scientific organisations in the Member States since 2007. EFSA aims to further develop outsourcing for various preparatory tasks, including in the area of review of regulated products by bringing investment in scientific cooperation with Member States. This activity will need to rely heavily on medium- and longer-term planning to support the needs of EFSA's risk assessment work[21, 22].

Increasing the involvement of MS' scientific organisations will contribute to maintaining and building their capacity. However, building capacity for the future will require such initiatives as training and developing expertise directly linked to the risk assessment process. EFSA has already investigated how training programmes could be organised within the context of the EU[23, 24]. As further discussed in the next section, EFSA will also identify and work on key initiatives for the harmonisation of existing and the development of new methodologies and approaches. More generally, it is necessary that the concerned organisations all adhere to the same core values.

20. EFSA Strategy on Cooperation and Networking with Member States (2006), www.efsa.europa.eu/en/keydocs/docs/msstrategyreview.pdf.
21. Scientific Cooperation between EFSA and Member States: taking stock and looking ahead (brochure) (www.efsa.europa.eu/it/corporate/doc/mediumtermplanning.pdf).
22. EFSA (European Food Safety Authority) 2011. Technical Report of EFSA. Scientific Cooperation between EFSA and Member States: taking stock and looking ahead (57pp.).

Cooperation with EU agencies, international organisations and organisations in third countries

While maintaining its cooperation with national organisations through its EU networks, EFSA also needs to cooperate with other European scientific organisations, international organisations and agencies in non-EU countries on topics of common interest in order to share the workload and avoid unnecessary duplication of work and inconsistencies. This activity would benefit from a more structured medium-term approach through the development of cooperation with European agencies (ECDC, ECHA, EMA) and international liaison groups in the area of food chemical and food microbiological safety, with a view to optimising the utilisation of resources. EFSA will in particular work with key partners on initiatives for the harmonisation of existing and the development of new methodologies (see next section). It will take the lead, where appropriate, in the development, harmonisation or implementation of risk assessment approaches. In addition, EFSA may engage in joint projects carried out with partners in the area of chemical risk assessment (e.g. the Joint Research Centre (JRC), ECHA, World Health Organisation (WHO), US Environmental Protection Agency (USEPA), US Food and Drug Administration (US FDA) and the Organisation for Economic Cooperation and Development (OECD)) and microbiological risk assessment (e.g. ECDC, US Center for Disease Control and Prevention (CDC), and US Department of Agriculture (USDA).

23. EFSA (European Food Safety Authority) 2011. Technical Report of EFSA. Technical specifications on training regarding principles and methods of food safety risk assessment. [22 pp.].

24. The European Commission's training programme on Food Safety Risk Assessment - Better Training for Safer Food and other similar initiatives will be useful in this respect.

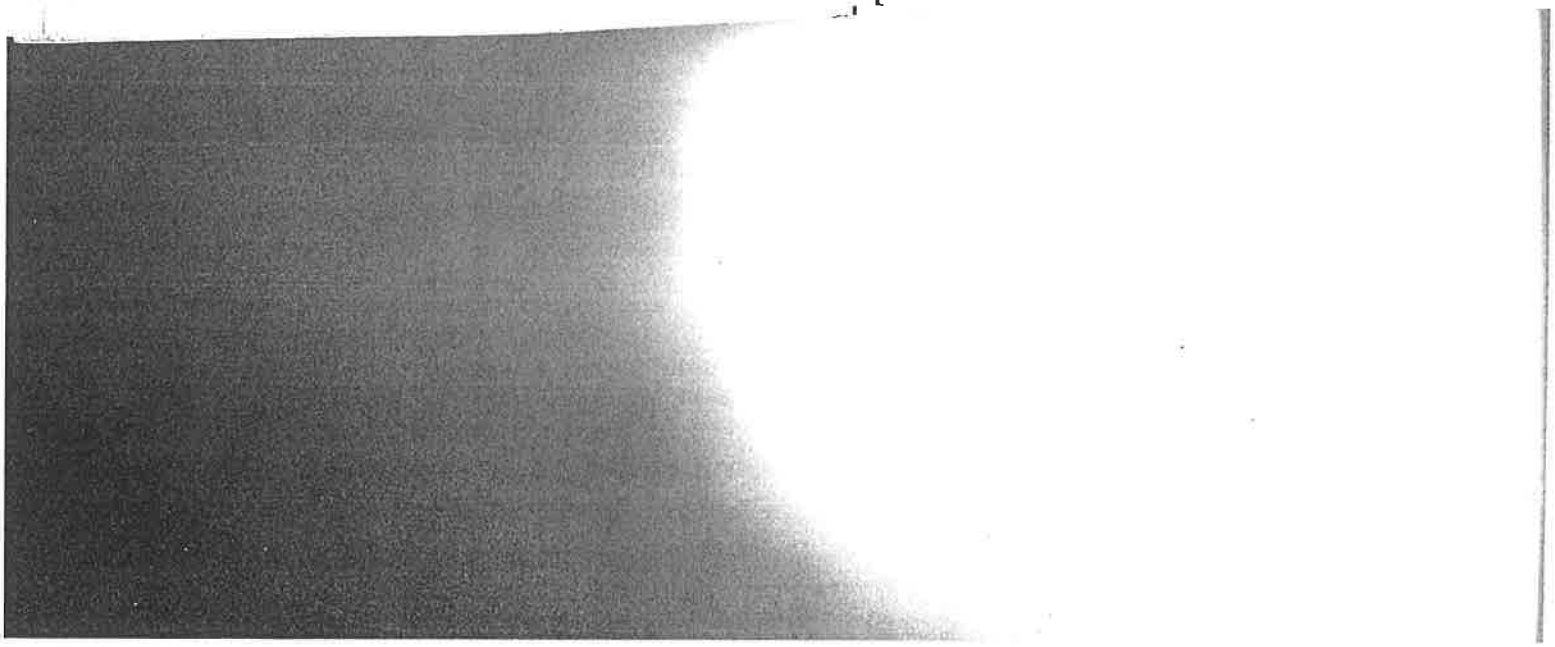
5.3 Develop and harmonise methodologies and approaches to assess risks associated with the food chain

Harmonisation

Although major progress has already been made during the last decade in the development of internationally harmonised risk assessment methodologies, there is still a need for further harmonisation between various domains within EFSA, with the Member States, with other EU agencies as well as at the international level. For example, the work towards improvement and harmonisation of risk assessment terminology, such as for addressing uncertainties (expressing these with transparency and relevance), needs to be reinforced.

EFSA will also strengthen the dissemination of cross-cutting guidance through training programmes for EFSA scientific experts and staff to ensure the uptake of guidance on cross-cutting risk assessment approaches.

Also the diversity and number of regulatory processes for the assessment of regulated products may need further consideration. While differences in legislation may be necessary, the current situation is challenging the efficiency of EFSA's scientific processes and the diversity makes it difficult to standardise the handling of dossiers and invest IT resources. In this regard, EFSA can contribute by identifying opportunities for harmonisation of methodologies across regulated areas within EFSA and possibly beyond (EMA, ECHA) and share its view as legislation is under preparation or being revised regarding their potential impact on efficiency and effectiveness of regulatory review processes.



New risk assessment methodologies

EFSA's *Strategic Plan 2009-2013* identifies the need for EFSA to be at the forefront of the development and implementation of risk and benefit assessment methodologies and practices in Europe and internationally.

This includes a broadening of the scientific discourse beyond safety and into areas such as health benefits and environmental risk assessment. In addition, there is a need to gradually move from an approach whereby a single chemical is assessed individually using a set of standard protocols (involving the use and sacrifice of numerous laboratory animals) for a particular use to a system which takes into account prior information, other routes of exposure, and the potential impact of other effectors. Taking into account available information about related chemicals may lead to tiered approaches for targeted testing protocols, thereby increasing the efficiency and effectiveness of safety evaluations. These concepts are further discussed in the Scientific Committee Scientific Opinion on the Threshold of Toxicological Concern[25]. The use of pragmatic, science-based approaches in EFSA has already begun. In the area of risk assessment of micro-organisms, the Scientific Committee adopted an opinion on the use of the Qualified Presumption of Safety (QPS) approach for setting priorities within the risk assessment of microorganisms used in food/feed production referred to EFSA (EFSA, 2007)[26]. This practical risk assessment approach meets the need of EFSA to assess the safety of large numbers of micro-organisms deliberately added to food and feed within an acceptable time frame.

25. http://www.efsa.europa.eu/en/consultationsclosed/call/110712a.htm

26. http://www.efsa.europa.eu/en/efsajournal/pub/587.htm

The potential simultaneous exposure to a multitude of hazards (chemicals, micro-organisms and other effectors) possibly through different routes also highlights the necessity to move beyond the single hazard approach and consider e.g. exposure to chemical mixtures. The EFSA Scientific Panel on Plant Protection Products and their Residues (PPR) has already elaborated a framework for the human risk assessment of mixtures of pesticides and applied it to triazole pesticides. Other Scientific Panels have also dealt with the risk assessment of chemical mixtures, but in these situations specific approaches were developed rather than a general framework. Other bodies, such as the US-EPA and WHO, have also developed frameworks for mixture toxicity assessment. EFSA is currently carrying out a critical review of such frameworks[27]. It will serve to support the further development of a harmonised and consistent approach for the human health risk assessment of chemical mixtures in food and feed.

In addition, the emergence of new technologies (nanotechnologies, new breeding techniques) may require existing risk assessment methods to be revised. In these new areas of work, EFSA will need to work closely with the European Commission's scientific services (DG-RTD and the JRC) and other scientific organisations and experts to maintain its overview of scientific progress which may have an impact on EFSA's risk assessment methods. In addition, through its series of Scientific Colloquia EFSA will continue to have an open scientific debate prior to developing or finalising new methods and guidance.

In light of the above and following consultation with key partners, EFSA will establish a multi-annual work plan on guideline review and development which takes into consideration work carried out elsewhere. In developing new methodologies, EFSA will continue to closely liaise with and provide assistance and advice to risk managers so that these new methodologies and approaches are adequately reflected in legislation.

Harmonisation of approaches on regulated substances

To improve the clarity and efficiency of the evaluation of regulated substances, current processes may need to be streamlined, where appropriate.

27. Internal Mandate proposed by EFSA to the EMRISK Unit for a Scientific report on international frameworks dealing with the human risk assessment of chemical mixtures.

5.4 Strengthen the scientific evidence for risk assessment and risk monitoring

EFSA's *Strategic Plan 2009-2013* identified the long-term need for EFSA to have access to high-quality scientific data to ensure that it is able to deliver scientifically robust assessments of risk and to identify emerging issues.

Regulatory reviews

For risk assessments concerning authorisations, EFSA most often receives comprehensive data and information from applicants (individually or as a consortium). The information to be provided by applicants is described in guidance documents and test protocols, including quality standards that need to be adhered to. This is not to say that other available scientific information will not be considered. For example, EFSA's new guidance document for applicants seeking approval of active substances in pesticides explicitly requires that studies found in peer-reviewed open scientific literature should be considered. The fact that particular standards, such as Good Laboratory Practices (GLP), need to be adhered for industry-sponsored studies should therefore not be equated to a refusal to consider evidence that would have come from non-GLP studies.

Data collection

For other assessments, all information generally has to be collected by EFSA itself, prior to it being able to conduct the risk assessment. EFSA does not generate these research data itself but rather relies on other organisations that have generated this information.

It is vital for EFSA to possess or have access to the right data to address key issues at the right time. In order to obtain data of adequate quality it is essential that data collection is planned over the medium to longer term[28]. For this it is necessary to develop multi-annual work programmes focused on filling data gaps and setting priorities for data collections.

EFSA's data collection for human exposure assessment generally relies on monitoring activities at MS level. The exposure assessment work uses on the one hand microbiological or chemical occurrence data and on the other hand food consumption information. EFSA has launched a key project on harmonised food consumption data collection (EUMENU)[29, 30], which aims to support harmonised food consumption data collection across the EU. EFSA's current annual and ad hoc occurrence data collection activities have begun to provide much of the basis for its microbiological and chemical risk assessment and risk monitoring activities. As is already the case for pesticide residues, it is envisaged that annual risk monitoring reporting will not only concern occurrence but also include exposure assessments.

Whereas the focus in the occurrence monitoring has initially been on microbiological and chemical contaminants, it is broadening into monitoring of chemicals which are subject to a marketing authorisation, such as plant protection products or food additives. This allows for assessment of whether the exposure envisaged at the time of marketing authorisation matches the true exposure when marketed (Annex 4).

Regular review of these activities in terms of representativeness, accuracy and compatibility is required to sustain the quality of the data. Also, further optimisation and priority setting of the collection of these data will be required

28. EFSA (European Food Safety Authority) 2010. Technical Report of EFSA. EFSA Report on Data Collection: Future Directions. EFSA Journal 2010; 8(5):1533. [35 pp.].

29. www.efsa.europa.eu/en/press/news/datex100212.htm

30. www.efsa.europa.eu/en/efsajournal/pub/1435.htm?wtrl=01

e.g. broadening of the investigation and reporting of food-borne adverse effects beyond microbiological hazards and into chemicals - including e.g. allergies; building of the harmonised food consumption database based on harmonised food consumption surveys conducted across the EU giving consideration to initiatives such as food composition data, total diet studies, data linked to the health status of the European citizen over time, use of bio-monitoring tools, and targeting subpopulations potentially more highly exposed - such as children[31] or groups that are more susceptible.

It is also important to identify where new areas for the harmonised collection of scientific data are needed. EFSA will aim to set priorities for the extension of the evidence base for risk assessment and risk monitoring, in collaboration with key partners and key organisations[32], for example with regards to the monitoring of any impact (including potential environmental effects) of compounds subject to pre-marketing authorisation.

EFSA needs to be able to assess risks resulting from the increasing worldwide trade of foods and related commodities, travel, migration and climate change. For this it may need to further expand and develop data collections itself or support other organisations, including international organisations such as e.g. European and Mediterranean Plant Protection Organization (EPPO) or World Organisation for Animal Health (OIE) through international scientific data collection networks as well as those at the European level. EFSA already cooperates with third country and international food safety bodies and this activity will continue to be important for EFSA to be able to develop clear insights in human, animal and plant health risks related to international trade in food of plant and animal origin as well as feed.

As it will also develop further with partners formalised data generation, collection and collation methods and protocols, there is a need to strengthen data sharing and data access agreements with other key national, European agencies (e.g. ECDC, EFSA, EMA) and international organisations (e.g. FAO, WHO, OECD).

31. EFSA (European Food Safety Authority) 2011. Technical Report of EFSA. Activities, Processes and Quality Assurance Elements on Data Collection Programmes with Member States. Supporting Publications 2011:127. [57 pp.].

32. EFSA (European Food Safety Authority) 2011. Technical Report of EFSA. Advisory Forum Discussion Group on Data Collection (to be published).

Scientific literature and reports

EFSA will ensure efficient access to and processing of information from scientific literature and unpublished scientific studies. For this, EFSA needs to further boost its capacity and efficiency to support EFSA's Scientific Committee and Scientific Panels to monitor and screen new scientific information and provide systematic literature review.

One element that needs further development concerns the establishment of a system to regularly identify and take stock of new information and identify new data which could require re-consideration of existing opinions. To be efficient and effective, the stock-taking of new evidence is a process which EFSA, in close liaison with the risk managers, plans to carry out in a structured, rather than ad hoc, manner.

Access to studies and risk assessment work of other organisations carrying out work in EFSA's remit is also needed. This also requires that the IEP and cooperation networks permitting information sourcing and sharing be further expanded e.g. international organisations such as WHO. To take into account the full breadth of risk assessments, EFSA has taken the initiative to develop a database for hazard characterisation, to be built in liaison with other agencies. In addition, it is acknowledged that not all relevant information is available as scientific documents. Other sources may need to be consulted, e.g. trade data and expert knowledge.

Research

Completed research projects are obviously an important source of data and information to which EFSA needs timely access, e.g. access to articles in print or key findings from EU funded projects. Such timely access may compete with the timelines for publication in peer-reviewed journals.

Future data needs may also necessitate the conduct of new research. EFSA, with its Scientific Committee and Advisory Forum, already contributes to the development of research priorities at the European level. Detailed forward planning with public research organisations in Member States and with European Agencies, the European Commission's Directorate General on Research and Innovation (DG-RTD) and the Joint Research Centre of the European Commission (JRC) is indeed important if information needs are to be filled including, as discussed, research needed on assessment methodologies to keep up with technological developments. For this, EFSA will continue to identify research priorities in EFSA's risk assessment areas in order to fill data gaps and work with key research partners to develop initiatives. This will be communicated through the submission of EFSA's annual and multi-annual research priorities to DG RTD and the JRC and the sharing of research priorities with other EU and Member States as well as international agencies and partners in third countries for the identification of joint research needs.

6 Conclusion

The trust that European consumers and stakeholders have in the quality of its scientific work - and thus the scientific basis for European risk management measures - is key for EFSA's authority. It reflects the degree to which EFSA will have managed to successfully implement its core values.

This ambitious strategy will ensure that EFSA can continue to support the European food safety system in the coming years through up-to-date science-based risk assessments. In so doing it contributes to improving the health and welfare of humans and animals as well as plant health. Through its contribution, EFSA fulfils not only its mission to protect consumers but also provides food operators a regulatory environment which is both demanding and predictable. This fosters technological innovation, thereby supporting sustainable growth and development.

The various initiatives proposed in this document will need prioritisation. Even with the extensive streamlining of its activities, efficiency gains and redeployment of staff and resources that is already underway at EFSA, investments will be required in order to successfully implement the strategy. For example, a key objective is also to streamline and simplify the process for regulatory submission and review through initiatives such as electronic submission and other IT-supported initiatives. The development of an electronic dossier submission platform as well as the further building of risk monitoring programmes are resource-intensive.

As these activities are in large part related to regulatory review and post-authorisation monitoring of regulated products, the level and origin of resources to fund these activities may impact the feasibility of these projects. Training of external and internal scientific experts is also a necessity. These investments will reap dividends as they will ultimately result in greater efficiency and enable EFSA to continue to uphold its core values.

Progress in implementing the strategy will be assessed annually against EFSA's corporate key performance indicators and any remedial actions will be included in the multi-annual work programme and annual management plans of the Authority. The strategy itself will also be reviewed at regular intervals to adjust the strategic direction in line with changes in the operating environment.

Adopted by EFSA's Management Board in December 2011

Annex 1

Overview of EFSA's scientific outputs

	2005	2006	2007	2008	2009	2010	2011*	Total
Activity 1. Provision of scientific opinions and advice & risk assessment approaches								
Opinion of the Scientific Committee/Scientific Panel	35	27	61	70	54	44	57	**348**
Statement of the Scientific Committee/Scientific Panel	5	6	2	3	9	8	1	**34**
Guidance of the Scientific Committee/Scientific Panel	0	1	2	1	5	2	5	**16**
Statement of EFSA	0	0	1	4	3	5	4	**17**
Guidance of EFSA	0	0	0	0	0	0	0	**0**
Scientific Report of EFSA	11	1	0	2	4	4	6	**28**
Total scientific outputs Act. 1	**51**	**34**	**66**	**80**	**75**	**63**	**73**	**442**
Activity 2. Evaluation of products, substances and claims subject to authorisation								
Opinion of the Scientific Committee/Scientific Panel	121	97	137	180	354	241	328	**1458**
Statement of the Scientific Committee/Scientific Panel	0	3	2	4	37	6	4	**56**
Guidance of the Scientific Committee/Scientific Panel	0	3	1	15	3	3	15	**40**
Statement of EFSA	0	0	1	0	0	0	2	**3**
Guidance of EFSA	0	0	0	0	2	1	2	**5**
Scientific Report of EFSA	3	1	2	0	0	2	4	**12**
Conclusion on Pesticides Peer Review	20	30	20	62	30	69	70	**301**
Total scientific outputs Act. 2	**144**	**134**	**163**	**261**	**426**	**322**	**425**	**1875**
Activity 3. Data collection, scientific cooperation and networking								
Guidance of EFSA	0	0	0	0	1	2	4	**7**
Reasoned Opinion	0	0	3	20	75	68	175	**341**
Statement of EFSA	0	0	0	0	1	1		**2**
Scientific Report of EFSA	0	1	6	10	16	15	18	**66**
Total scientific outputs Act. 3	**0**	**1**	**9**	**30**	**93**	**86**	**197**	**416**
TOTAL SCIENTIFIC OUTPUTS (Activities 1, 2 and 3)	**195**	**169**	**238**	**371**	**594**	**471**	**695**	**2733**
Supporting Publications								
Event report	1	2	3	4	4	5	9	**28**
External Scientific Report	0	0	1	2	39	37	42	**121**
Technical report	0	0	1	3	15	32	50	**101**
Total supporting publications	**1**	**2**	**5**	**9**	**58**	**74**	**101**	**250**

* Output targets 2011-11-28

Annex 2

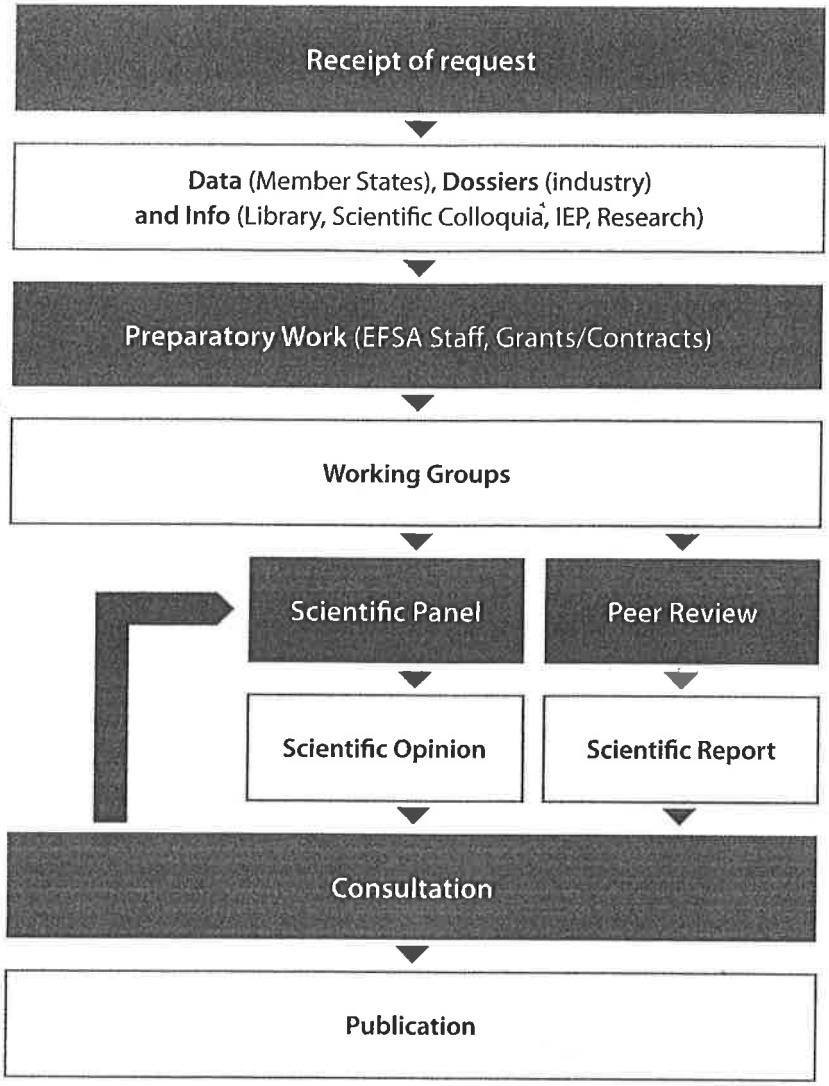
Summary of the main fields of expertise and scientific activities carried out by EFSA*

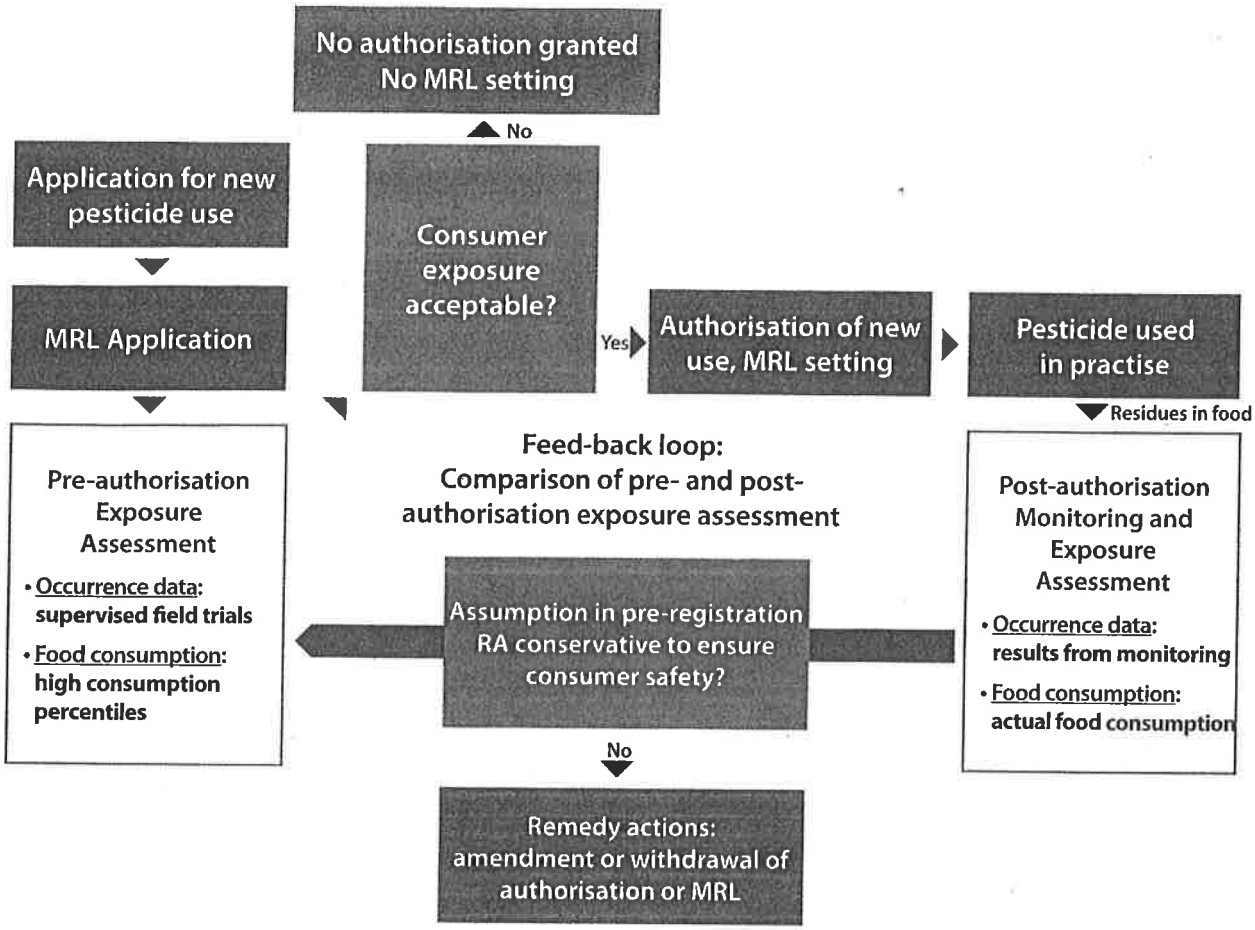
EFSA's main areas of work

	Animal Health	Biological hazards/ zoonoses	Food/ feed contam-inants	Feed additives	Flavourings, Food additives, Food contact materials	Genetically modified organisms	Nutrition	Novel foods	Pesticides	Plant health
Chemical risk assessment (including residues)										
Hazard identification & characterisation			x	x	x	x	x	x	x	
Exposure assessment			x	x	x	x	x	x	x	
Risk characterisation			x	x	x	x	x	x	x	
Microbiological risk assessment and animal welfare assessment										
Hazard identification & characterisation	x	x		x		x				x
Exposure assessment	x	x		x		x				x
Risk characterisation	x	x		x		x				x
Environmental risk assessment										
Environmental fate & behaviour	x			x		x			x	
Eco-biodiversity	x			x		x				x
Import risk assessment										
	x									x
Benefit/efficacy assessment										
Human		x					x		x	
Animal				x						

* The scientific Committee is not listed explicitly as its role is overarching.

Scientific process workflow

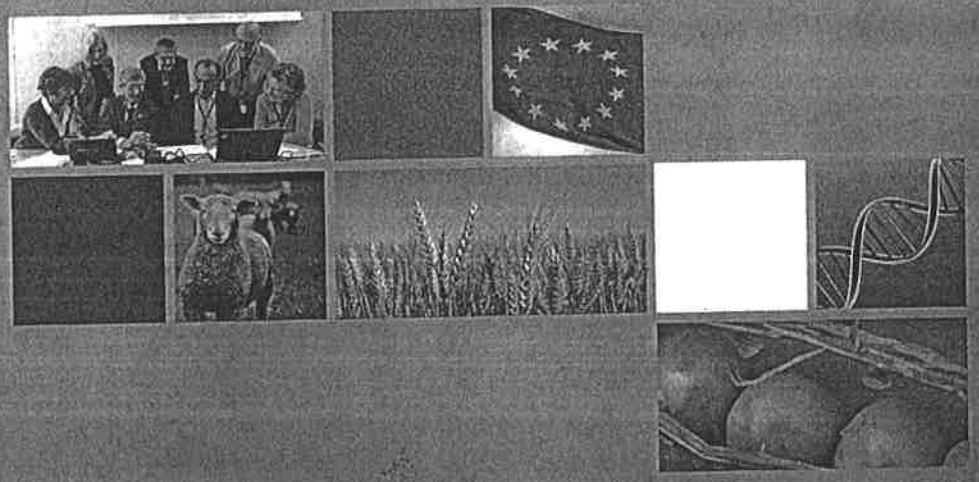



No authorisation granted
No MRL setting
No
Application for new pesticide use
Consumer exposure acceptable?
Yes
Authorisation of new use, MRL setting
Pesticide used in practise
MRL Application
Residues in food
Feed-back loop:
Comparison of pre- and post-authorisation exposure assessment
Pre-authorisation Exposure Assessment
• Occurrence data: supervised field trials
• Food consumption: high consumption percentiles
Assumption in pre-registration RA conservative to ensure consumer safety?
Post-authorisation Monitoring and Exposure Assessment
• Occurrence data: results from monitoring
• Food consumption: actual food consumption
No
Remedy actions: amendment or withdrawal of authorisation or MRL

Glossary of Terms

CDC	US Center for Disease Control and Prevention
EBA	European Budgetary Authority
ECDC	European Centre for Disease Prevention and Control
ECHA	European Chemical Agency
EMA	European Medicines Agency
EPPO	European and Mediterranean Plant Protection Organization
EU	European Union
IEP	Information Exchange Platform
JRC	Joint Research Centre of the European Commission

MS	EU Member States
NGO	Non-Governmental Organisation
OECD	Organisation for Economic Cooperation and Development
OIE	World Organisation for Animal Health
Risk monitoring	Surveys conducted to measure, for example, the occurrence and concentrations of chemicals and micro-organisms in food
USFDA	United States Food and Drug Administration
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
WHO	World Health Organisation



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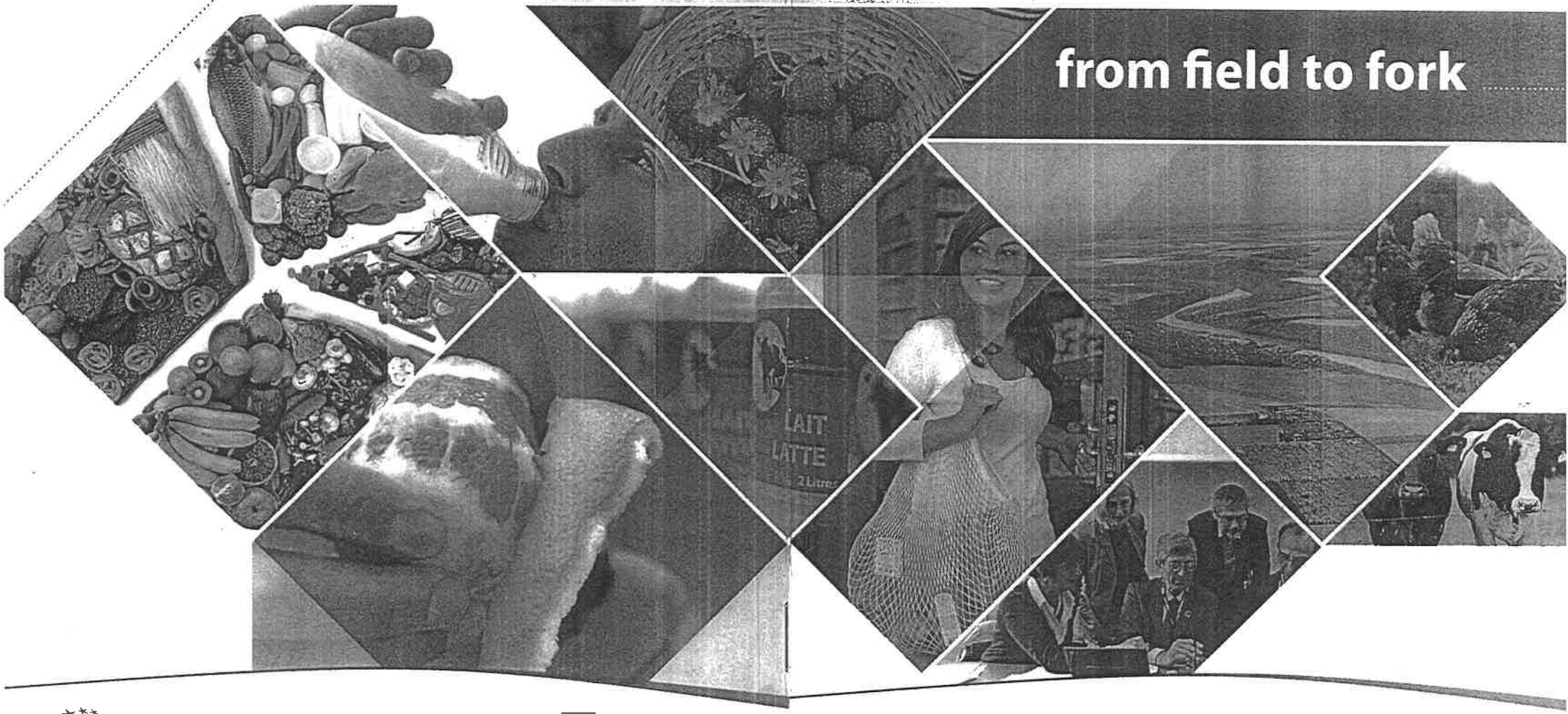
Science protecting consumers

from field to fork



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Committed to ensuring that Europe's food is safe

efsa
European Food Safety Authority

EFSA – a science-based organisation that protects and informs consumers

■ The European Food Safety Authority (EFSA) provides impartial, high-calibre scientific advice to help inform decisions of policy makers about food-related risks. This is a crucial part of an institutional framework in the European Union (EU) that ensures the safety of consumers, as well as animals and the environment from any risks associated with the food chain. EFSA's key activity is scientific risk assessment, a specialised field of applied science that involves reviewing scientific data and studies in order to evaluate risks associated with certain hazards. The Authority also has an important role in communicating its advice to its principal partners, stakeholders and the public at large in a timely, clear and meaningful way, helping to bridge the gap between science and the consumer.

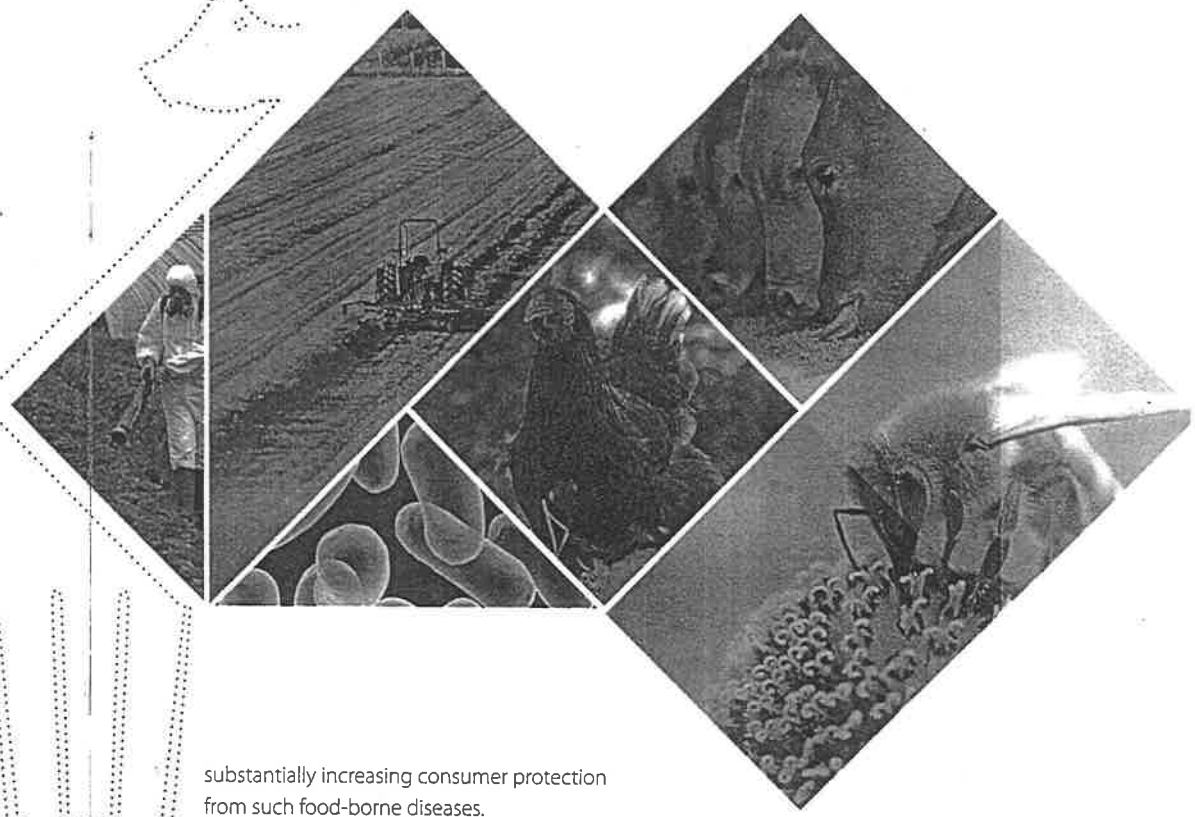
Europe working together for safer food

■ In 2002 after a series of food-related alerts that impacted on human health and shook public confidence, the EU adopted the General Food Law (Regulation EC 178/2002), providing a comprehensive framework for the EU's science-based food regulatory system. Key elements were the functional separation of risk assessment and risk management and the establishment of EFSA with its emphasis on scientific excellence, independence, openness, transparency and responsiveness – still EFSA's key values today. While EFSA took on the role of risk assessor, EU risk managers (European Commission, European Parliament and EU Member States) retained control over regulatory decision-making, policy and prevention and control measures.

A crucial aspect in the success of this system lies in the active engagement and co-operation with stakeholders and partners at European and national levels. Through its Advisory Forum EFSA works in close co-operation with the national food safety authorities on scientific, data collection and monitoring, and communications activities. The Authority also holds regular meetings with organisations representing consumers, industry, environmental NGOs and other stakeholders to encourage their involvement and understanding of its work.

THE FOOD CHAIN – FROM FIELD TO FORK

Europe's food chain is continually evolving and EFSA's remit has evolved to cover an increasingly complex number of areas related to the safety of the food chain: food-borne diseases, contaminants, animal health and welfare, plant protection, food production and distribution, food sector innovation to name a few. Today, the advice that EFSA provides to risk managers underpins many of the laws and regulations in place to protect European consumers from food-related risks – from field to farm and factory to fork.



Field and farm

Plant protection

■ Agricultural crops provide the bulk of our food and feed supply. EFSA helps to protect consumers by providing the scientific advice that underpins the regulation of the safe use of pesticides and other plant protection products. The Authority has helped the EU to evaluate hundreds of active substances used in pesticides and to establish common science-based limits for permitted residue levels in Europe. EFSA's scientists also evaluate the risks posed by pests and weeds to plant health including farm crops and, in turn, on the environment.

Animals

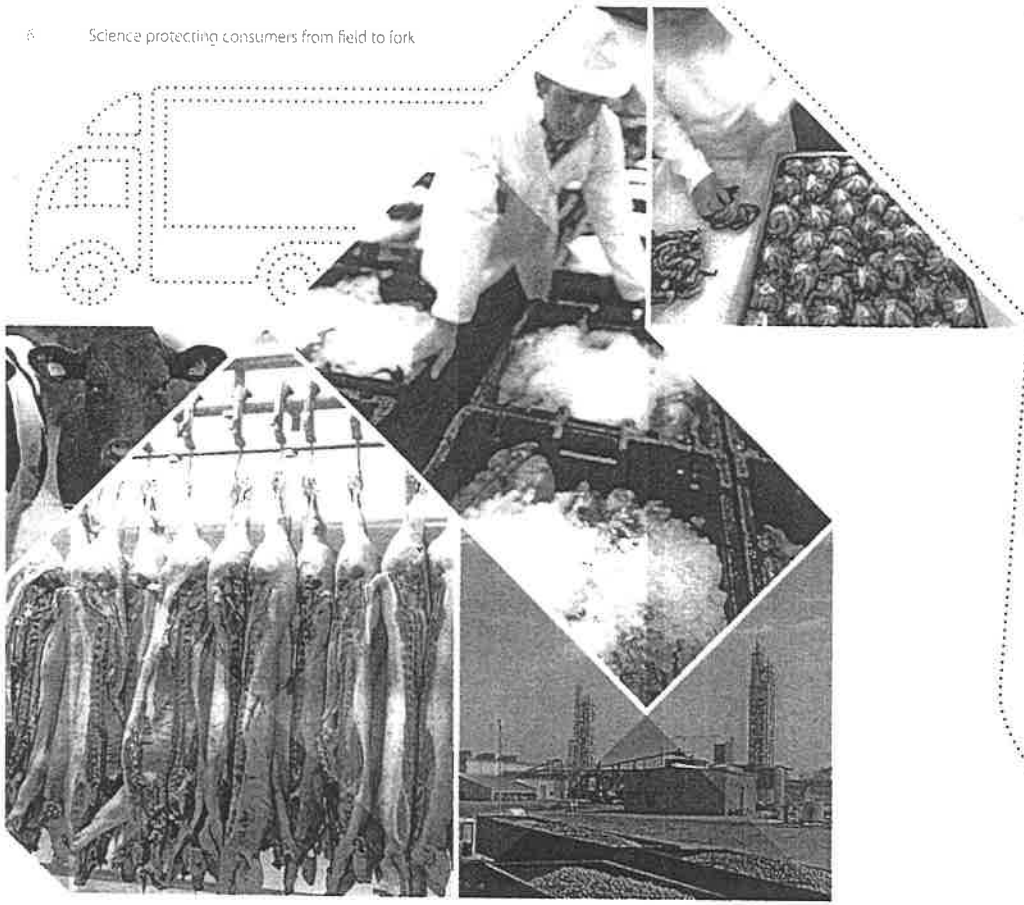
■ The health and welfare of food-producing animals (such as cattle, chicken and pigs) during breeding, rearing, transportation and slaughter can have important consequences for human health. EFSA assesses the impact that the conditions and treatment of animals can have both on animal and human health, including industry operators.

About 75 % of the new diseases that have affected humans since 2000 have originated from animals or products of animal origin. So-called "zoonotic" diseases are diseases that can be transmitted to humans by animals, including through food. EFSA's scientific advice, data collection and monitoring have contributed to an EU-wide campaign to control and reduce the presence of bacteria like *Salmonella* and *Campylobacter* that, when present in animals, can infect food. As a result, over five years human cases of salmonellosis were reduced by one-half to 100,000, substantially increasing consumer protection from such food-borne diseases.

EFSA also assesses the safety of animal feed, which is important for the health of animals, the environment and for the safety of foods of animal origin. Since EFSA's establishment in 2002, the Authority's risk assessment and monitoring work has been a continual, strong thread supporting the ongoing risk management efforts that have seen the number of cases of BSE in cattle reported across the EU drop from several thousands in the early 2000s to 44 in 2010.

Environment

■ Increasingly, EFSA is required to consider the food chain's possible impact on the biodiversity of plant and animal habitats. For example, the Authority performs environmental risk assessments of genetically-modified crops as well as pesticides and feed additives used by farmers. EFSA also assesses possible risks to human and animal health from environmental contaminants. Air, soil, water and plants can be contaminated by environmental pollutants and substances, for example metals in soil or toxins produced by certain types of funghi. This can often be the result of human activities such as industrial emissions or car exhausts. People can be exposed to them from the environment or by ingesting contaminated food or water. Their accumulation in the body can lead to harmful effects over time.



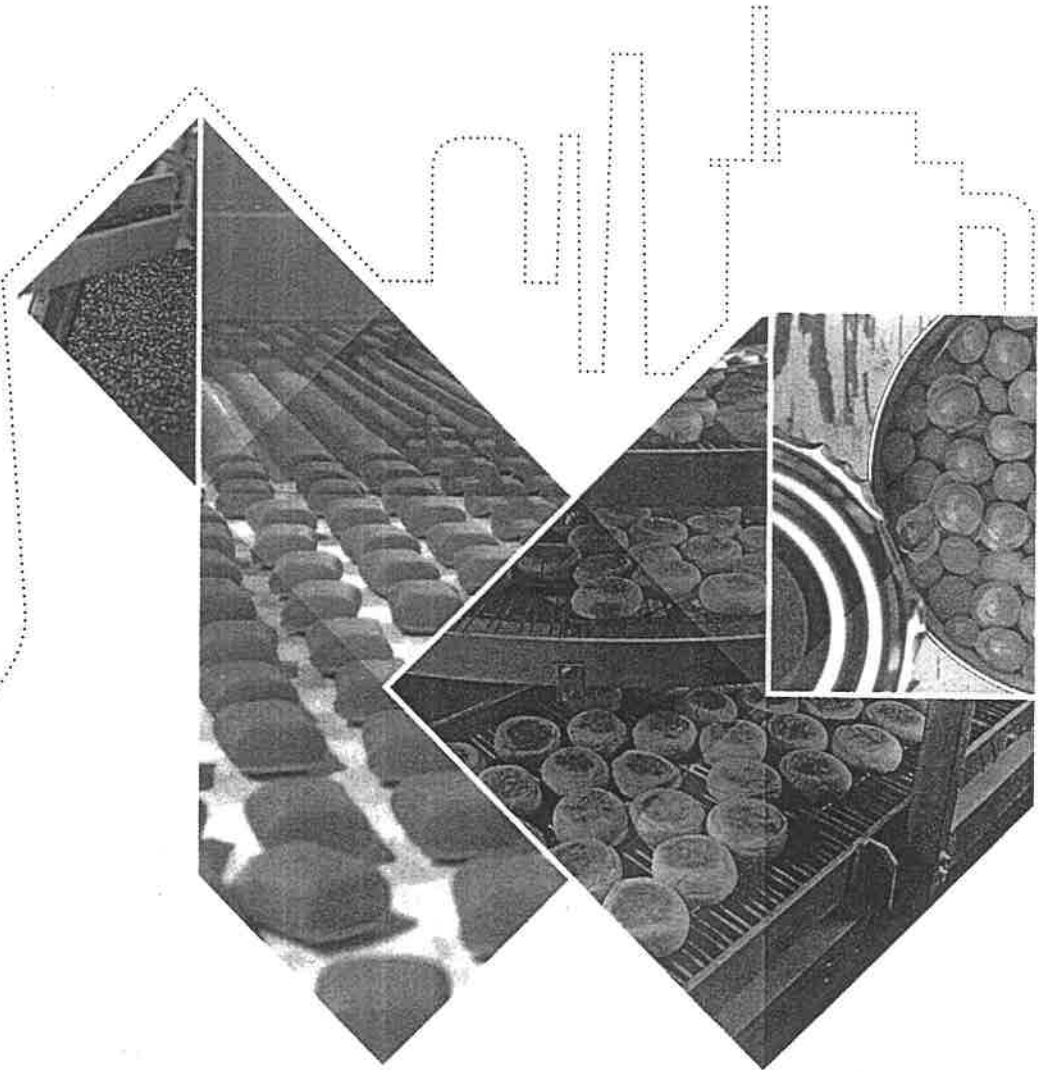
Factory to fork

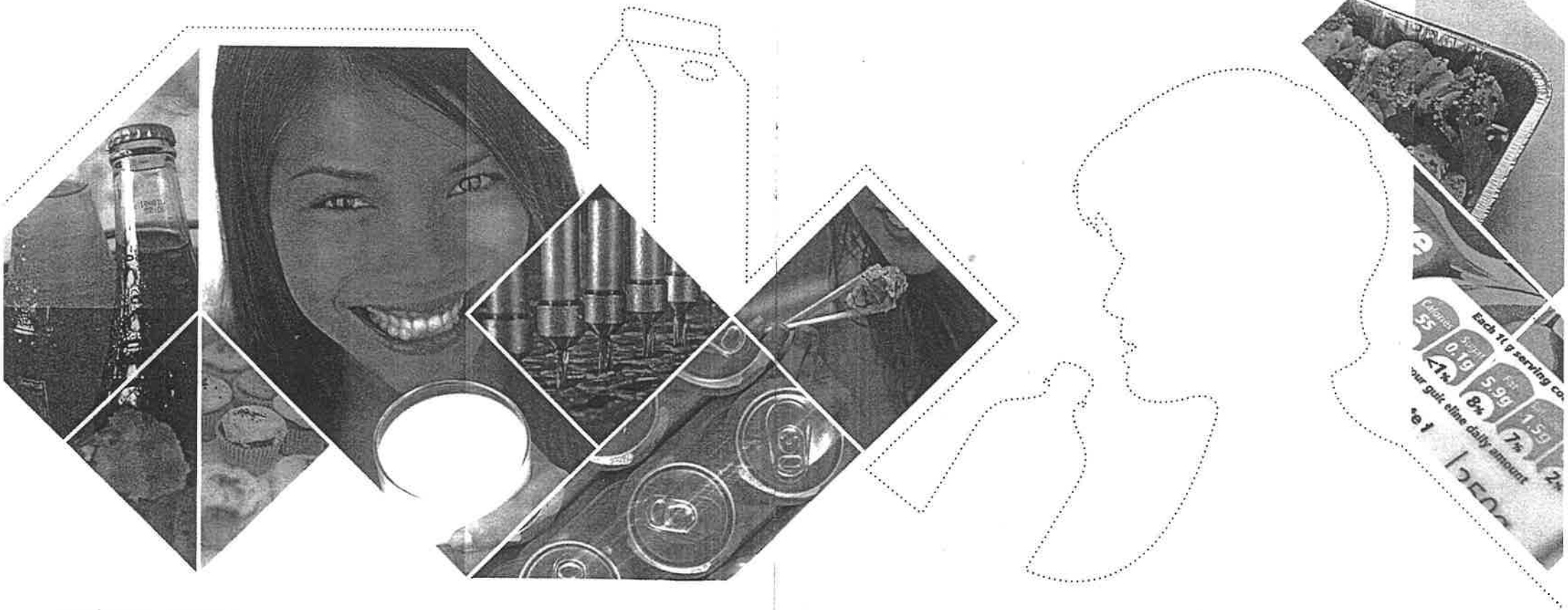
Transportation and storage

■ Raw materials used in food production or animals and animal carcasses in transit or in storage may be exposed to potential risks from biological infection and chemical contamination. For example, there may be chemical residues from previous cargoes found in freight containers used to transport edible oils and fats. EFSA assesses the risks of such contamination from contact with, for instance, machinery, vehicles and packaging materials, and provides scientific advice to risk managers on possible measures to limit these risks.

Food preparation and production

■ In Europe, the food sector is regulated to protect consumers from potential risks related to food and feed while also leaving room for companies to innovate. The Authority evaluates the safety of regulated food ingredients such as additives, flavourings, enzymes and nutritional substances with a view to supporting risk managers in authorising their use in foods. For example, EFSA has evaluated thousands of flavourings used in foods and by 2020 is scheduled to complete the re-evaluation of all food additives authorised in the EU prior to 2009. EFSA's scientific advice informs the decisions of risk managers regarding the safety and permitted uses of these ingredients; in some cases, some flavourings and additives have been removed from the EU market as a consequence of EFSA's work. The Authority also assesses the safety of food production processes (for instance recycling of plastics used in food packaging) and processing aids used by the food industry.





Food sector innovation

■ Consumers demand much more from their food in terms of choice, quality, price, nutritional value and availability than only a generation ago. The food sector has responded to these product and information needs by innovating, through new ingredients, technologies, food products and related communications. As Europe's food safety watchdog, together with its partners at European and national level, EFSA is directly involved in assessing the science behind such innovations with respect to their safety and in some instances, their efficacy.

In the biotechnology area, for example, EU legislation required that EFSA develop a comparative risk assessment approach to consider the potential impact of genetically modified (GM) crops or animals that evaluates their effects against traditional non-GM equivalents. The Authority has also provided scientific advice on cloning and novel foods and now considers nanotechnology in its risk assessments of several food sector products, including additives and food packaging.

Claims made about the nutrition or health benefits of foods can provide information which can help consumers in choosing a healthy diet. EFSA evaluates the scientific basis of such claims to help ensure that they are not misleading. By the end of 2012, EFSA had evaluated more than 3,000 health claims.

Food consumption

■ Underpinning all of EFSA's work are the huge strides made in the area of data collection on food consumption trends and habits. EFSA has consistently increased its support to data collection and other scientific cooperation with Member States, allocating in 2012 over €9 million to these activities. This progress helps us to understand better what we eat, informing EFSA's work both in the area of food safety and that related to advice on nutrition, diet and health.

EFSA's scientific work also supports decisions about nutritional guidance; its reference values for nutrient and energy intakes take account of the latest studies and help public authorities in Member States to establish nutritional recommendations and provide practical food-based dietary advice.

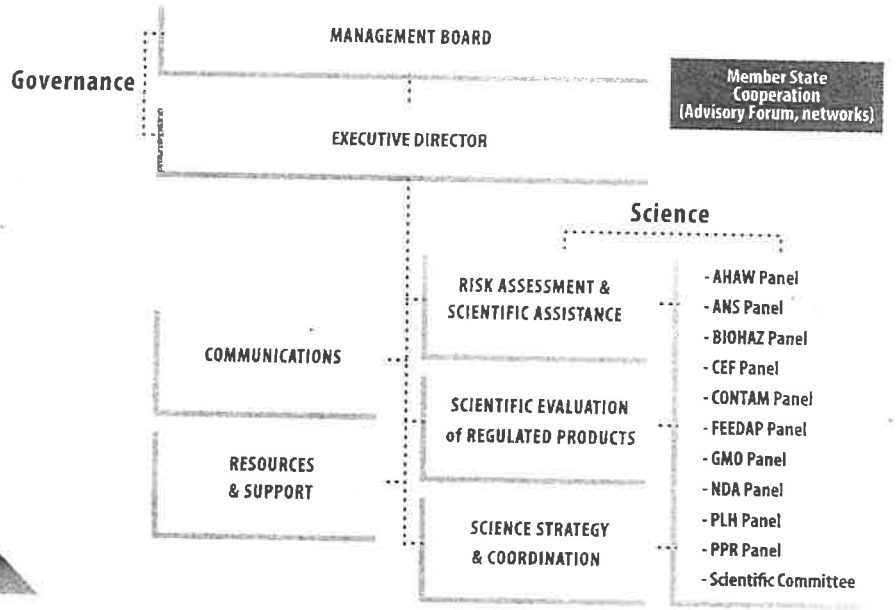
In recent decades there has been a proliferation of materials and products used in food packaging, containers, receptacles and utensils. The Authority assesses potential risks related to the use of plastics, paper, active and intelligent substances, inks and resins used in food contact materials, including recycled materials, before they are authorised for use in the EU.

How **EFSA** works

■ EFSA is governed by an independent Management Board whose members are appointed to act in the public interest and do not represent any government, organisation or sector. The 15-member Board sets EFSA's budget and approves the annual work programme. EFSA's Executive Director is the legal representative of the Authority. S/he is responsible for all operational matters, staffing issues and drawing up the annual work programme in consultation with the European Commission, European Parliament and EU Member States.

EFSA's scientific work is led by its Scientific Committee and its 10 Scientific Panels composed of leading scientists in their fields. Additional experts participate in working groups when more specialised knowledge is required. The Scientific Committee provides advice on cross-cutting issues while the Panels carry out risk assessments and provide expert guidance in specific areas:

- **Additives and products or substances used in animal feed**
- **Animal health and welfare**
- **Biological hazards, including BSE-TSE-related risks**
- **Contaminants in the food chain**
- **Dietetic products, nutrition and allergies**
- **Food additives and nutrient sources added to food**
- **Food contact materials, enzymes, flavourings and processing aids**
- **Genetically modified organisms**
- **Plant health**
- **Plant protection products and their residues**



The scientific advice of EFSA's experts is the outcome of collective deliberations and decisions, each member having an equal say. In addition, EFSA applies a robust set of internal mechanisms and working processes to safeguard the independence of its scientific work, including demanding declaration of interests requirements.

The highly-qualified scientific staff in EFSA's three scientific directorates support these groups and carry out evaluations themselves in some areas, such as the peer review of active substances used in pesticides. Together with national partners, EFSA staff also play a vital role in harmonising and expanding the scope of data collection and monitoring activities – for example on food consumption, zoonotic diseases, pesticides, contaminants – that improve the quality of EFSA's risk assessments.

Guided by its Science Strategy, the Authority stays in tune with international scientific developments, including new risk assessment methodologies and breakthroughs, thanks to the knowledge of its experts and ties with scientific networks and food safety agencies around the globe.

Through its risk communications activities, EFSA seeks to raise awareness and further explain the implications of its scientific assessments. As laid down in its Communications Strategy, the Authority does this by analysing public perception of risks linked to food and explaining and contextualising risks associated with the food chain. Working with key actors including national authorities, stakeholders and media helps EFSA to relay messages to different audiences. The Authority also promotes consistency of messages by co-ordinating communications with other risk assessment bodies and risk managers such as the European Commission and EU Member States.

UNIVERSITÀ CATTOLICA del Sacro Cuore

With the Patronage of EXPO MILANO 2015
FEEDING THE PLANET
ENERGY FOR LIFE

Cremona Executive Education Program - Expo 2015

May 1st – October 31st 2015 – Cremona (Italy)

During the EXPO 2015 semester, Università Cattolica del Sacro Cuore is going to arrange, in Cremona, an extraordinary program, consisting in international top-class executive courses. These courses are addressed to professionals with a specific interest in Expo 2015 themes, such as sustainable food, innovative practices in agriculture and zootechnics, agro-food safety and food security. The purpose of the courses is to enable participants to acquire skills and advanced competences in specific fields strictly related to the Universal Exposition themes.

Courses will take place during EXPO 2015 semester, from 1st May 2015 up to 31st October 2015, and represent a great opportunity to flank the visit to the most important international Exhibition about food and nutrition, to a high level training experience.

Executive courses with an international perspective

The whole program is tailored made for professionals and executive in the agro-food industry. In particular, courses are addressed to entrepreneurs and foreign entrepreneurial associations belonging to agro-food industry, buyers and traders of food products on the international markets, experts and managers of public institutions, governments and international organizations, academics, scientists, researchers and PhDs, which are studying the topics related to EXPO, experts and NGO and international cooperation's managers, multinational agro-food (and green chemistry) related companies' managers, journalists from scientific and economics journals.

CEEP represents a unique experience since it includes a mix of lessons leaded by experts in an international perspective, and field trips in the whole Po food valley, with visits into the most prestigious Italian productive realities.

CEEP Partners: institution and research for international executive courses

Cremona Executive Education Program has got the official Patronage of EXPO Milano 2015 organization. Moreover, it numbers among its official Partners the most important Italian and European authorities involved in the agro-food industry:

- Italian Ministry of Agriculture, Alimentary and Forestry Policies
- Ministry of Agriculture of Regione Lombardia
- Università Cattolica del Sacro Cuore di Milano
- Politecnico di Milano
- ANMVI – Associazione Nazionale Medici Veterinari Italiani (Italian National Association of Veterinarians)

Cremona: a unique context in the heart of the food valley

Cremona, small medieval town in the fertile plain of the Po river, is located in the heart of the Italian food valley (far 1 hour by car from Milan), where excellence in agriculture, zootechnics and food industry have been developed, during the centuries, to create a perfect synergy. The Po food valley is a fertile land, whose high quality food production and tradition originates some of the most famous and appreciated Italian products, as Parmigiano Reggiano, Prosciutto Crudo di Parma and Grana Padano.

Cremona and the Po Valley represent the perfect context where a millenarian knowledge in agro-food techniques developed in a unique basin, where agriculture, industry and scientific research, work side by side to create a unique value. Indeed, the area is characterized by an important number of excellences in the above fields, thanks to the presence of successful and innovative enterprises, and, meanwhile, prestigious research centers which strongly support the competitiveness of the local supply chains.

A prestigious location: Palazzo Trecchi in Cremona

Palazzo Trecchi, built in 1496 to be Marchesi Trecchi's home, is in the hearth of the historic center of Cremona. During the centuries, the palace had been visited by members of aristocracy and European courts, as Charles V, Federico Gonzaga and members of the Medici family. With his neo-gothic decorations, elegant columns and precious ceilings it is now a prestigious location for international congresses, meetings and international Master classes. Indeed, it is provided with top standards furnishings and equipment for professional training, conference services and excellent catering

The learning experience

Course structure -_CEEP is made to provide professionals with the best possible educational experience in the fields of *food safety, food security, food sustainability, management* and *innovation in farming and zootechnics*, combining the opportunity to know the frontiers of knowledge in these fields with the possibility of being surrounded by the culture and the beauty of Cremona. This comprehensive experience implies **4 sessions of classroom lectures** (usually in the morning), held by university professors, from Università Cattolica del Sacro Cuore and Politecnico di Milano, two of the most important universities related to the food sector and agriculture. Moreover, external experts will participate, for some of the specific features of each course. Besides the traditional lectures, each course includes different **fieldtrips**, which will show the most innovative and technologically advanced realities related to the agro-food in the Northern Italy. Additionally, within the course week, in order to remark the importance and the strict connection with the Universal Exposition in Milan, it is scheduled a **whole-day trip in Milan to EXPO 2015**, where the participants can fully enjoy the most important food & related fair in the world. Besides the formative aspects, during the whole week, several **cultural events** are scheduled, in order to make the attendants able to know and appreciate the historical beauties of Cremona: examples of these are music concerts, guided tours and hearings of Stradivari's violins, in the brand new Museo del Violino (MdV), a uniqueness in the World. The course will end with a **round table**, scheduled for the last afternoon, when professionals with experts and professors will have the opportunity to discuss and summarize the topics addressed during the week.

Local travel agencies will arrange incoming and accommodation services for the participants, included transfers from and to the main Milan airports.

Course Catalogue

The course catalogue is composed by 6 different major categories, each one representing a core theme from EXPO 2015 Milan, in order to provide the participants with a holistic experience regarding the most advanced innovations in agro-food topics. The six main categories are the following: *a)* Food Safety; *b)* Food Security; *c)* Food Sustainability; d) Management; e) Innovation in zootechnics; f) Innovation in agriculture.

Food safety - With this category, CEEP will provide courses explaining the best practices addressed to ensure that the handling, the preparation and the storage of food is done in the best possible way to prevent any hazard cause by food poisoning and food spoilage. Under the main theme of "food safety", several other practices are considered: food labeling, food hygiene, the usage of food additives and all the residues that the final consumer finds on the food in the supermarket. Another aspect regards all the policies, issued by public and private institutions, which are related to biotechnology, import/export and certification systems.

Food Security - The concept of "food security" is strictly related to the availability of food in a defined area. This crucial issue is tackled by CEEP through different courses, whose topics reflect the four pillars stated by the WHO and FAO: (1) food availability, which includes several factors, such as land availability (and the issue of land grabbing), soil management and crop/livestock selection and management; (2) food access, which is one of the main reasons of hunger and malnutrition in developing countries; (3) food utilization, which is strictly related to food safety and the quality of the food that is eaten; (4) food stability, which is the ability of obtaining the food over time.

Food Sustainability - In broad terms, sustainability is a recurrent topic in many aspects of our lives. Particularly, it is often applied to food and agriculture: indeed, natural resources, like water, soil and ecosystems are vital for our health and quality life; however, the current consumption rate, as well as the environmental pressure, is not sustainable in the long run. CEEP is covering in details these topics with courses related to innovations in bioenergy, strategies to reduce food waste and losses and good sustainable practices in the most important supply chains, as milk and wine.

Management - The management in the agro-food system is of primarily importance to implement the good practices related to agriculture production and food manufacturing and to handle the complicated relationships between actors in the supply chains. Regarding this broad topic, CEEP provides the best courses to give insights and solutions about the main issues related to the management of the agro-food system: from the geographic trademarks (PDO, PGI), done to exalt and protect the territory through food and agriculture, and the development of an efficient marketing strategy to promote the products, to the collaboration strategies between farmers and retailers and the most effective and successful forms of cooperation in agribusiness.

Innovation in Zootechnics - This section of the CEEP course catalogue is dedicated to technical innovations, occurring in zootechnics, animal husbandry and livestock management, with a special consideration for sustainability. Under the category "Innovation in Zootechnics", several courses are provided, aimed to explain and bring solutions about the main livestock productions practices, such as beef, pork and poultry, through the innovative branch of the precision livestock farming. Moreover, special courses related to livestock breeding methods and genetics are provided by the Institutes of Zootechnics of Università Cattolica del Sacro Cuore, which is working internationally with the most prominent experts in the world.

Innovation in Agriculture - This last category includes all the courses related to the innovation in agricultural production and farming. Innovation is fundamental in order to increase the crop productivity through reduction of cost, time and environmental pollution, to reduce the waste and manage efficiently the usage of resources like water, fertilizers and agro-chemicals. CEEP covers all these topics, with courses related to precision farming in herbaceous and arboreal crops, as well as innovative irrigation systems and organic farming management.

Some examples of courses included in the catalogue (very first draft of titles):

a) Food safety

- The European Food and Agricultural Import Regulations and Standards: the requirement for importing food in the European Union.
- Evaluation and assessment of policies and regulations about pesticides in the European Union: risk assessment, development and customs clearance management.

- Plant protection control and certification: pesticides policies, IPM (Integrated Pest Management) principles and development of ISO certifications.
- Ensuring safety and sustainability in the packaging of the food industry: innovations and certifications
- Preventing contamination by mycotoxins in intensive agriculture: techniques and methodologies
- The management of zoonotic diseases: the evolution of European legislation on safety and traceability of meat products and the role of veterinarians in the prevention and limitation of the risk
- The control and assurance of food safety in the dairy chain
- The control and assurance of food safety in the beef, pork and poultry chains
- The traceability systems in the food chain for safe and quality agricultural production: the international experience

b) Food Security

- Enhancing the agricultural resources with local processing: the case of tropical products
- Poverty Eradication: tools and strategies to ensure access to land and access to food

c) Food Sustainability

- Sustainability in the agro-food industry: application of the LCA (Life Cycle Assessment)
- Quality and sustainability in the wine production: new technologies and best practices
- Crop production: strategies and techniques to limit the harvest losses in the field
- The contribution of logistics and supply chain management for the limitation of food waste
- Producing milk according to nutritional quality criteria and environmental sustainability
- Biomass, biogas, biofuels and vegetable oils: technologies at the service of sustainable energy
- Production and consumption of heat and electricity in rural areas not connected to the electric network

d) Management

- Building and developing a sustainable short supply chain in the agro-food sector
- Collaboration between small-scaled farmers and large-scaled retailers: solutions, tools and potentialities
- The system of certificates of origin and geographical trademarks of food products (PDO, PGI, DOC, DOCG): policies, instruments and dynamics of territorial development
- The world wine market: the structural characteristics, emerging trends and competitive strategies of territorial production systems
- The co-operative model in the wine industry: an opportunity for small producers to compete in the market
- The milk market: structural characteristics, emerging trends and organizational forms of the producers organization

e) Innovation in zootechnics

- Livestock precision farming for sustainability and wellness of the cattle breeding
- Livestock precision farming for sustainability and wellness of the pig breeding
- Genetic resources, sustainability and traceability: an integrated program to enhance and protect the products made in Italy and conserve biodiversity in the livestock sector
- Organic production in the livestock supply chain: methods and solutions to produce and sell organic meat

f) Innovation in agriculture

- The second life of food waste
- The role of precision farming in herbaceous crops: sustainable innovations and applications
- The role of precision farming in arboreal crops: sustainable innovations and applications
- Enhancing the value of water in agriculture: irrigation techniques and water management for the environmental sustainability
- The management of the supply chain in the organic crop production: from farm to fork

Camera di Commercio
Cremona

Cremona Executive Education Program

EXPO MILANO 2015
NUTRIRE IL PIANETA
ENERGIA PER LA VITA

From 1° May to 31° October 2015

UNIVERSITÀ CATTOLICA del Sacro Cuore

UCSC ExpoLAB

Cremona, June 15th 2014

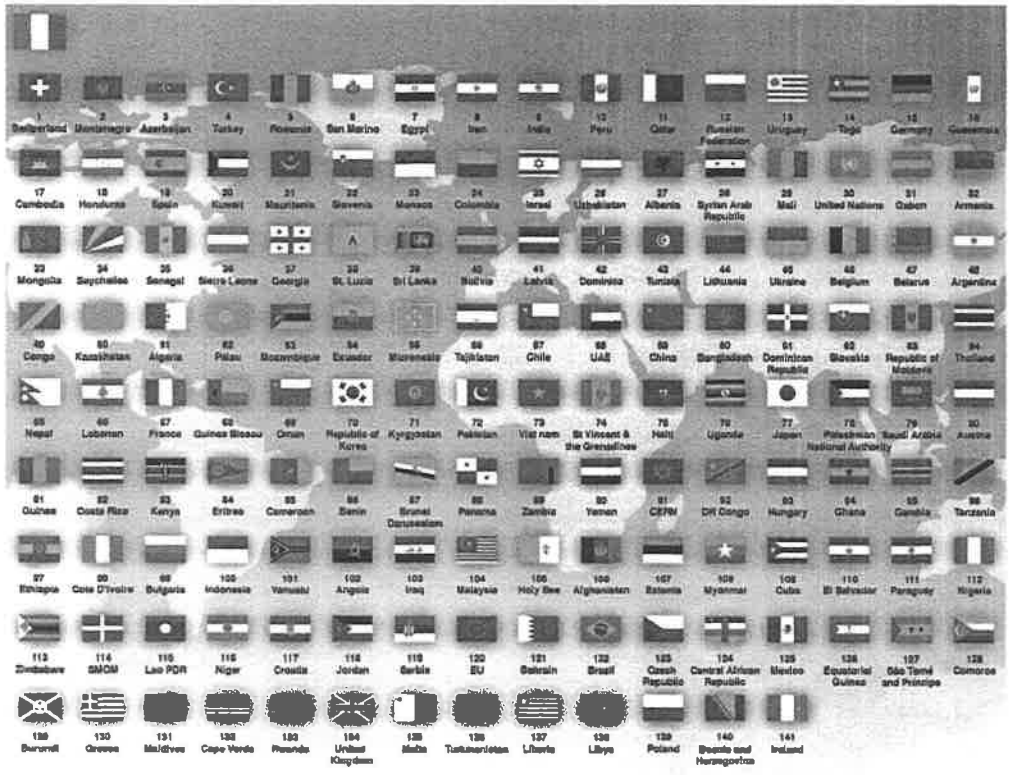
UNIVERSITÀ CATTOLICA del Sacro Cuore

142 participants, the 88% of the world's population

CERSI
CENTRO DI RICERCA PER LO SVILUPPO IMPRENDITORIALE

EXPO
MILANO 2015

142
OFFICIAL PARTICIPANTS



THE VISITORS IN THE SEMESTER

- 184 days, 26 weeks.
- Explora Spa estimates **20 million visitors,** split into 6-7 millions internarional and 14-13 millions Italians
- **Top 10 European countries**: France, UK, Germany, Spain, Switzerland, NL, Austria, Sweden, Denmark, Croatia.
- Three million will be **non-European**: China, USA, Australia, Russia, Canada, India, Brazil, Japan, UAE, South Korea.
- Regarding Lombardia, only the foreigners reflect an increase in the **touristic turnover of 3 billion and 798 million euro**.
- If it is confirmed the arrival of a million of Chinese tourists, the increase will be even higher, reaching **4 billion and 401 million euro.**

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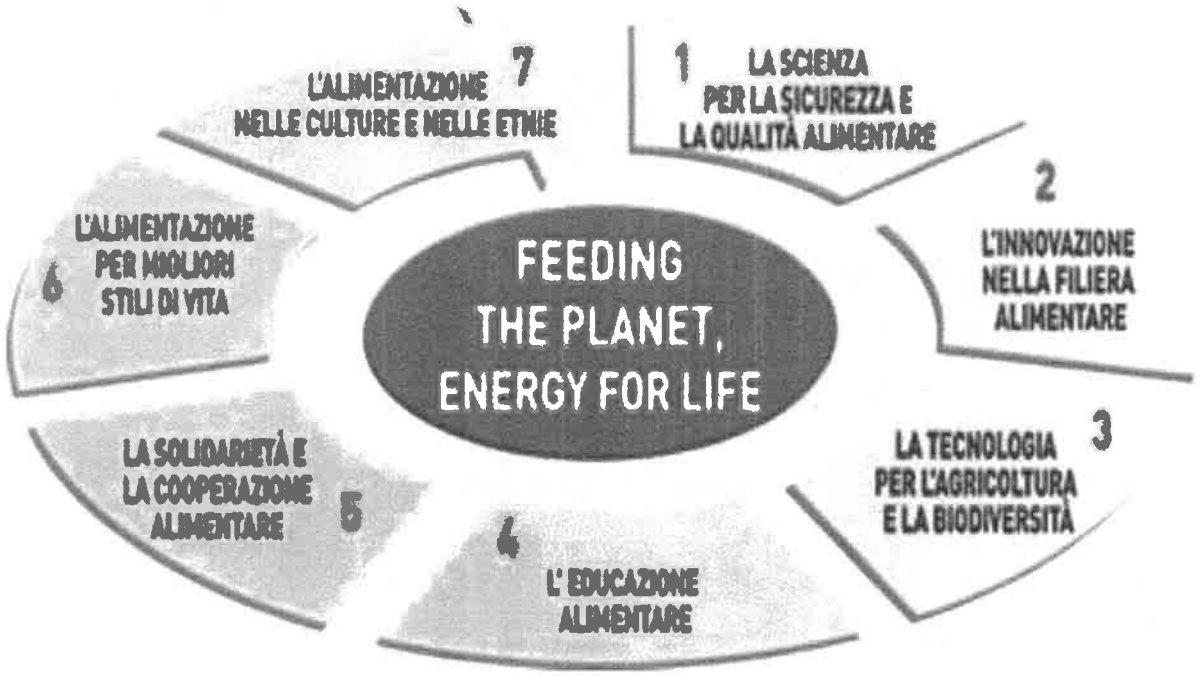
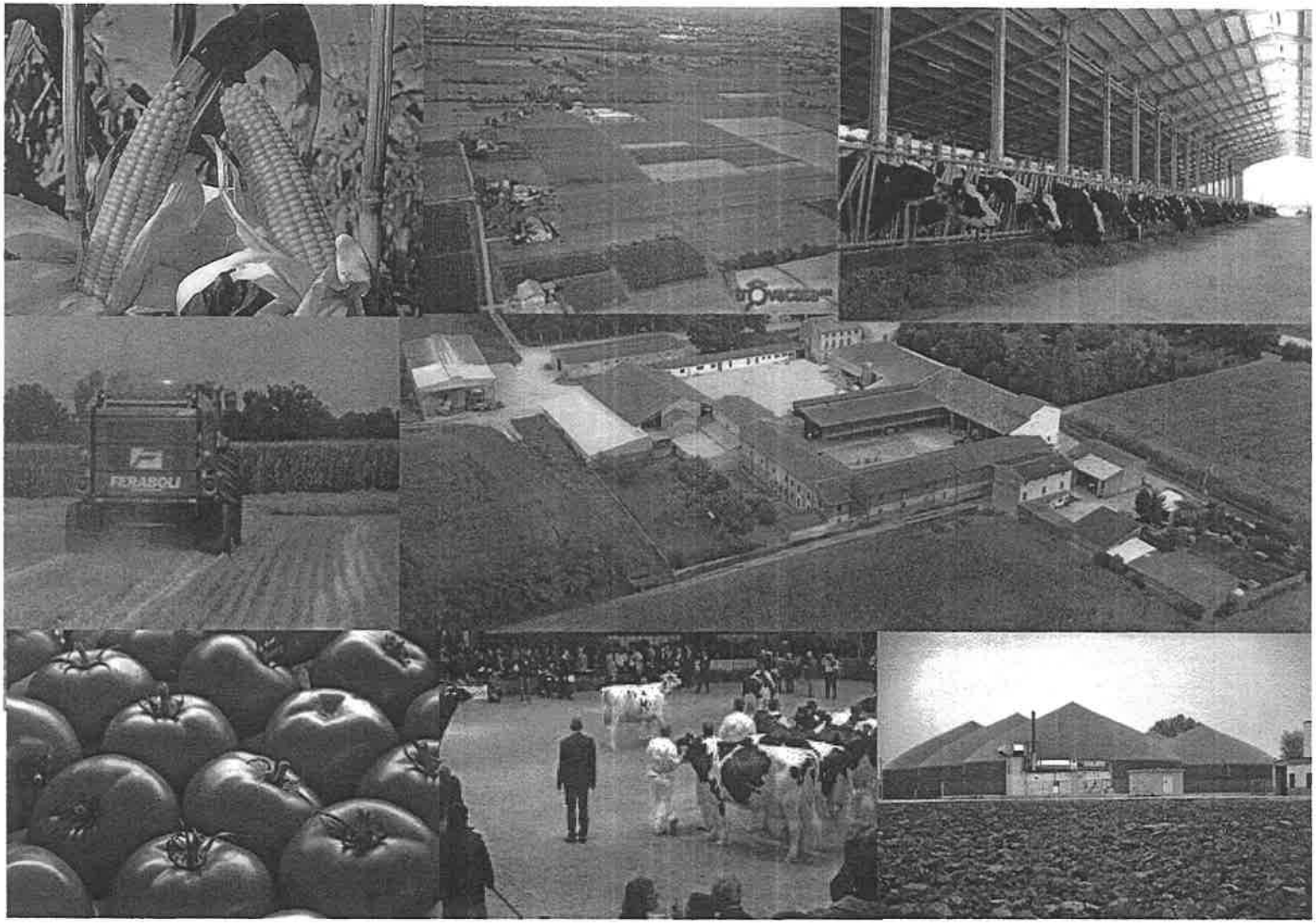
EXPO 2015's main theme and sub-themes

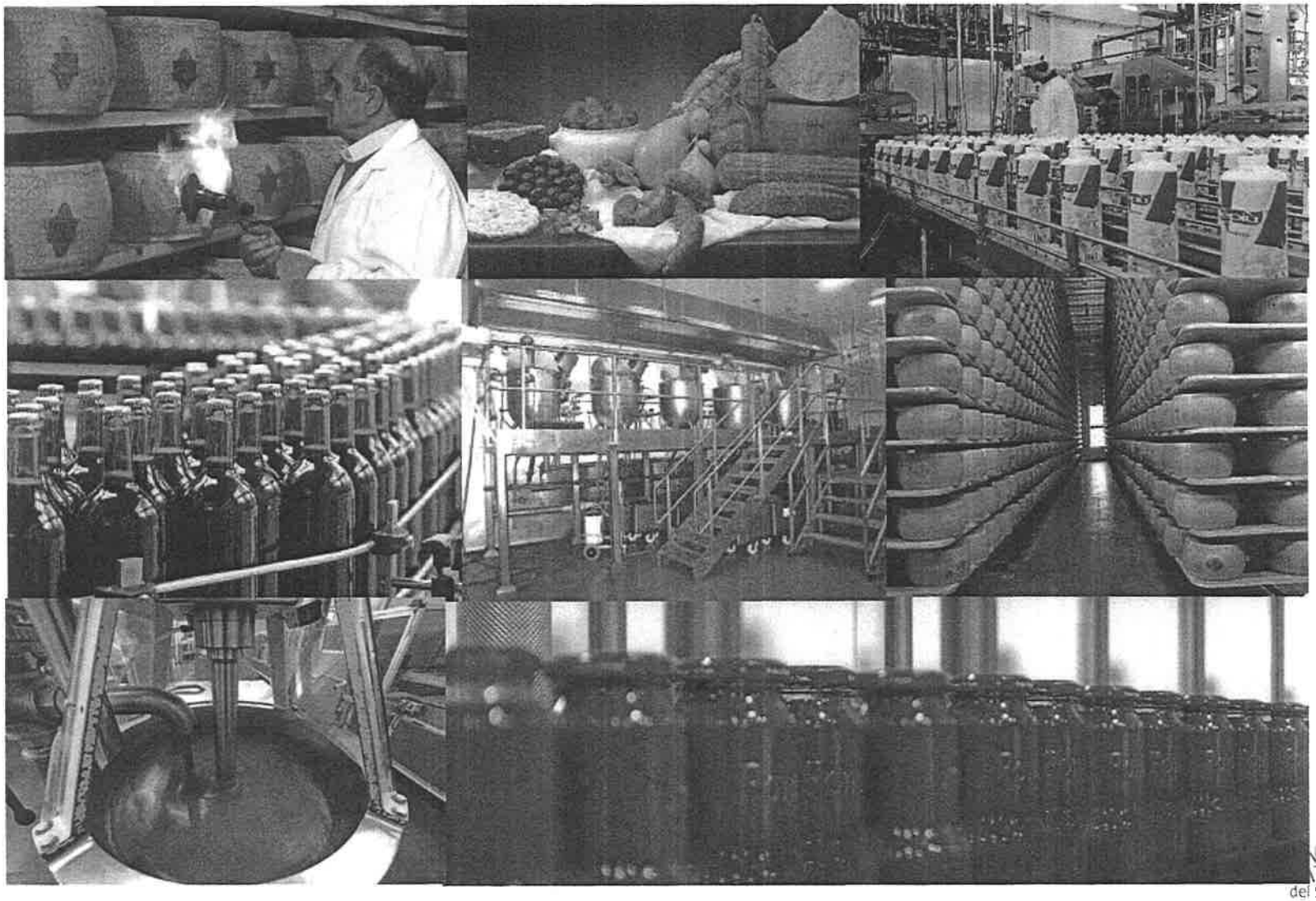


During the EXPO 2015's semester, the Catholic University is going to arrange, in Cremona, an extraordinary program, which consists in international top-class executive courses, addressed to operators of the agricultural, zootechnical and food-related industry (production, distribution, quality check, innovation, policies). These courses are including experts' lessons, as well as field trips in the whole Po food valley, in collaboration with international institutions.

Cremona: Agricultural and zootechnical excellence



Cremona: Food production excellence



Cremona: Food safety excellence

CEEP is now officially under the patronage of EXPO 2015

Con il Patrocinio di

EXPO MILANO 2015
NUTRIRE IL PIANETA
ENERGIA PER LA VITA

With the Patronage of

EXPO MILANO 2015
FEEDING THE PLANET
ENERGY FOR LIFE

"After the approval of the CEO of Expo 2015 S.p.A., Dott. Giuseppe Sala, we are pleased to communicate the granting of the Patronage of Expo Milano 2015 for the initiative "***Cremona Executive Education Program for Expo 2015***".

La Commissione Patrocini di Expo 2015 S.p.A.

Milan, April 18th 2014

CEEP's official partners

CERSI
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EXPO MILANO 2015
NUTRIRE IL PIANETA
ENERGIA PER LA VITA

MINISTERO DELLE POLITICHE AGRICOLE ALIMENTARI E FORESTALI

Institutions that signed for the Agreement Protocol and of the ATS Cremona

UNIVERSITÀ CATTOLICA del Sacro Cuore

POLITECNICO MILANO

Parco Tecnologico Padano
La ricerca si fa impresa
Entrepreneurial research in ag-biotech

ANMVI
ASSOCIAZIONE NAZIONALE MEDICI VETERINARI ITALIANI

Other partners to contact:

efsa
European Food Safety Authority

Italian business companies

Multinational companies

RegioneLombardia
Agricoltura

UN agencies based in Rome (FAO, IFAD and WFP)

Commissione europea

Cremona's food companies (business and cooperatives)

Fair system

Other potential stakeholders, to be identified

Example of course schedule

	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Morning		*Airport arrival and bus transfer to Cremona.* *Hotel accommodation*	**(8:30am-12:30am) Classroom training with university professors**	**(8:30am-12:30am) Classroom training with university professors**	**TOUR EXPO2015 IN MILAN:** - Departure from the hotels at 8:30am. - Tour of Expo from 10:30am to 9pm - Return in hotel at 11 pm.	**(8:30am-12:30am) Classroom training with university professors**	**(8:30am-12:30 am) Classroom training with university professors**	Departures: bus *transfer to Milan's airports.*
		Free lunch	**Catering**	**Catering**		Catering	Catering	
Afternoon	*Airport arrival and bus transfer to Cremona.* *Hotel accommodation*	*Airport arrival and bus transfer to Cremona.* *Hotel accommodation* **(5:30pm) City guided tour**	**(2pm-6pm)** **Fieldtrip** (from 6pm) Free time in the city	**(2pm-6pm)** **Fieldtrip** (from 6pm) Free time in the city		**(2pm-6pm)** **Fieldtrip** (from 6pm) Free time in the city	**(2pm-5pm) Round table with experts** (from 5pm) Free time in the city	
	Free dinner	Free dinner	Free dinner	**GALA DINNER**		**FINAL DINNER**	Free dinner	
Evening	Free	Free	Free	**Evening tour and violin audition at MdV**		**Party with music**	Free	

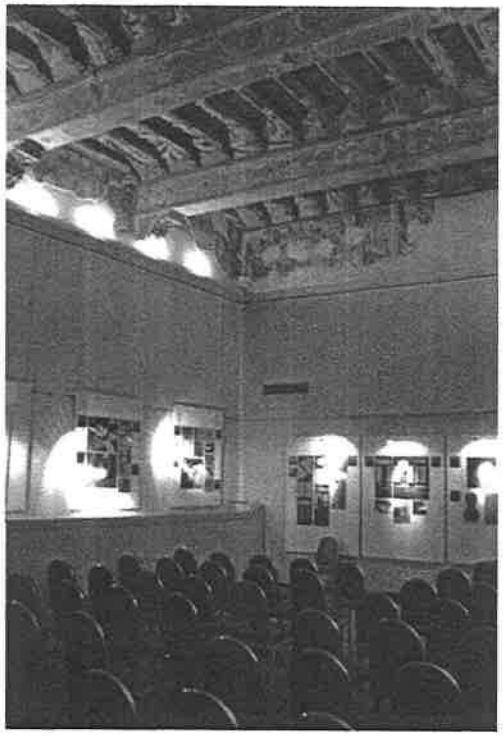
Classrooms at our disposal

CERSI
CENTRO DI RICERCA PER LO SVILUPPO IMPRENDITORIALE

OFFICE SPACE

This room, decorated with a fresco from 1500 attributed to Giovanni Battista Trotti called il Malosso (1555/1619), is going to act as permanent secretariat for the summer courses.

The nearby **SALA DEI VIOLINI** (36 seats) with coffered ceiling, is going to be the main classroom for the executive courses during the EXPO semester.



SUPERFICIE ED ALLESTIMENTI POSSIBILI

mq.	Aula
68	36

UNIVERSITÀ CATTOLICA del Sacro Cuore

Classrooms at our disposal

UNIVERSITÀ CATTOLICA del Sacro Cuore
CERSI
CENTRO DI RICERCA PER LO SVILUPPO IMPRENDITORIALE

SALA GRADELLINI

This room is purely dedicated to the training. There are 36 seats available (theater style) with fixed tables. A fixed cabin for the simultaneous translation is also available.

SUPERFICIE ED ALLESTIMENTI POSSIBILI

mq.	Aula
58	36

AULA ORO (GOLDEN ROOM)

The impressive double-truss ceiling and the big wooden frames date back to 1626. In the room it is possible to appreciate the ancient «lion paw-shaped» fireplace, made of Verona's red marble. The room, equipped as classroom, can accommodate up to 28 people.

SUPERFICIE ED ALLESTIMENTI POSSIBILI

mq.	Teatro	Sala consiglio	Aula	Ferro di cavallo
72	60	20	28	24

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How to promote them? The marketing strategy

CERSI
CENTRO DI RICERCA PER LO SVILUPPO IMPRENDITORIALE

B2C Channel: *free sales of the courses available in the catalogue*, through an international marketing campaign on professional addresses

B2B Channel: *sale of customized courses for specific institutions, public or public, Italians or international* (list and relations).

Partnership: *companies sponsorships,* which send, at their own expenses, people of interest to our standard courses.

Lead generation	Key account manager	Direct contacts

WEBSITE with the official Patronage of EXPO 2015 Milan
Multilanguage (ITA, ENG, FR, SPA, PORT, RUS, CIN)

PROGRAM PRESENTATION – INTERACTIVE COURSE CATALOGUE - LOCATION & TERRITORY PARTNER & COMPETENCIES – SUBSCRIPTION TO THE COURSES (& PAYMENT) – BOOKING OF ACCOMODATION AND TRANSFER SERVICES – MATERIALS DOWNLOAD - **LINKs**

Creation of an **international database** with institutions and people that are potential contacts

'Content marketing" (e-book, newsletter, materials, video) in order to address the traffic to our website.

Creation of specific partnerships, for each course, with public or private institutions and scientific communities, Italian and international.

Web marketing campaign (adwords, SEM, blog, social network, etc.)

Organic alliance with **Expo Milano** to have the participant countries (mailing, educational, ecc.)

Center for Veterinary Medicine

OIP's Educational Forum for Washington D.C.-Based Embassy Officials

FDA's Regulatory Framework

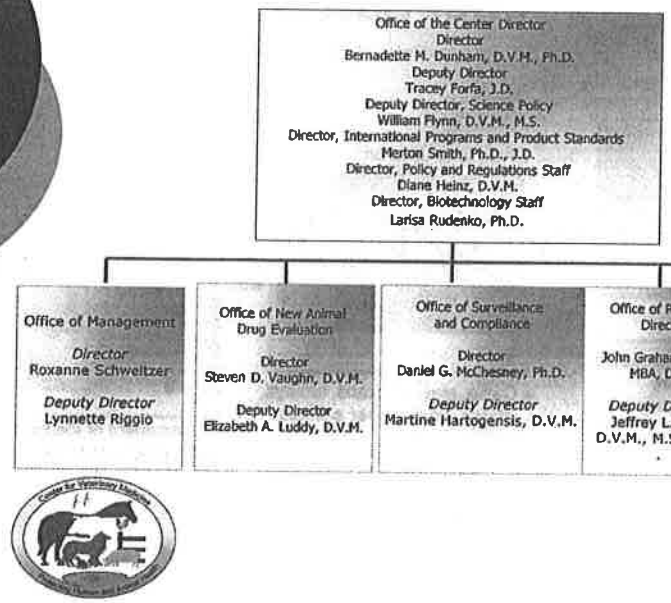
July 7, 2014

Presented by

International Programs and Product Standards

Office of the Center Director, CVM

CVM Organizational Chart



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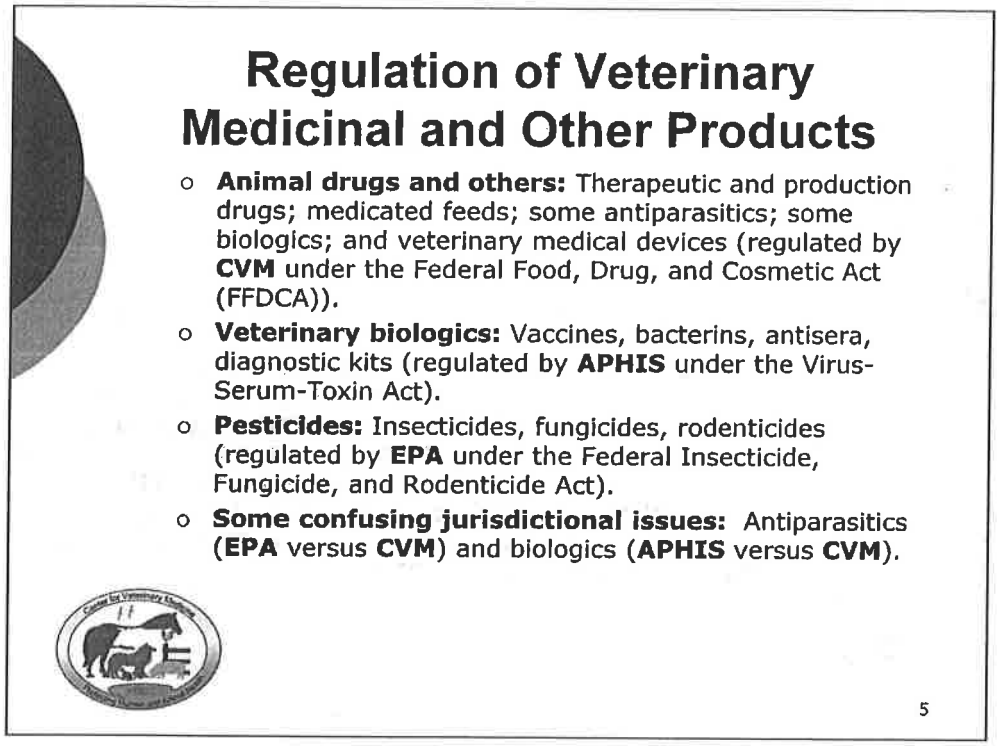
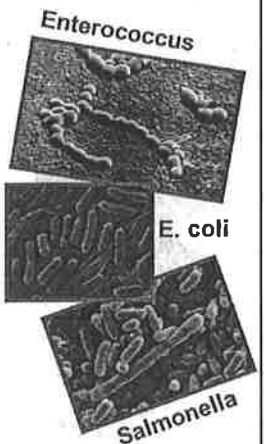


Production drugs include those used for reproduction, growth promotion, feed efficiency and can be hormones and antibiotics and others.

Antimicrobial Resistance

- FDA initiatives to provide for the safe use of antimicrobials in food animals while ensuring that significant human antimicrobial therapies are not compromised or lost.
  - Guidance on *"Judicious Use of Medically Important Antimicrobial Drugs in Food-producing Animals"* (April 2012).
  - Enhancing the quality and accuracy of data on antimicrobial drug sales and distribution.
  - Guidance for drug sponsors to voluntarily withdraw performance uses from specific antimicrobial products and revision of the Veterinary Feed Directive (December 2013).
- Continue monitoring resistance among enteric pathogens in both animals and humans through the National Antimicrobial Resistance Monitoring System (NARMS).



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NARMS is a joint program among FDA, CDC, and FSIS.

Plant Biotechnology – Genetic Engineering

- Process in which recombinant DNA (rDNA) technology is used to introduce desirable traits into plants.
- Policy statement published in May 1992 on *'Foods and feeds derived from new plant varieties, including plants developed by recombinant deoxyribonucleic acid (rDNA) techniques."*
- **CFSAN** and **CVM** regulate food and feed from GE crops through the food additive and GRAS provisions of the FFDCA and by voluntary consultation procedures.
- FDA also shares some regulatory responsibilities over GE plants with APHIS and EPA: **APHIS** makes sure that all new GE plant varieties pose no pest risk to other plants; **EPA** regulates pesticides, including GE food crops, to make sure they are safe for human and animal consumption and do not pose unreasonable risks of harm to human health or the environment.

9

Potential for Genetically Engineered Animals

- Biopharm (e.g., ATryn goat that produces a human anticoagulant biologic was approved on February 6, 2009)
- Research
- Xenotransplantation
- Disease resistance
- Animal derived food products

11

Off-Label or Extra-Label Uses of Animal Drugs

- Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) veterinarians can prescribe extra-label uses of certain approved animal drugs and approved human drugs for animals under specific conditions.
  - Extra-label use refers to the use of a drug in a manner that is not in accordance with the approved label directions.
  - Requires that any extra-label use must be by or on the order of a veterinarian within the context of a veterinarian-client-patient relationship and must not result in violative residues in food-producing animals.
  - A list of drugs specifically prohibited from extra-label use appears in the Code of Federal Regulations (21 CFR 530.41).
- CVM does not regulate the practice of veterinary medicine (**States** serve this function through controls on licensing veterinarians and dealing with any concerns regarding malpractice).

13

International Activities (continued)

- CVM experts are working with OIE and others from the EU, Japan, Australia, New Zealand, Canada, and South Africa in the International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH). VICH also reaches other countries through its VICH Outreach Forum meetings.
  - VICH guidelines cover studies needed to assess human food safety of drug residues, drug product quality including impurities and stability, target animal safety, environmental impacts, metabolism and residue kinetics, bioequivalence, combination products, pharmacovigilance, efficacy, and good clinical practices.
- CVM experts participate in the development and review of the OIE Terrestrial and Aquatic Animal Health Codes (e.g., BSE controls, antimicrobial resistance controls, and controls on drug use and management in aquaculture).
- All of these Codex and OIE standard-setting activities have important significance to the Agreement on the Application of Sanitary and Phytosanitary (SPS) Measures of the World Trade Organization.

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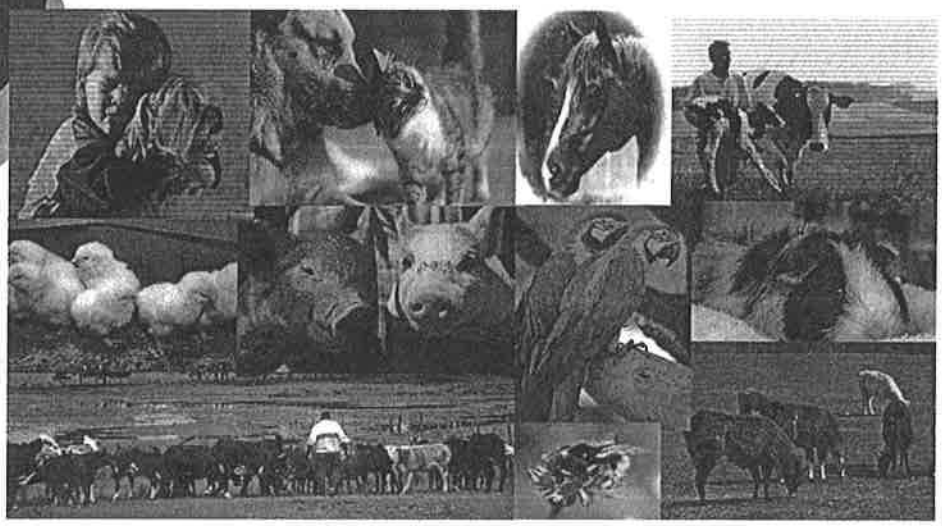
Protecting both Human and Animal Health
THANK YOU!!



July 9, 2014 agenda for Dr. Su-San Chang

11-11:30	Introduction to CVB	Mark Pagala
11:30-12:00	General Licensing considerations and Intro to PEL, PEDV	Geetha Srinivas
12:00-12:15	Product for export only and FDA-EREA	MB Evans and Carol Gibbs
12:15-1	Lunch and description of other groups in the building, PEDV	Paul Hauer
1-1:50	Risk assessment and biotech	Pat Foley
2-2:50	Introduction to IC	Ruben Osorio
3-3:30	Rabies Vaccines	Alethea Fry and Larry Ludemann
3:30-3:50	Licensing products for minor species	Larry Ludemann
4-4:30	Tour and introduction to the lab	Kylius Wilkins

Kylius will be here for her visit (I am traveling July 9 and not in the office).

Kylius can be reached at : Office: 337-7831, Home: 337-1198, Mobile: 515-441-9688.

July 9, 2014 agenda for Dr. Su-San Chang

11-11:30	Introduction to CVB and house keeping	Mark Pagala
11:30-12:00	General Licensing considerations and Intro to PEL, PEDV	Geetha Srinivas
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We have reserved Room 2136 (conference room at the far end of the BACT lab) for Dr. Chang and the people talking with her. She is only here for the day. If you have a presentation, please bring a lap top down or handouts for Dr. Chang.

Kylius will be here for her visit (I am traveling July 9 and not in the office). Kylius can be reached at : Office: 337-7831, Home: 337-1198, Mobile: 515-441-9688.

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ICAB Inspection and Compliance

Stability of vaccinia-vectored recombinant oral rabies vaccine under field conditions: A 3-year study

Joseph R. Hermann, Alethea M. Fry, David Siev, Dennis Slate, Charles Lewis, Donna M. Gatewood

Abstract

Rabies is an incurable zoonotic disease caused by rabies virus, a member of the rhabdovirus family. It is transmitted through the bite of an infected animal. Control methods, including oral rabies vaccination (ORV) programs, have led to a reduction in the spread and prevalence of the disease in wildlife. This study evaluated the stability of RABORAL, a recombinant vaccinia virus vaccine that is used in oral rabies vaccination programs. The vaccine was studied in various field microenvironments in order to describe its viability and facilitate effective baiting strategies. Field microenvironments influenced the stability of this vaccine in this study. This study emphasizes the importance of understanding how vaccines perform under varying field conditions in order to plan effective baiting strategies.

Résumé

La rage est une maladie zoonotique incurable causée par le virus de la rage, un membre de la famille des rhabdovirus. La maladie est transmise suite à la morsure par un animal infecté. Les méthodes pour limiter cette maladie, incluant des programmes de vaccination orale (ORV), ont entraîné une réduction dans la dissémination et la prévalence de cette maladie dans la faune sauvage. La présente étude visait à évaluer la stabilité du RABORAL, un vaccin recombinant de la vaccine qui est utilisé dans les programmes de vaccination orale contre la rage. Le vaccin a été étudié dans différents micro-environnements de terrain afin de décrire sa viabilité et faciliter des stratégies efficaces d'appâtage. Dans la présente étude la stabilité du vaccin était influencée par les micro-environnements de terrain. L'étude met l'emphase sur l'importance de comprendre la performance des vaccins afin de planifier des stratégies d'appâtage efficaces.

(Traduit par Docteur Serge Messier)

Introduction

Rabies virus is an enveloped, negative-sense, single-stranded ribonucleic acid (RNA) virus of the genus *Lyssavirus* in the family *Rhabdoviridae* (1). Rabies causes acute, progressive, incurable viral encephalomyelitis and is usually transmitted through the bite of an infected animal. It is a zoonotic disease that causes 40 000 to 100 000 human deaths annually worldwide (2). Wildlife is the primary reservoir for rabies virus and the most important potential source of infection for both humans and domestic animals in the United States (3). Wildlife accounted for 93% of the reported cases of rabies in 2008; 35% of these cases were raccoons (3). The raccoon reservoir has resulted in an increased spread of raccoon variant rabies in North America (4) and plays a major role in the epidemiology and epizootiology of the disease (5,6).

Control methods to reduce the spread of raccoon rabies include population reduction, trap-vaccinate-release, and oral rabies vaccination (ORV) programs (7,8). Oral rabies vaccination programs in North America, including large-scale campaigns undertaken by the United States and Canada, have led to a reduction in the prevalence of raccoon, fox, and canine-variant rabies (8–14). Oral vaccination programs continue to focus on preventing the spread of raccoon-variant rabies from the eastern United States (15).

A number of variables affect the success of ORV programs in reducing the spread of rabies (16), including effective oral vaccination strategies (17). Effective strategies for vaccinating wildlife require that the target animals ingest the dispersed baits before environmental degradation of the vaccine below a titer that elicits a protective neutralizing antibody response.

Two types of vaccines have been implemented worldwide in ORV programs: modified live-virus (attenuated) vaccines and live recombinant (recombinant) vaccines (18). Recombinant oral rabies vaccines express the vaccinia-rabies glycoprotein (V-RG) by insertion of the Evelyn-Rokitnicki-Abelseth (ERA) rabies strain glycoprotein gene into the thymidine kinase gene of the vaccinia virus (Copenhagen strain) (19,20). It has been shown that recombinant vaccines derived from attenuated vaccinia virus are more stable in vitro than attenuated vaccines derived from the Street Alabama Dufferin (SAD) rabies virus (21). Although the stability of SAD vaccines under field conditions has been described (22), the authors are unaware of any reports detailing the stability of recombinant vaccines at various locations in the field for purposes of comparison. Thus, the objective of this study

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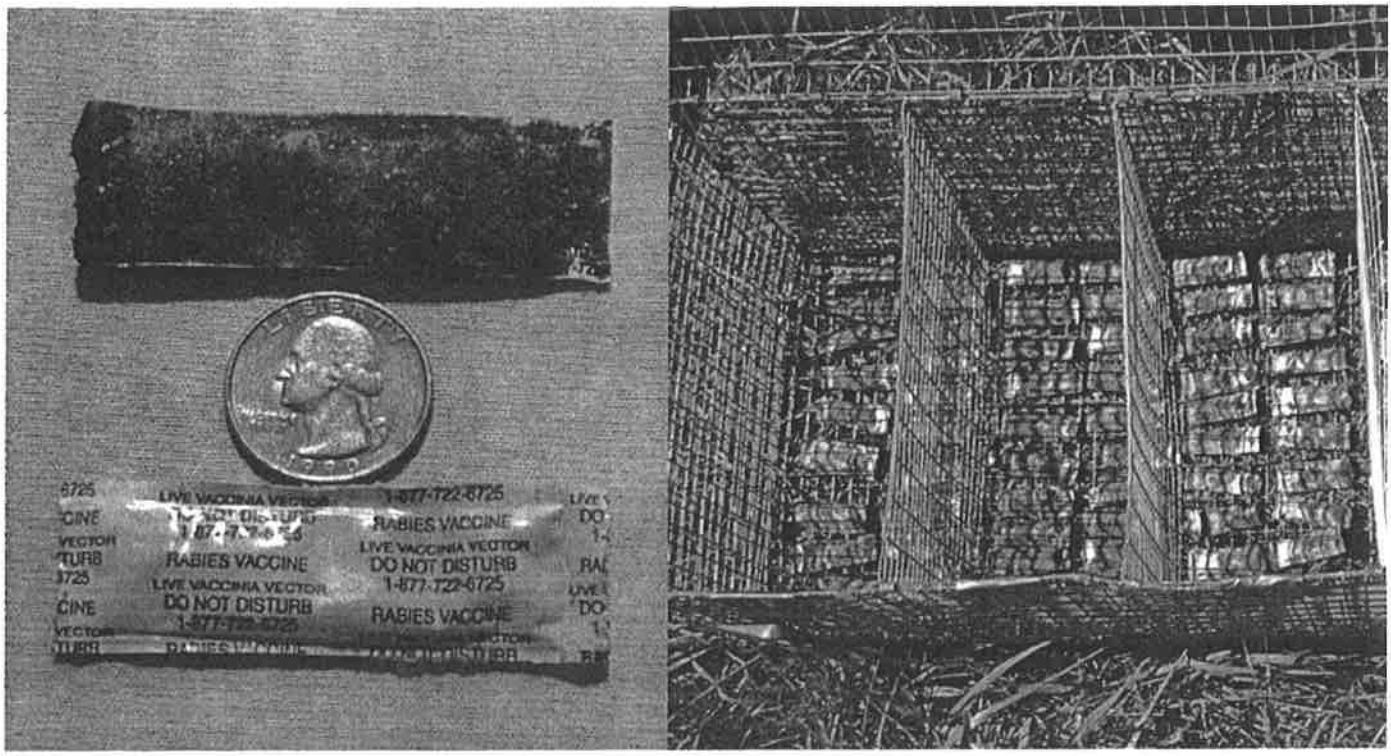

Figure 1. A — RABORAL V-RG coated sachet (CS) bait. Baits consist of a sachet coated with fishmeal polymer crumbs and filled with vaccine (top). Uncoated, polyethylene plastic sachet is shown for comparison (bottom). B — Distribution of RABORAL V-RG coated sachet baits in wire mesh protective cage.

was to evaluate the stability of a recombinant vaccinia virus vaccine under various field microenvironments to further understand vaccine viability and to plan effective baiting strategies.

Materials and methods

Vaccine virus

RABORAL vaccinia-rabies glycoprotein (V-RG) (Mérial, Athens, Georgia, USA) is an oral rabies vaccine designed specifically for wildlife. It is used in coordinated ORV programs in the United States and Europe. The product is licensed by the United States Department of Agriculture (USDA) for the oral vaccination of raccoons or coyotes against disease caused by pathogenic rabies virus. The baits consist of a sachet coated with fishmeal polymer crumbs and filled with vaccine (Figure 1). Each vaccine dose contains a minimum titer of $\geq 1 \times 10^{7.7}$ median tissue culture infective dose ($TCID_{50}$) at the time of manufacture.

Study design

Production lots of RABORAL V-RG that are eligible for distribution through the Wildlife Service's Oral Rabies Vaccination Program were evaluated for environmental stability. The study was carried out in 3 geographic locations (Youngstown, Ohio; Greenville, Tennessee; and Potsdam, New York), included 3 microenvironmental treatment groups [forest canopy (FC), forest edge (FE), or open field (OF)] at each location, and spanned 3 calendar years (2007 to 2009). The microenvironmental treatments were defined as: 1) FC — tree canopy providing full protection from sunlight; 2) OF — direct exposure to sunlight due to no protection from forest canopy; and 3) FE — the marginal zone of altered microclimate represented by the area between the tree trunks of the outermost canopy and the lower-lying vegetation of the open field (23,24).

The number of geographical locations evaluated varied from year to year. Each year a production lot of vaccine for a different geographic location (state) was randomly selected for stability evaluation and distributed to all microenvironments (Table I). By design, therefore, the lot is confounded with state/year. Consequently, no inference was attempted on potential differences between states or years. Inference was limited to microenvironments across state/year combinations. If interaction occurred between the microenvironment and state/year or lot, it would have invalidated generalized inference about microenvironments on the stability of rabies vaccines. While such interactions may not be impossible, they are implausible enough in this setting for us to feel comfortable with our conclusions about the role of microenvironments in general.

Vaccine baits were maintained at 2°C to 7°C in a refrigerated trailer during transportation to each microenvironment. Twenty-five baits per microenvironment were dispersed evenly in 0.64-cm wire mesh protective cages [91.4 cm (L) × 30.5 (W) × 30.5 cm (H)] that were staked to the ground (Figure 1). Hinged tops allowed the baits to be removed from the protective cages. Five replicate baits were collected from each treatment group on days 0, 1, 7, 14, and 28 and stored at 2°C to 7°C until shipment. After the study was completed, baits were shipped to the USDA's Animal Plant Health Inspection Service (APHIS) Center for Veterinary Biologics (CVB) at Ames, Iowa

Table I. Location, vaccine lots, and dates of distribution and collection for V-RG rabies field stability study

Location (State)	Vaccine lot	Dates of distribution and collection of baits
Ohio	13441B	09/01/07 to 09/29/07
Tennessee	13450A	10/12/07 to 11/09/07
Ohio	13475C	09/04/08 to 10/02/08
Tennessee	13508D	10/14/08 to 11/04/08
New York	13455B	08/25/08 to 09/22/08
New York	13519A	09/02/09 to 09/30/09

V-RG — Vaccinia-rabies glycoprotein.

and stored at 2°C to 7°C until tested. Baits were tested for potency over the course of 14 d after receipt. To preserve bait titers during transport to study locations and storage before testing, retention samples from each vaccine production lot maintained at CVB were assayed and compared to day 0 baits collected from the field.

Titration of vaccine

Vaccine fluid was removed from sachets using a 3-mL syringe and 21-gauge needle and titrated on confluent monolayers of Vero cells (Lot 96-01; Center for Veterinary Biologics, Ames, Iowa, USA) in 96-well tissue culture plates. Cell monolayers were prepared by seeding each well with 4×10^4 cells suspended in minimum essential media (MEM)-F15 growth medium [MEM with Earles (F15) supplemented with 5% fetal bovine serum (FBS), 100 μg/mL of L-glutamine (G7513; Sigma Chemical, St. Louis, Missouri, USA), and 50 μg/mL of gentamicin (G1272; Sigma Chemical)]. The plates were then incubated at 37°C in a humidified incubator for 18 to 30 h. After incubation, the growth medium was discarded and 100 μL of maintenance medium [MEM with Earles (F15) supplemented with 1% FBS, 100 μg/mL of L-glutamine, and 50 μg/mL of gentamicin] was added to all wells. Serial 10-fold dilutions (10^0 to 10^{-8}) were prepared in MEM with Earles (F15) and supplemented with 100 μg/mL of L-glutamine and 50 μg/mL of gentamicin. Each dilution (50 μL) was added to 10 replicate wells. Thereafter, plates were incubated at 37°C in a humidified 5% CO_2 incubator for 7 d. Infected monolayers were examined for cytopathic effects (CPE) daily.

At the end of the incubation period, samples from days 0, 14, and 28 were tested for the expression of rabies glycoprotein. Maintenance medium was discarded and the cells were washed with 0.01 M phosphate-buffered saline (PBS) and fixed with aqueous 85% acetone (H451-06; Mallinckrodt Baker, Phillipsburg, New Jersey, USA). Fifty microliters of monoclonal antibody (MAb) (Mérial, Lyon, France) specific for the rabies glycoprotein was added to each well and incubated at 378C for 60 min. Wells were washed twice with 200 mL of 0.01 M PBS and 50 mL of fluorescein isothiocyanate (FITC)-conjugate anti-IgG antibody (31569 ImmunoPure; Thermo Scientific, Rockford, Illinois, USA) was added. Monolayers were incubated at 37°C for 60 min and washed twice with 200 mL/well of 0.01 M PBS. Monolayers were observed for rabies-specific fluorescence using an ultraviolet (UV) microscope (Model IX70; Olympus, Center Valley, Pennsylvania, USA). Virus titers were based on the number of infected [virus-specific cytopathic effect (CPE) and/or positive fluorescence reaction] and uninfected wells at a given dilution. Monolayers infected with parental vaccinia virus served as positive controls and mock-infected monolayers served as negative controls.

Statistical analysis

Viral counts were estimated from the titrations with a binomial generalized linear model using the complementary-log-log link function:

$$\log_e\{-\log_e(1-\pi)\} = \alpha + \log_e(dilution)$$

where: π is the probability of a positive response and α is the natural logarithm of the viral count in undiluted material (25). The estimated counts were converted to titers, expressed as median infective dilution per dose of vaccine, by setting the response probability (π) equal to 1/2 in the preceding equation, thereby giving:

$$\log_{10}(TCID_{50}) = \log_{10}(e^{\alpha}) - \log_{10}(\log_e(2))$$

Averages were taken as weighted geometric means (WGM), using the inverse of the variance of the viral counts as weights. The loss in viability between any 2 sampling times was estimated by taking the difference between their WGMs. When possible, the pattern of viability loss was described by weighted regression models of the form:

$$\log_{10}(e^{\alpha}) = A + B \times day^D$$

which is a flexible Weibull model used to fit microbial decay curves of various shapes (26). In addition to its empirical value, in some circumstances it may also reflect the mechanism of viability loss underlying the shape of the curve (discussion follows) (27). Note that when the model's shape parameter D is equal to 1, the resulting curve is an exponential decay curve, a special case of the Weibull model. Models were fit by nonlinear least squares (28), as implemented in the nls function of R version 2.11.1 (29).

Results

Titration of vaccine

The volume of vaccine recovered from the collected baits at time of testing ranged from 0.5 to 1.5 mL. Upon completion of testing, the wells expressing rabies glycoprotein were in concordance with those with visible CPE, varying by $< 10^{0.1}$ logs. Based on well data from the micro-infectivity assay, the limit of detection,

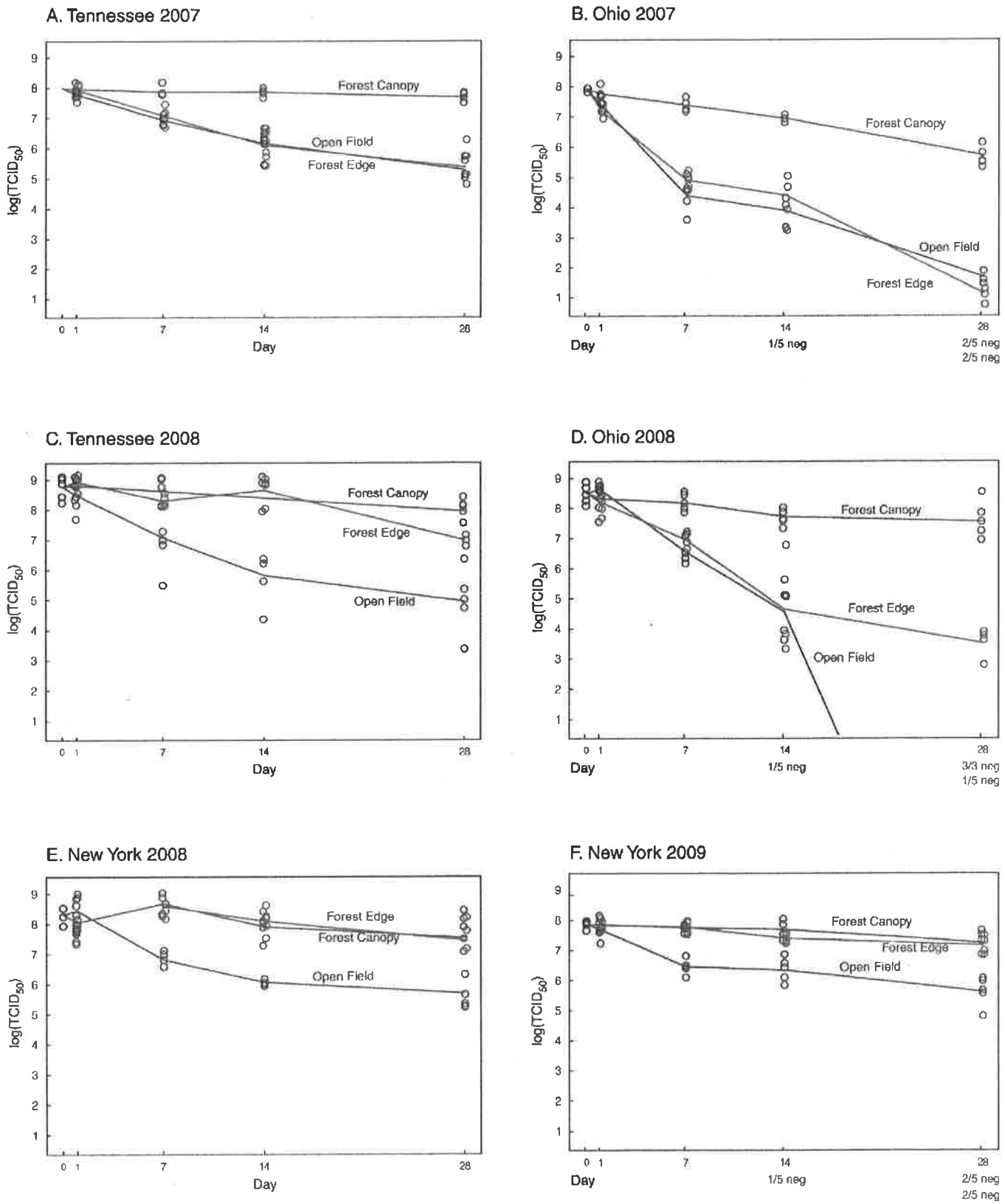

Figure 2. Titers by microenvironments of field samples collected on days 0, 1, 7, 14, and 28. Lines join the weighted geometric mean titer at each collection time. Points are slightly offset to aid visualization. Samples below the titration limit of detection are indicated as negative.

Table II. Weighted geometric mean 2-week titer loss (in common logarithms)

State	Year	Forest canopy (FC)	Open field (OF)	Difference (95% CI)
Tennessee	2007	0.1	1.8	1.7 (1.5, 1.9)
Ohio	2007	1.0	4.0[a]	3.0 (2.8, 3.3)
Tennessee	2008	0.4	3.0	2.6 (2.3, 2.8)
Ohio	2008	0.8	4.0[a]	3.2 (2.9, 3.4)
New York	2008	0.4	2.2	1.8 (1.6, 2.1)
New York	2009	0.2	1.5	1.3 (1.1, 1.6)
Column average		0.5	2.6	2.2 (2.1, 2.3)

[a] Analysis does not include 1/5 samples that were negative.
CI — Confidence interval.

defined as the concentration with 50% response probability, was 0.44 plaque-forming units (PFUs) per 50 μL of aliquot, or approximately $10^{1.0}$ PFUs per milliliter.

Effect of transportation and storage on vaccine titer

No difference in titers was observed between retention samples and day 0 baits. The day 0 baits had a mean of titer $10^{8.2}$ $TCID_{50}$/dose and a range of $10^{7.9}$ to $10^{8.8}$ $TCID_{50}$/dose at the time of distribution.

Effect of field microenvironment on vaccine titer

The virus viability of the vaccine baits collected from different microenvironments was compared. Baits in the FC microenvironment retained higher levels of virus viability than those exposed to the OF microenvironment (Figures 2A to 2F). Over the 4-week study periods, titers from the FC microenvironments decreased an average of $10^{0.9}$ [95% confidence interval (CI): $10^{0.8}$, $10^{1.0}$] $TCID_{50}$ and titers from the OF or FE microenvironments decreased an average of $10^{3.3}$ (95% CI: $10^{3.2}$, $10^{3.4}$). (The OF estimate should be regarded as a minimum since it does not include the Ohio 2008 samples taken at 28 d, which were all below the titration's limit of detection.)

Titers from baits exposed to the FE microenvironments were similar to those from either the FC or the OF locations and, in most cases, the FE profiles nearly overlaid one or the other (Figure 2). This suggests that the FE was not a distinct microenvironment, but simply reflected an amount of exposure that was similar to either the FC or OF microenvironments. The greatest reduction in vaccine titer was observed in the first 2 wk of field exposure. Baits placed in OF decreased an average of $10^{2.2}$ $TCID_{50}$ (95% CI: $10^{2.1}$, $10^{2.3}$) more than baits placed in FC. The 2-week difference between the OF and the FC microenvironments ranged from $10^{1.7}$ to $10^{3.2}$ $TCID_{50}$ (Table II).

The OF titers were fit with a nonlinear model that corresponds to a short half-life early on, indicated by the steep initial part of the curve, followed by an increasing half-life as the study period progresses, indicated by the gradual flattening of the curve. By contrast, viability loss in the sheltered locations was slow and constant during the study period. An example of this is shown in the regression models for the Tennessee data (Figure 3). For OF, the Weibull shape parameter estimate is $D = 0.51$. When the shape parameter is less than 1, curves are concave upward, which corresponds to increasing half-life (decreasing hazard). By contrast, the shape parameter estimate for FC was not significantly different than 1 (likelihood ratio test $P = 0.74$). The FC titers are therefore fit with a straight line, which indicates a constant half-life over the course of the study, as in a typical exponential decay model.

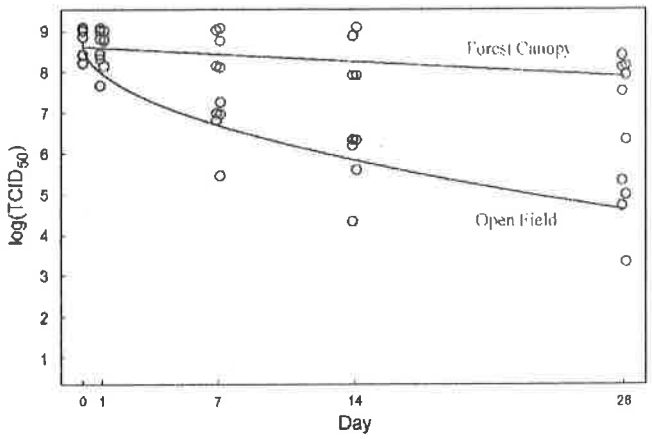

Figure 3. Tennessee 2008 — Model Fit.

Decreasing hazard Weibull distributions can arise as mixtures of exponentials (27). It is therefore reasonable to speculate that there are underlying sub-populations of virus of varying susceptibility. This differential lability may not be evident under mild conditions, but may be exposed by harsher conditions of UV radiation, heat, desiccation, and possible enzymatic action. The fact that several inactivating mechanisms are acting simultaneously or sequentially would increase apparent differential lability. Under such conditions, the most susceptible virions may be rapidly inactivated initially, leaving the more resistant particles to be inactivated more slowly. Varying resistance may be due to random physical phenomena such as clumping, inherent features that require multiple hits to multiple targets, or successive exposure to different inactivants (30). By contrast, under the milder conditions of the sheltered locations, inactivation proceeds slowly enough that the effect of differential lability is not readily evident and decay appears linear on a logarithmic scale. The Weibull model encompasses all of these possibilities.

Discussion

Veterinary biological products licensed in the United States are required to have acceptable potency throughout their dating period.

Specifications for potency are based on the composition of the vaccine serial (lot) used to demonstrate product efficacy for licensure; the potency of this serial defines the minimum protective dose. Additional potency may be required at time of manufacture to allow for some degradation throughout the dating period, while still maintaining the minimum protective dose. Potency specifications assume that the product is handled and stored according to label recommendations (usually at 2°C to 7°C). Licensing regulations do not provide for oversight or consideration of product stability under field use conditions (31). It is therefore incumbent on the end user to evaluate this aspect of product use and take appropriate steps to optimize product performance. The present study was intended to estimate the stability of RABORAL V-RG rabies vaccine under varying field conditions.

Field microenvironments influenced the stability of RABORAL V-RG in this study. Environmental variables that affect vaccine stability include temperature, UV radiation, and duration of exposure (32,33). Previous studies demonstrated that prolonged exposure to elevated temperatures and UV radiation decrease the stability of V-RG rabies vaccines (21). Although environmental data, such as temperature and UV radiation, are lacking from the present study, the decrease in vaccine titer observed is contrary to previously published field stability data. This may be explained, however, by seasonal differences during the collection periods (21).

Results from this study suggest that vaccine titer within the bait was consistent in both the FC and OF microenvironments. The FC has climate-buffering effects provided by the tree canopy on all sides. The variability in the data from the FE could be explained by the physical gradients that are dependent on the availability of light and direct beam radiation. It has previously been shown that direct beam radiation can affect conditions in microenvironments, especially in areas that have lost lateral protection on 1 or more sides, as is true with the FE location (23,24).

Local direct beam radiation in the FE microenvironment can lead to increased near-ground temperature, drying of leaf litter, and changes in the vapor pressure density, all of which could lead to a decrease in vaccine titer (23). Depending on the cardinal compass direction, the directness of the radiation may cause the baits in the FE microenvironment to act in a similar manner to baits in the FC or OF. For example, the Tennessee 2007 data could be explained by the vaccine baits being located in an FE location in which the lateral protection, the forest, was located on a side that caused the bait to be exposed to direct sunlight for a maximum amount of time. This mimicked those conditions found in an OF location. For the Tennessee 2008 data, the opposite occurred, which is probably because the forest provided lateral protection from direct sunlight for a significant portion of the day.

As described in previous studies (12,34), 83% to 100% of baits are consumed within 7 d of distribution. On day 7 of this study, the combined average vaccine titer of the baits in the FC microenvironment exceeded the minimum protective dose ($10^{7.7}$ $TCID_{50}$), while the average titer of baits in the OF environment fell below the minimum protective dose. The efficacy of the baits in the OF environment at day 7 and beyond is therefore uncertain.

In conclusion, while it is beneficial to understand and confirm the stability of the V-RG rabies vaccine when stored under appropriate conditions, building a knowledge base that makes it possible to predict the performance of the vaccine under field conditions provides a mechanism for planning effective baiting tactics in the future. Data from this study may be used to assess and improve current baiting strategies.

Acknowledgments

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United States Department of Agriculture

Animal and Plant Health Inspection Service

General Licensing Requirements in the United States

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Objectives

- Definition
- Historical perspective
- Regulatory framework
- Establishment requirements
- Product license requirements

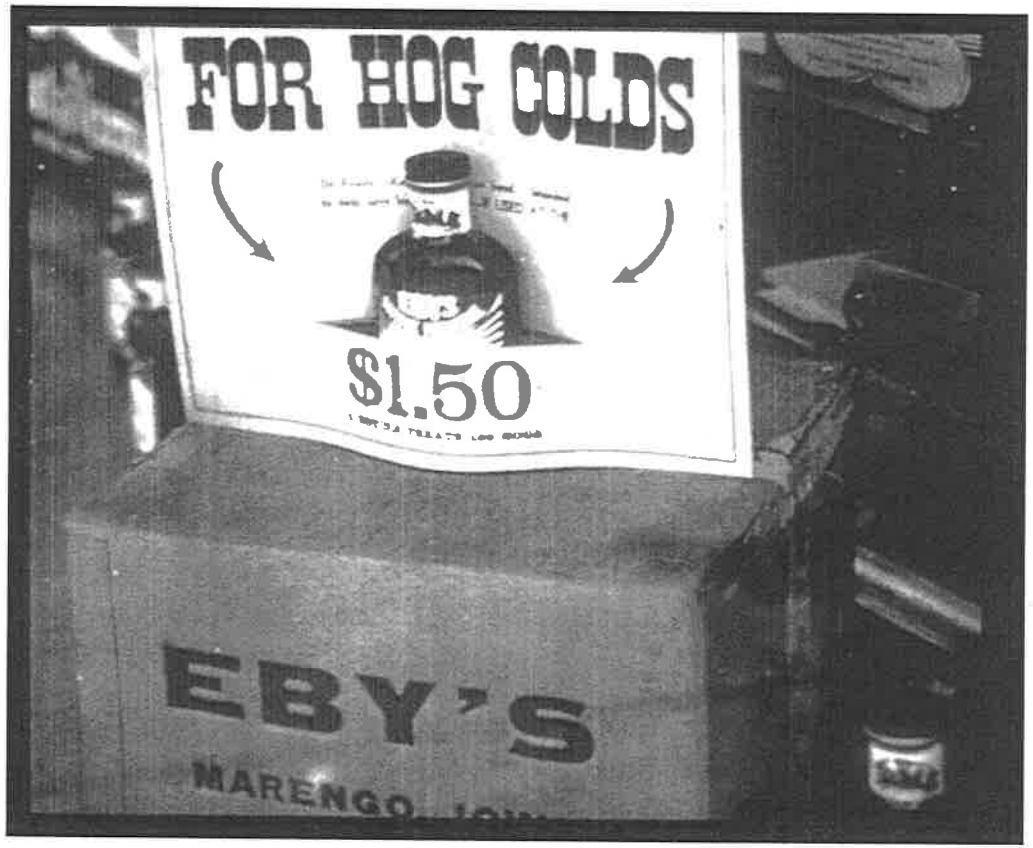
14 reviewers

"Biological Product[1]" - Definition:

- **all viruses, serums, toxins, or analogous products.....which are intended for the use in the treatment of animals and which act primarily through.....the immune system or immune response.**

[1]vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components…

Virus-Serum-Toxin Act of 1913



Virus-Serum-Toxin Act of 1913

...it is unlawful to:

Sell Worthless, Dangerous, Contaminated, or Harmful (W-D-H-C) biologics

Ship biologics unless they are:

- **prepared in compliance with USDA regulations**
- **prepared in a licensed establishment**

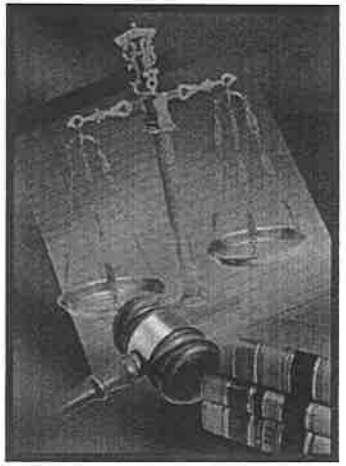
Virus-Serum-Toxin Act (cont.)

- Authorizes USDA to make and issue regulations to prevent preparation and marketing of W-D-C-H biologics

- Provides for inspection of:
  - manufacturing facilities
  - manufacturing processes
  - biological products

Virus-Serum-Toxin Act (cont.)

- Provides for suspension and revocation of licenses (hearing)
- Requires Permits for imported biologics
- Provides for examination of biologics prior to importation



Amendment to the Virus-Serum-Toxin Act

(Passed December 23, 1985)

- Provides for:
  - Regulation of all veterinary biologics (intrastate)
  - Licensing for export
  - Conditional or Special Licenses
  - Detentions, seizures and condemnations and injunctions

- Exemption from licensure by regulations for certain products

Licensing Exemptions

- Official USDA Program, emergency disease situation, or USDA experimental use
- Veterinarian-client-patient relationship
- Animal owners
- Products under State license
- FDA Export Reform and Enhancement Act of 1996: Note – *No* U.S. Establishment # is on the label
  - U.S. Veterinary License No. xxx
  - U.S. Vet. License No. xxx
  - U.S. Vet Lic. No. xxx

Regulatory Framework

- Virus-Serum-Toxin Act (1913 & 1985)
  (21 U. S. Code, Sections 151-159)
- Title 9 Code of Federal Regulations
  (Parts 101-122)
- Veterinary Biologics Memorandums and Notices
- General Licensing Considerations

Types of Veterinary Biologics Licenses Issued

- Establishment License
  - Regular
- Product License
  - Regular (with or without restrictions)
  - Conditional
  - For further manufacture
  - For export only

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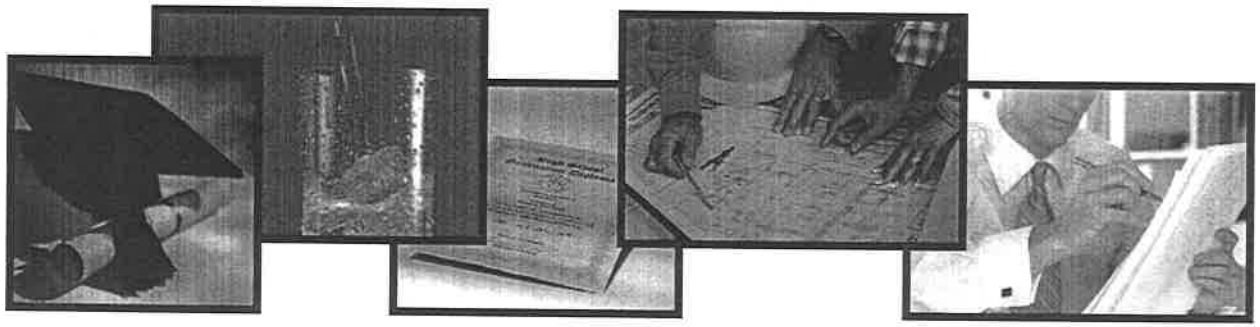
Requirements for U.S. Veterinary Biologics Establishment License

- ❑ Application—APHIS Form 2001
- ❑ Supporting materials:
  - Articles of Incorporation
  - Water quality statement
  - Plot plans, blueprints & legends
  - Personnel qualifications



Requirements for U.S. Veterinary Biologics Establishment License

- Prelicense inspection
  - record keeping systems
  - validity of blueprints and legends
  - condition of the facility
  - laboratory practices
  - sampling, testing, and other compliance requirements

- One product qualified for licensure

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Requirements for U.S. Veterinary Biologics Establishment License

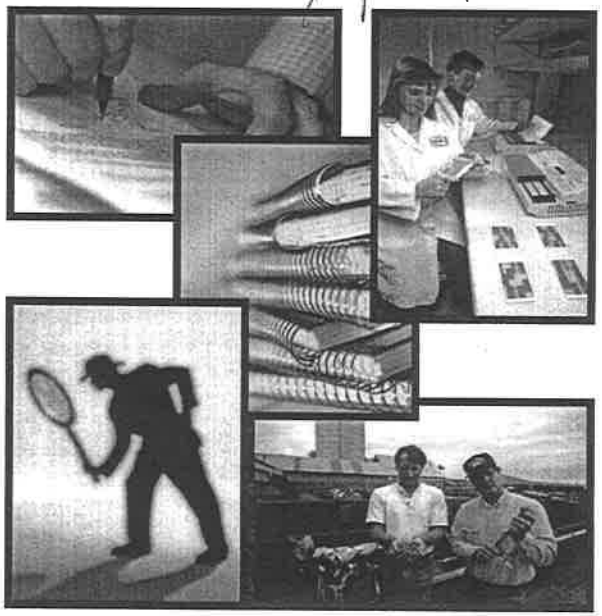
- Application—APHIS Form 2003:
  One for each product

- Supporting materials
  - Outline of Production
  - Supporting data
    - research data
    - laboratory test records
    - field testing reports

GMP like

personnel data

equipments



Product Types

- Vaccine
- Bacterin and Bacterial Extract
- Toxoid
- Bacterin-Toxoid
- Antitoxin
- Antiserum and Antibody
- Diagnostic
- Immunomodulator and Immunostimulant
- Allergenic Extract

Basic Biologics Product License Requirements

- Should reflect "good science" and "good sense "
- Data review:
  - case-by-case basis
  - standard licensing requirements
  - general and special licensing considerations
- Purity, Safety, Potency and Efficacy

Basic Biologics Product License Requirements

- When application and all required supporting material have been received and filed as satisfactory, the establishment and first product licenses are issued
- Subsequent product licenses are issued as requirements for each application are completed

Key Licensing Elements

- Characterization of Master Seed
- Characterization of Master Cell Stock
- Host animal efficacy
- Backpassage Tests (live)



Key Licensing Elements (cont.)

- Field Safety
- 3 consecutive Serials
- Serial release testing (purity, safety, potency)
- Stability

General Licensing Considerations

- Data must represent the product
  - In accordance with the Outline of Production
  - In licensed production facilities
- If Product is made in research facilities:
  - Does scale represent commercial production?
  - Must establish the validity of test products (preferably in advance of studies)

General Licensing Considerations (cont.)

- Submission of protocols for APHIS review prior to initiation of studies is recommended
  - Protocols should include proposed indications and recommendations for the product
  - Should include dates of initiation and challenge so APHIS can observe if desired

General Licensing Considerations (cont.)

- Master Seeds should be established for all products
- Outlines of Production must be complete, accurate, and represent one standard method of production
  - This is most important when using *in vitro* testing for killed products where small changes in production could effect the correlation of the potency test with host animal efficacy

General Licensing Considerations (cont.)

Purity

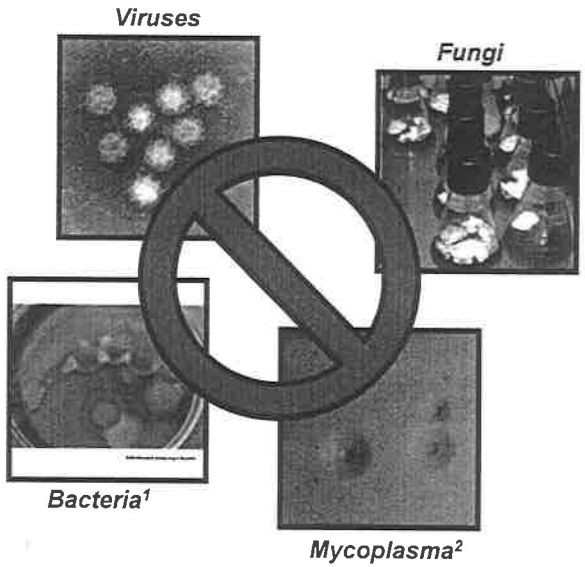
Safety

Potency

Efficacy

Supporting Data Must Demonstrate Purity of:

- ❑ Master Seed
- ❑ Master Cell Stock
- ❑ Ingredients
- ❑ Completed Product
  - bacterial/fungal contamination
  - inactivation



Supporting Data Must Confirm Safety of:

- ❑ Prelicense experimental product in
  - Laboratory animals
  - Environment
  - Host animal field studies
- ❑ Prelicense production serials
  - Varies by product

Supporting Potency and Efficacy Data Must Demonstrate:

- ❑ Support of label claims (age, route, etc.)
- ❑ Established laboratory animal or *in vitro* minimum potency levels
- ❑ Master Seed immunogenicity (host animal vaccination/challenge)
- ❑ Duration of immunity
- ❑ Stability
- ❑ Completed product potency

Types of Veterinary Biologics Product Permits

Transit Shipment

Research and Evaluation

Distribution and Sale

Requirements for U.S. Veterinary Biological Product Permit

- Not for product from countries with exotic diseases if it may endanger the livestock or poultry of the United States (risk-based assessment)
- Not for product prepared in the United States (except for small quantities of exported product for in-vitro research and evaluation)
- Must meet the same requirement as products licensed by APHIS if for distribution and sale

Common Mistakes

- Failure communicate with the CVB early in the process
- Failure to submit protocols before studies conducted
- Failure to conduct studies with Master Seed
- Failure to prepare enough Master Seed
- Assumptions that studies approved by foreign authorities will be acceptable

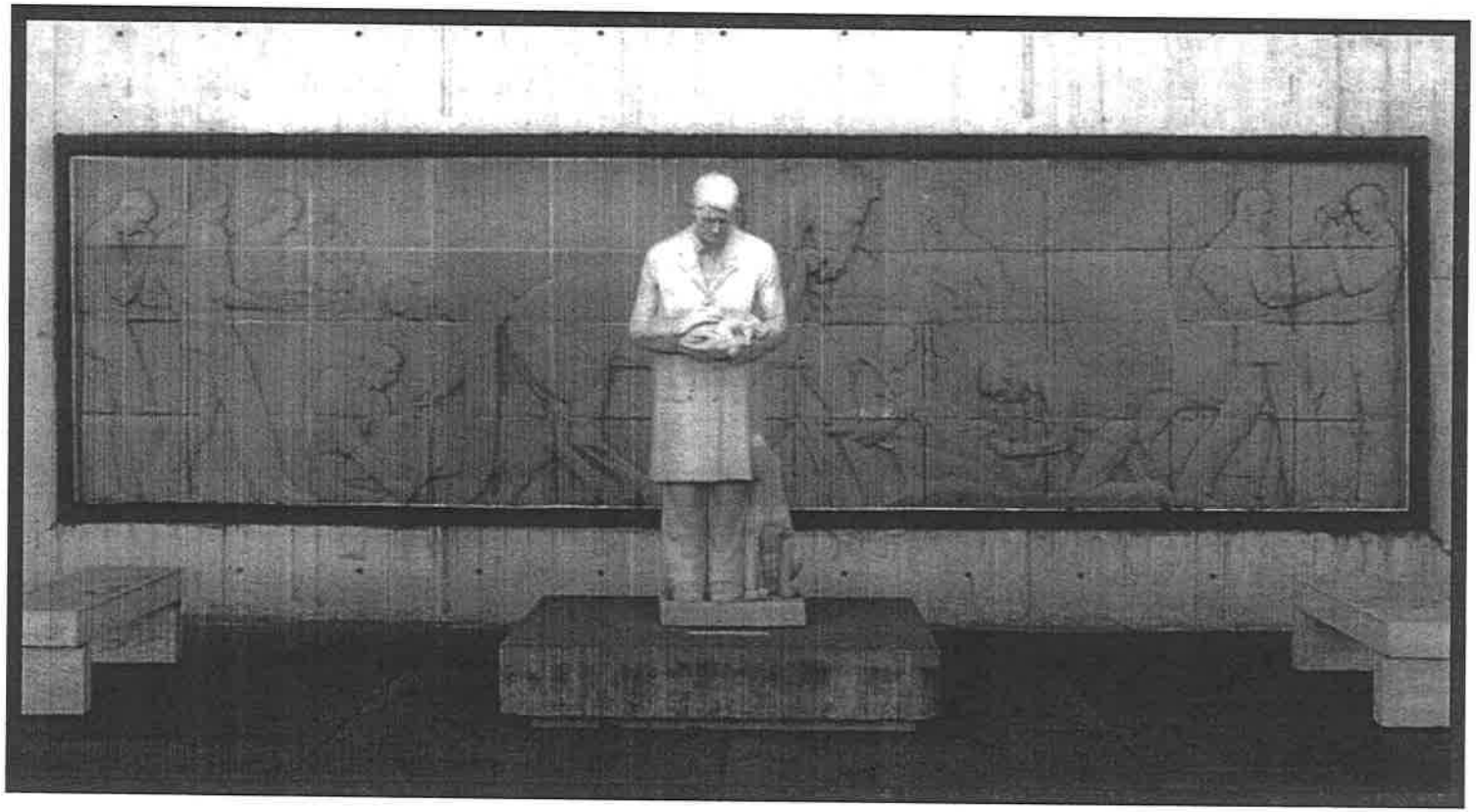
Summary

- Science-based
- Risk-based
- Transparent
- Equitably applied

Goals

- Appropriate and adequate standards
- Uniform and consistent application of the regulations
- Availability of Quality (Pure, Safe, Potent, and Effective) biologics to the consumer

Questions?



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Animal and Plant Health Inspection Service

Inspection of Veterinary Biologics in the United States

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Inspection and Compliance

Animal and Plant Health Inspection Service

Inspection and Compliance

- Compliance
  - Pharmacovigilance
  - Violations
- Inspection
  - Batch Release
  - Facilities Inspection
- Safety and Security Unit
- Information Management Unit

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Animal and Plant Health Inspection Service

Mission Statement

Assure that Veterinary Biologics are **produced** and **maintained** in accordance with the **Virus-Serum-Toxin Act** and the regulations.

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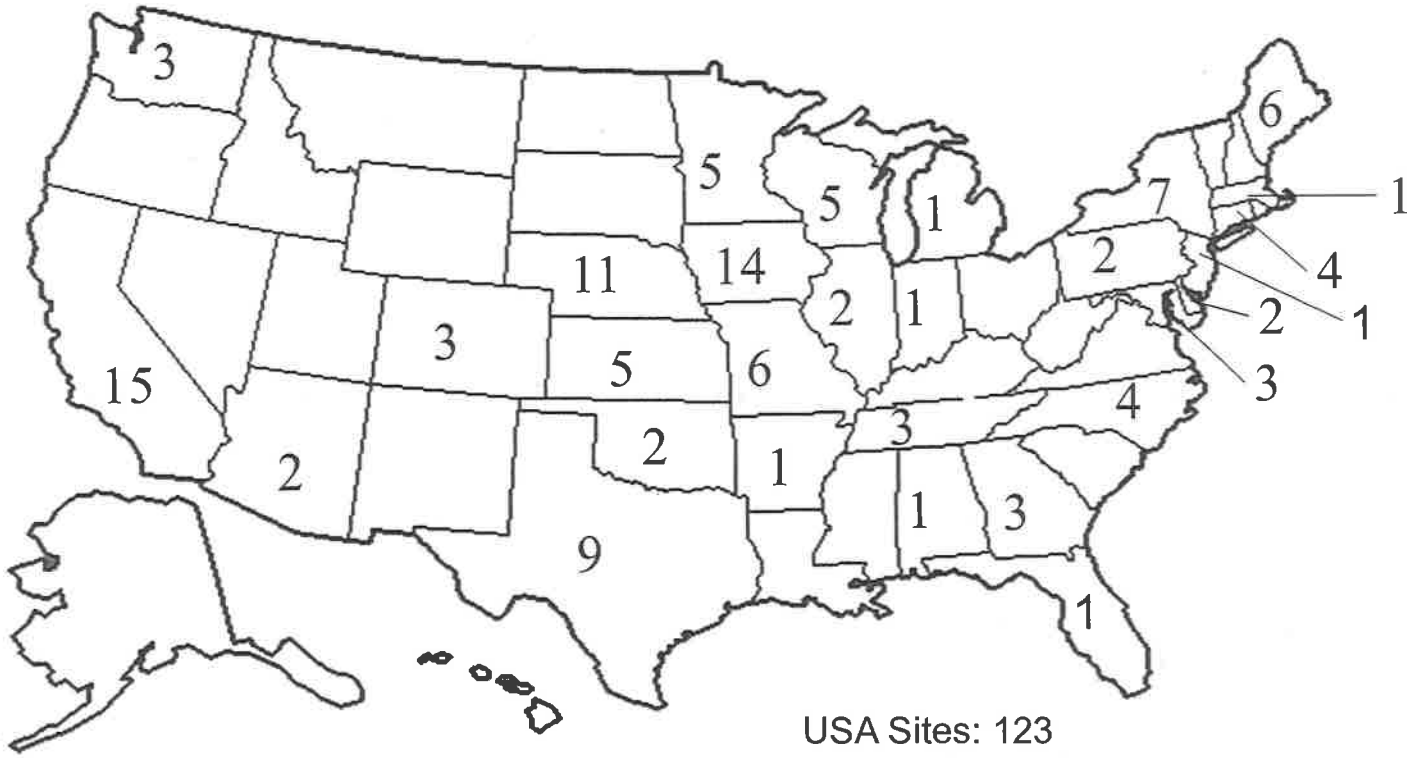
Animal and Plant Health Inspection Service

Number of Licensed/Permitted Inspection Sites



USA Sites: 123
Foreign Sites: 31
February 2014

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Animal and Plant Health Inspection Service

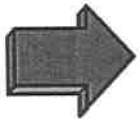
United States of America

Laws
Funds ($)

Administrative
Laws

Assure laws are
administered
properly and
fairly

Virus-Serum-
Toxin Act



USDA
9 CFR

Violation
Penalty

Animal and Plant Health Inspection Service

Legal Authority for Inspection

- Virus-Serum-Toxin Act – 21 U.S.C 151-159
  - Inspect premises, product and process
- Federal Regulations – 9 CFR Part 101-122
  - Inspect day or night without notice
  - Inspect everything at manufacturing site
  - Inspect product anywhere
- Program policy memoranda and notices
  - 800 series, CVB Notices
  - Describes inspection activities

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Animal and Plant Health Inspection Service

Inspection and Compliance Responsibilities

Surveillance or Inspection

to ensure

Firms and Products

are in

Compliance

Methods of Inspection or Surveillance

- Check testing by CVB Policy, Evaluation and Licensing staff
  - Random sampling
- Batch release by Inspection and Compliance
  - Review of firms test results
- Unannounced in-depth site inspections
- Pharmacovigilance

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Inspection and Compliance Principles

- Find facts, not faults
  - Inspection is not a punitive activity
- Stimulate cooperation and voluntary compliance
  - Not conflict and confrontation
- Lead firms into compliance
  - Do not force them

Compliance through Education

Inspection and Compliance Principles

continued

- Reasonable but tough
  - –Be prepared to use regulatory authority to prevent the distribution of worthless, contaminated, dangerous or harmful products
- Uniformity and fairness

Animal and Plant Health Inspection Service

Regulatory Activities

- CVB Inspection and Compliance is responsible
  - Investigations
    - Distributing unlicensed products or products that are worthless, contaminated, dangerous or harmful
  - Regulatory actions
    - Stop distribution and sale
    - Warning letters
    - Infraction notice
    - Case prosecution

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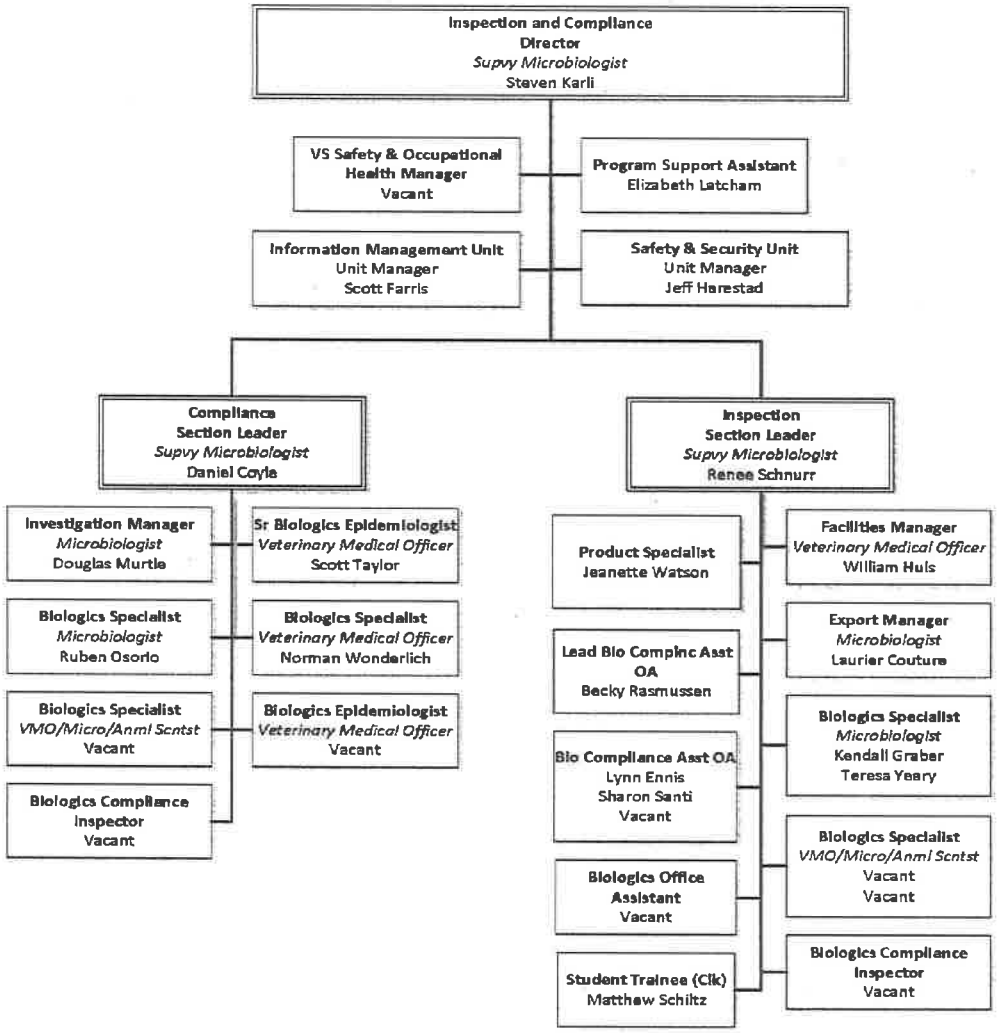
Center for Veterinary Biologics

Inspection and Compliance

2/1/2014



Animal and Plant Health Inspection Service

Inspection and Compliance Personnel

- Biologics Specialists
  - Responsible for on-site inspections, batch release, investigations and assuring compliance
  - Quality Management
- Biologics Compliance Inspectors
  - Administrative Inspections
  - Investigation Assistance

Animal and Plant Health Inspection Service

Inspection and Compliance Personnel

continued

- Senior Biologics Specialists
  - Specialized functions
  - Trade enhancement (Export), Facilities, Investigations
- Section Leaders
  - Policy development and implementation
- (Senior) Biologics Epidemiologist
  - Pharmacovigilance activities

Animal and Plant Health Inspection Service

Inspection and Compliance Personnel

continued

- Program Operations Support
  - Biologics Compliance Assistants
  - Program Support Assistant
  - Director
- NCAH Shared Services (Support to NCAH Campus)
  - Safety and Security Unit
    - Physical Security, Occupational Health, Industrial Hygiene and Safety
    - Safety and Occupational Health, Environmental Protection
    - Select Agent, Biosafety/Biosecurity
  - Information Management Unit
    - IT Specialists, Computer Clerk, Illustrator, Visual Inf, Librarian

Questions?

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百合車前草嵌紋病毒防疫監測作業手冊(草案)

前　言

百合為本省具經濟重要性之球根花卉，百合栽培過程中受病毒感染而影響切花品質。目前臺灣的百合種球大多仰賴國外進口，病毒可能隨帶毒種球而引進國內，造成國內百合栽植與生育品質之風險。記錄上共有十餘種病毒可危害百合，目前國內已鑑定可感染百合之病毒包括百合斑紋病毒 (*Lily mottle virus*，簡稱 LiMV) 、胡瓜嵌紋病毒 (*Cucumber mosaic virus*，簡稱 CMV) 、百合隱徵型病毒 (*Lily symptomless virus*，簡稱 LSV)、百合 X 病毒 (*Lily virus* X，簡稱 LVX) 及草莓潛隱輪斑病毒 (*Strawberry latent ringspot virus*，簡稱 SLRSV) 等。

2003年間，由日本學者首次證實車前草嵌紋病毒 (*Plantago asiatica mosaic virus*，簡稱PlAMV)可感染百合；荷蘭於2010年由其植物保護署 (Protection Service of the Netherlands) 報導指出此病毒引起溫室所種植之百合植株之葉片會出現壞疽，造成花卉產值下降[註1]。根據國外的報告顯示，百合植株被PlAMV感染後，造成百合植株葉片呈現黃化壞疽型病徵，嚴重影響植株之生育與開花品質；2010年荷蘭首次證實其國內本土栽培之百合發生PlAMV，荷蘭為全球最大的百合育種與種球供應國，荷蘭之百合種球生產，除於國內本土與歐洲的法國外，也大量輸出小球於於南半球的智利、紐西蘭等國作養球與開花用種球的出口。2011年首次於進口百合種球於后里地區所

栽培之百合植株上以及進口種球取樣樣品檢出PlAMV。近年來因應全年生產百合切花之需要，國內之百合種球來源，每年由前述國家進口百合種球（資料來源：農委會農產貿易統計查詢系統[註2]）。台灣於2011年首次由田間進口種球栽培之百合上也鑑定出此病毒之發生，促使我國重視此病毒隨種球進口傳入並造成危害的風險，而啟動對本病毒之防檢疫監測措施。

車前草嵌紋病毒簡介

車前草嵌紋病毒 (*Plantago asiatica mosaic virus*，簡稱 PlAMV)，為 *Potexvirus* 屬病毒成員，病毒顆粒呈絲狀，長度約 490-530 nm，鞘蛋白分子量約為 22 kDa。PlAMV 首次於 1976 年在前蘇聯之車前草 (*Plantago asiatica*) 上發現，主要藉由機械性傷口及種苗帶毒而傳播。此病毒主要分布在中亞地區，近年來於世界各地陸續有不同寄主被報導有此病毒的發生，包括蘇聯、日本、美國、荷蘭、智利、紐西蘭等。PlAMV 寄主範圍廣，包括美國之小蘗科南天竹 (*Nandina domestica*)、日本之歐洲櫻草、百合屬之胭脂花及天女報春花 (*Primula sieboldii*)。人工接種之寄主包括奎藜 (*Chenopodium quinoa* Willd.)、紅藜 (*C. amaranticolor*)、煙草 (*Nicotiana benthamiana* & *N. occidentailis*)、千日紅 (*Gomphrea globosa*)、菠菜 (*Spinacea oleracea*)、番杏 (*Tetragonia expansa*) 等，其他寄主則尚未定論。

在百合上，此病毒主要經由種球帶毒長途傳播，此途徑使得此病毒容易隨進口種球而有引進國內之風險；若種植帶毒種球後，透過汁液機械傳播方式，

於切花採收過程的切離傷口使得剪枝工具上沾有病毒汁液，則病毒會隨連續切花程序而有將病毒傳播於健康植株上的風險。若將帶毒種球留種，該二代球即成為病毒之田間傳染源。PlAMV 於田間之傳播尚未有蟲媒之報導記錄。

百合種球的選擇 (檢疫處理)

行政院農業委員會於 103 年 1 月 6 日公告(農防字第 1021493998A 號函)修正「中華民國輸入植物或植物產品檢疫規定」，增訂乙、有條件輸入植物或植物產品之檢疫條件第一點第三十六項車前草嵌紋病毒規定；並訂定「荷蘭百合種球輸入檢疫條件」規定，內容包含生產者條件、田間檢疫、種球輸出條件、輸出檢疫及輸入檢疫、不符規定處理方式等規範，於百合進口種球上強化對此病毒之檢疫措施以防堵病毒隨種球而輸入國內，以確保國外(荷蘭)百合種球輸入國內之品質。另於 103 年 9 月 19 日修正「中華民國輸入植物或植物產品檢疫規定」乙、有條件輸入植物或植物產品之檢疫條件第一點，訂定「智利產百合種球輸入檢疫條件」，並修正乙、有條件輸入植物或植物產品檢疫條件第一點第三十六項車前草嵌紋病毒規定，於檢疫條件欄增列「智利產百合種球輸入依智利產百合種球輸入檢疫條件辦理輸入」規定。

發現車前草嵌紋病毒之處理

診斷百合車前草嵌紋病毒發生，可透過病徵(附件 1)目視觀察或取樣進行病毒檢測。發現有此病毒發生時，除通報監測單位進行診斷鑑定外，確診之

罹病株應予立即拔除銷毀，針對發生此病毒病之百合田栽植之種球以不留二代球為上策。

田間防疫工作之執行

防檢局防疫組於 100 年起每年定期做百合 PlAMV 病毒病之防治宣導，發放百合之車前草嵌紋病毒診斷鑑定與防治摺頁提供農民參考，並鼓勵農民做好田區清潔管理以及發現病毒病株時能主動通報監測單位。田間防疫措施可行方式說明如下表:

方 式	說 明
拔除病株及田間清潔	1. 零星發病株建議整棵連根拔除以去除感染源 (根系也會帶病毒) 。 2.大量發生者所拔除之病株可置田間曝曬至少 2 周後再犁鋤於田土；或將拔除之病株送環保單位垃圾清運車，運至焚化廠銷燬(植物性廢棄殘渣屬一般事業廢棄物，屬焚化廠可焚化種類)。 3. 徹底做好田區雜草防治以避免病毒之野生寄主。
(水田)輪作或換地種植	1.為預防萎凋病（Fusarium wilt)，田間慣行採百合與水稻輪作、或換地耕作之栽培方式，至次季種植已隔半年，病毒若經犁鋤整地及淹水處理一段時間後，可能會隨殘株分解而消除。 2.依農民之田間經驗顯示，目前觀察同一發病田經水田輪作後再種植之病毒發病率有降低現象。
土壤蒸汽消毒	1. 本方式適用於山區無法用水田輪作之田區。 2. 熱蒸氣處理費預估約 40 萬元/公頃。
工具消毒	1.使用發病株及未發病株之專用刀剪工具。發病株隨時拔除或以專用刀剪剪除病株，或跳過發病株不採收以避免刀剪受病株汁液汙染。 2.不採收的病株可以專用工具剪下銷燬或充分曝曬後再翻犁入土浸水，使病毒快速降解以降低再感染風險。
發病田之種球不留二代球	根據田間調查經驗顯示PlAMV發病田於第一年若有零星發病，若留種球做為二代球繁殖則次年之病毒發生率大為提高。因此發病田區之百合於切花採收完成後，不留二代種球繁殖並徹底犁鋤田區進行淹水或水

	田輪作可收防治效果。

通報與鑑定

PlAMV 之田間監測，由農民通報送並填具通報單(如附件 2)以及研究人員主動赴田間調查。目前由百合進口種球於田間種植之採樣株，有檢出 PlAMV 之百合品系包括 Conca Dor、Gracia、Manissa、Marco Polo、Moutezuma、Robina、Yelloween、Lakecary、Belladonna、Tampico 及 Donato 等，顯見 PlAMV 已普遍發生於不同進口百合品系上。病毒之鑑定方式，除目測已發病株之典型病徵(嵌紋壞疽或黃化壞疽)外，於實驗室之生化檢測上以農試所已開發之 PlAMV 抗血清及核酸引子對，應用免疫檢測法進行病毒檢測或是以 RT-PCR 進行病毒核酸分子之檢測鑑定。

備註：

註 1 引用自網路資料 http://www.vwa.nl/txmpub/files/?p_file_id=2001424。

註 2 農委會農產貿易統計查詢系統網址 http://agrapp.coa.gov.tw/TS2/TS2Jsp/TS20202.htm。

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Review

High-impact animal health research conducted at the USDA's National Animal Disease Center

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ABSTRACT

Commissioned by President Dwight Eisenhower in 1958 and opened with a dedication ceremony in December 1961, the USDA, Agricultural Research Service (ARS), National Animal Disease Center (NADC) celebrated its 50-year anniversary in November 2011. Over these 50 years, the NADC established itself among the world's premier animal health research centers. Its historic mission has been to conduct basic and applied research on selected endemic diseases of economic importance to the U.S. livestock and poultry industries. Research from NADC has impacted control or management efforts on nearly every major animal disease in the United States since 1961. For example, diagnostic tests and vaccines developed by NADC scientists to detect and prevent hog cholera were integral in the ultimate eradication of this costly swine disease from the U.S. Most major veterinary vaccines for critical diseases such as brucellosis and leptospirosis in cattle, porcine respiratory and reproductive syndrome (PRRS), porcine parvovirus and influenza in swine had their research origins or were developed and tested at the NADC. Additional discoveries made by NADC scientists have also resulted in the development of a nutritional approach and feed additives to prevent milk fever in transition dairy cattle. More recently, NADC's archive of historic swine influenza viruses combined with an established critical mass of influenza research expertise enabled NADC researchers to lead an effective national research response to the pandemic associated with the novel 2009 H1N1 influenza virus. This review commemorates some of the key animal health contributions in NADC's first 50 years, recaps the newly completed modernization of the center into new facilities, and offers highlights of the ongoing research that will define NADC's mission going forward.

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1. Introduction

The National Animal Disease Center (NADC) was established in Ames, Iowa in 1961, following a nation-wide search and selection process to identify a suitable location. Key factors that ultimately drove the selection of Ames for the new USDA research center were its close proximity and programmatic alignment with the Iowa State University College of Veterinary Medicine, a central location within the nation's major livestock producing region, and availability of an attractively-priced parcel of land suitable for constructing the new facility. At the time, the NADC represented the state-of-the-art in design and construction of high-containment animal health research facilities. Indeed, the original facilities served the center and the nation well in supporting research on some of the most infectious livestock diseases of the era. As a historical note of interest, these original facilities were decommissioned in 2011 after NADC staff moved into new state-of-the-art laboratories and administrative facilities at the same Ames location.

Since its inception, the NADC has combined a unique blend of multi-disciplinary technical and scientific expertise with state-of-the-art facilities and infrastructure to investigate the country's most significant animal health problems. NADC researchers specialize in performing high-level biocontainment research (BSL-2 and BSL-3 levels), involving infectious and potentially zoonotic disease challenge studies in cattle, swine, sheep and poultry. To respond to a growing national concern that traditional zoonotic diseases such as tuberculosis, brucellosis, or emerging diseases such as chronic wasting disease can become established in wildlife reservoirs and then re-emerge in livestock or humans, NADC has established the scientific and animal handling expertise to incorporate elk, bison, feral swine, white-tailed deer and other cervids, and a range of other species into routine disease pathogenesis, transmission and vaccinology research. Indeed, NADC's new high biocontainment facilities were designed with unique penning and gating systems required to support infectious disease research in these wildlife and livestock species.

Many of the infectious diseases of livestock that were present back in 1961 remain as significant disease threats today (e.g. leptospirosis, brucellosis, Johne's disease, and others (Hartskeerl et al., 2011; Kennedy, 2011; Pappas, 2010). With global mobility of people and animals at higher levels than ever before, the speed and potential for both 'historic' and newly emerging infectious diseases to significantly impact both animal and human health is ever-increasing. Today, as throughout its history, the challenge for NADC is to keep the country one step ahead of current and emerging disease threats in livestock through research. This review will showcase research that enabled NADC to meet this challenge during its first 50 years, and will highlight the capabilities of its modernized facilities, which along with the strategic application of basic science, promises to define its mission going forward.

2. Highlights of NADC's first 50 years

Initially named National Animal Disease Laboratory (NADL), construction of the facilities began in 1958 in Ames, Iowa (Fig. 1). All USDA animal health-related research at that time was conducted at facilities in Beltsville, Maryland, and it was a major undertaking to move established animal colonies, dedicated to existing research projects, to Ames. With these logistical obstacles overcome, the first scientific experiments began in 1961 at the same time the first director, William A. Hagen, was hired. The new facilities were dedicated on June 27, 1961 and the diseases to be studied included hog cholera, tuberculosis, brucellosis, vibriosis, mastitis, leptospirosis, vesicular stomatitis virus, swine erysipelas and bovine shipping fever. The first two research articles stemming from research conducted at the new NADL were published by October of the same year, one reporting the presence of *Leptospira* on a Pennsylvania farm (Clark et al., 1961) and the second examining culture conditions for the swine pathogen *Erysipelothrix rhusiopathiae* (White and Shuman, 1961). One particularly noteworthy achievement, among several major research accomplishments from NADC's initial years, was the development of an economically feasible and rapid diagnostic test that enabled eradication of hog cholera and the concurrent establishment of NADC's world-class team of swine virology researchers.

3. Swine viral diseases caused by classical swine fever virus, porcine parvovirus, hemagglutinating encephalomyelitis virus and PRRS virus

In the 1800s and first half of the 1900s, outbreaks of hog cholera swept over the countryside, and the causative agent, classical swine fever virus, was considered endemic across the United States. Hog cholera caused losses that

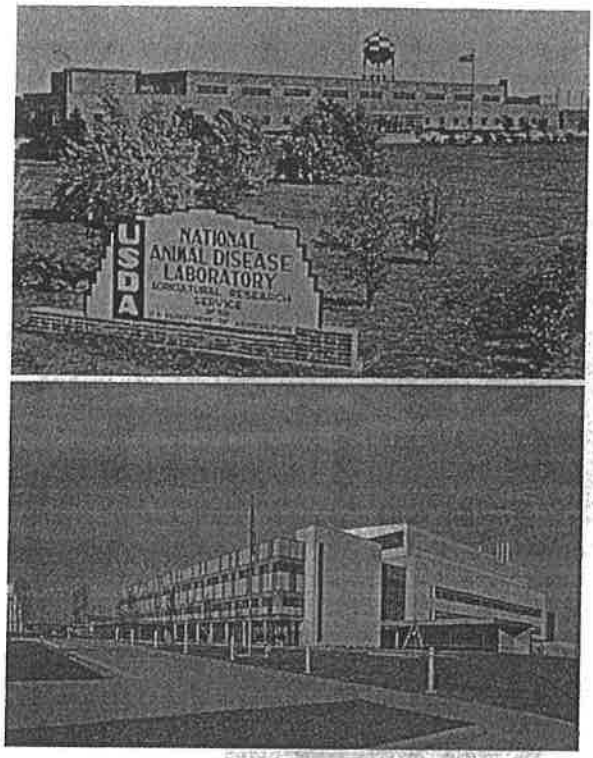

Fig. 1. NADC facilities located in Ames, Iowa when it first opened in 1961 (A) and today (B).

devastated the hog farming industry at the time and still cost swine producers $50 million a year by the 1960s (U.S. Department of Agriculture, 1978). In 1963, NADC scientist Dr. William Mengeling and coworkers developed a rapid immunofluorescent antibody test that took less than a day to diagnose classical swine fever virus infection (Mengeling et al., 1963). No other economically feasible diagnostic test was available at the time, and no equal or better test has since been developed. This rapid test enabled one of the greatest accomplishments in NADC's history, the eradication of hog cholera in the United States by 1978.

Dr. Mengeling (Fig. 2) and his colleagues later applied their expertise in viral diseases of swine to make significant advancements in vaccine development for PRRS (Mengeling et al., 1999a,b,c) and porcine parvovirus (Mengeling et al., 1979; Paul and Mengeling, 1984, 1986). He was the first to isolate porcine parvovirus (Mengeling, 1972) and to definitively establish, under both field and laboratory conditions, its role in maternal reproductive failure of swine. Prior to the availability of an effective vaccine, porcine parvovirus-induced reproductive failure was estimated to cost the swine industry between $25 and $75 million annually. A strain of porcine parvovirus (NADL 2) isolated and characterized at NADC was used to develop both inactivated and attenuated vaccines for porcine parvovirus-induced reproductive failure. All commercially available vaccines on the market today contain the NADL 2 strain of virus, and their production and testing was patterned after the procedures described at the NADC. Millions of vaccine doses have been distributed and used since it was first licensed.

4. Integrating veterinary pathology and animal health research

The close partnership between the Iowa State University College of Veterinary Medicine and NADC has fostered the professional development of numerous veterinary pathologists, and the integration of veterinary pathology into most of NADC's research programs. A number of NADC's scientists, including Drs. Lawrence H. Arp, Norman F. Cheville, Randall C. Cutlip, Janice M. Miller, and Harley W. Moon, have been board certified veterinary pathologists who went on to make significant contributions to the basic understanding of pathophysiological mechanisms underlying various diseases. For example, Dr. Cheville is internationally known for his work in characterizing ultrastructural changes in disease and for his seminal book on the topic (Cheville, 2009). Dr. Arp's greatest contributions were in describing pathophysiology and lesions of various diseases in turkeys. Dr. Cutlip made contributions in the areas of transmissible spongiform encephalopathies (TSEs), adenovirus, pasturellosis, ovine progressive pneumonia, and other respiratory pathogens. Contributions by Drs. Miller and Moon are particularly noteworthy and are summarized in the next two sections.

5. Discovery of bovine leukemia virus and immunohistochemical detection of prion proteins

Dr. Janice M. Miller (Fig. 2) began her career at NADC in 1968 working as a pathologist on bovine leukemia virus (BLV). She not only discovered BLV (Miller et al., 1969), but also developed an antibody test, targeting a glycoprotein to detect the virus (Miller and Van Der Maaten, 1977). During her career, she also worked on bovine herpesvirus (Miller et al., 1991), bovine immunodeficiency-like virus (Whetstone et al., 1991), bovine tuberculosis (Miller et al., 2002), and other major cattle diseases, greatly reducing their threat to U.S. livestock production and exports. She finished her career working in transmissible spongiform encephalopathies (TSEs) including transmissible mink encephalopathy in cattle, chronic wasting disease in cervids and scrapie in sheep. She developed immunohistochemical (IHC) techniques for detection of the prion protein in brain tissue of sheep with scrapie (Miller et al., 1993). This IHC test was subsequently applied globally to TSEs that affect other animal species, and continues to serve as a definitive diagnostic test for TSEs to this day. Dr. Miller (NADC's first female veterinarian researcher) had a highly distinguished career that culminated in her becoming a member of both the US National Academy of Sciences and the ARS Hall of Fame. However, despite her considerable professional achievements, she would frequently and humbly quote, "I'm a jack of all trades, but master of none."

6. Enteropathogenic *Escherichia coli* infections in animals

Dr. Harley Moon's research team at the NADC examined the interactions between diarrheagenic *E. coli* and animal intestinal tissues at the molecular, cellular and tissue levels, employing state-of-the-art technologies as they became

Fig. 2. NADC scientists in the ARS hall of fame. Clockwise from upper left: Ron Horst, William Mengeling, Harley Moon and Janice Miller.

available. His research and that of his collaborators identified and characterized fimbriae (pili) as specific and essential virulence factors enabling enterotoxigenic *E. coli* to attach to enterocytes in neonatal cattle, pigs, and lambs. Efficacious fimbrial-based vaccines providing passive protection against colibacillosis for neonatal farm animals evolved from this research (Moon and Bunn, 1993), and remain a prime example of a technology successfully transferred from USDA-ARS laboratories to commercial production.

Dr. Moon (Fig. 2) published the first detailed description of enteropathogenic *E. coli* (EPEC) attachment to pig and rabbit intestinal epithelial cells, an attachment associated with exfoliation of epithelial cell microvilli (Moon et al., 1983). He originated and popularized the term "attaching and effacing" (AE) for the distinct appearance of this colonization mechanism first described by researchers at Oklahoma State University (Staley et al., 1969). The intestinal cells form pedestals or 'cups' into which the *E. coli* bacteria nestle. The AE colonization mechanism is typical of colonization of cattle intestines by strains of *E. coli* which are foodborne pathogens of humans, e.g. *E. coli* strain O157:H7. Dr. Moon's foundational observations opened new fields of research with a focus on molecular pathogenesis, immunology, and genetics of AE *E. coli* and new strategies for controlling *E. coli* foodborne infections (Sharma et al., 2011).

Not only at the NADC, but around the world, Dr. Moon was a role model veterinary scientist for several generations of scientists investigating microbial-host interactions in pathogenesis. With nearly 200 highly cited publications, he remains one of the most productive researchers to have worked at the NADC. Dr. Moon served as NADC's fourth director from 1988 to 1995. He was elected to the U.S. National Academy of Sciences in 1991 and inducted into the ARS Hall of Fame in 2000.

7. Metabolic disease: milk fever and vitamin D research

NADC's research portfolio has historically consisted of a balance between infectious and metabolic diseases. The

most notable metabolic disease research investigated metabolic diseases of cattle and was led by Drs. Ronald Horst, Jesse Goff and Tim Reinhardt. This group is renowned internationally for their work on milk fever in dairy cattle and vitamin D metabolism. Milk fever results from a metabolic imbalance of calcium that occurs at the onset of calving and affects ~6% of cows at a cost to the dairy industry of $250 million annually. In milk fever cases, the animal is unable to mobilize enough calcium stores to compensate for losses through milk secretion and thus becomes hypocalcemic and exhibits clinical symptoms that include loss of appetite, lateral recumbency, tetany and eventual death if left untreated. Secondary diseases are a common sequelae to milk fever and include ketosis, displaced abomasum and mastitis. Dr. Horst (Fig. 2) and co-workers' research led to the discovery that milk fever was caused by high levels of dietary cations (K^+, Na^+, Ca^{2+}, and Mg^{2+}), which resulted in a metabolic alkalosis that prevented the action of parathyroid hormone in the periparturient cow. This lack of parathyroid activity resulted in a loss of calcium regulating mechanisms and a life-threatening drop in blood calcium. These studies broke with conventional veterinary textbook dogma at the time–that high dietary calcium was the cause of milk fever. They found that the simple addition of chloride ion to feed would alleviate this metabolic alkalosis and overcome the blockade to parathyroid function imposed by excessive dietary potassium and thereby dramatically reduce the incidence of milk fever (Goff and Horst, 1998). This research has resulted in the commercialization of the product Soy-Chlor, a feed additive for dairy cattle that is still on the market and remains effective against the condition.

Dr. Horst's team also elucidated the processes of activation and deactivation of fat-soluble vitamins, especially vitamin D. Drs. Reinhardt and Horst developed a quick and easy assay to measure 1,25-dihydroxyvitamin D that remains NADC's most cited article to date (Reinhardt et al., 1984), and has also been applied to vitamin D studies in human medicine to enhance the understanding of renal failure, osteoporosis and neoplasia (Koszewski et al., 1999; Salusky et al., 1990; Slatopolsky et al., 1984). More recently, Drs. John Lippolis and Reinhardt discovered that vitamin D profoundly affects innate immune function in cattle and that when co-administered with antibiotics into the mammary gland can augment and enhance the efficacy of antibiotics in treating chronic mastitis (Lippolis et al., 2011; Nelson et al., 2010). Dr. Horst authored or co-authored over 330 peer-reviewed publications, the most of any NADC scientist. He received the Presidential Rank Award of Meritorious Senior Professional, and was inducted into the ARS Hall of Fame in 2010.

8. Discovery and eradication of bovine leukocyte adhesion deficiency

A team of scientists led by Dr. Marcus E. Kehrli, Jr., from NADC made a serendipitous discovery that led to the virtual elimination of an autosomal recessive lethal condition in Holstein dairy cattle around the world (Shuster et al., 1992b). This was the result of an observation on a control calf in an unrelated experiment in 1989 with a syndrome reminiscent of human leukocyte adhesion deficiency. The occurrence of this condition led to experiments describing the molecular nature of what was later confirmed to be a β2-integrin adhesion molecule deficiency on bovine leukocytes (Kehrli et al., 1992, 1990). This condition was defined as bovine leukocyte adhesion deficiency and the acronym BLAD was coined, which it is now known throughout the dairy industry. Research demonstrated this condition existed in U.S. Holstein cattle since 1941 and was likely around long before that time. Genetic testing is now routinely performed for this condition around the world. Around the time of its discovery, the prevalence of BLAD was slowly but steadily increasing. In 1991, BLAD was estimated to account for over 100,00 annual global calfhood deaths and its global prevalence was steadily increasing. The NADC-led research team defined the molecular basis for the function of the defective protein, and sequenced the normal and defective bovine CD18 alleles in Holstein cattle (Shuster et al., 1992a), and they developed a diagnostic PCR assay to genotype cattle on the basis of their CD18 alleles. It was immediately recognized that BLAD was carried by several of the most prominent sires and cows of the Holstein-Friesian breed over the previous 50 years. However, as a result of the patented diagnostic test, the number of young bulls enrolled as artificial insemination bull studs and carrying the defective allele causing BLAD has been virtually zero since 1993. This research solved a major but previously unrecognized problem of considerable importance to dairy farmers and practitioners of veterinary medicine throughout the world.

9. Innovation in laboratory biosafety/biosecurity

Novel safety innovations designed and built at NADC include a finger pipetting device that eliminated the need for mouth pipetting of harmful substances (Songer et al., 1971), a portable ethylene oxide chamber used for sterilizing heat-labile materials (Songer and Mathis, 1969), and an ultra filter for germ free animal isolation units (Songer et al., 1978, 1974). Furthermore, NADC scientists evaluated the effectiveness of standard safety practices. For example, the effectiveness of decontaminating boots using various methods was first assessed at NADC (Braymen et al., 1974). This study found that footbaths were an ineffective method at removing microorganisms on the surface of footwear. The results of this study were later used by the shrimp farming industry to stop the practice of footbaths (Moss, 2002), which may actually foster the propagation of microorganisms. Also extensive testing of harmful disinfectants such as formaldehyde and phenol was conducted and reported (Braymen and Songer, 1971; Songer et al., 1972). These results were used as guidelines for the decontamination of *Bacillius anthracis* at the U.S. Post Office in Landover, MD (Canter et al., 2005). More recently, NADC facilities have hosted several international biosafety conferences, including a gathering of high-containment laboratory directors from around the world.

10. The Ames Modernization Project and NADC's current research

Plans to modernize and replace the NADC and USDA APHIS animal health facilities co-located on the USDA Ames campus were initiated in the mid-1990s. These modernization plans came to be known as the 'USDA Ames Modernization Project' and ultimately represented the largest construction project ever undertaken in USDA history. The USDA Ames Modernization Project was strongly supported by a broad-based coalition of animal production and health stakeholders who successfully influenced bipartisan Congressional and Presidential support to win approval for funding totaling $467 M. Design of the new facilities commenced in 2001 and construction was completed in 2009. The newly constructed facilities are among the most extensive and advanced high-containment large animal disease research facilities in the world; there are fewer than five comparable facilities worldwide. These state of the art facilities combined with concurrent advances in the scientific fields of genomics, microbial ecology, immunology, and systems biology are converging to create an unprecedented opportunity for NADC scientists to build upon their strong tradition of leadership in animal health research and continue to define innovation and global leadership in animal health and food safety research.

Dr. Kurt Zuelke became NADC's seventh Director in 2006. To coincide with the transition into the new facilities in 2009, the NADC leadership team developed an ambitious five-year business plan that leveraged the new facilities with ongoing scientific advances in genomics and the life sciences to address the nation's most pressing animal health problems. NADC is now focused around four strategic research themes that include ruminant diseases and immunology; emerging diseases (most notably viral and prion diseases); zoonotic diseases in wildlife and livestock species; and, microbial ecology in food safety and animal health. Although the core of animal health research continues to revolve around basic disease pathogenesis and transmission research, NADC researchers across all four of these strategic themes are pioneering early development and integration of high-throughput genomics and systems biology platforms to yield new and exciting breakthroughs in molecular-based diagnostic and disease intervention technologies.

11. Genomics and metagenomic studies of agriculturally important species

NADC is at the forefront of genomics, functional genomics and metagenomics research as it relates to infectious diseases and foodborne diseases of animals. *Pasteurella multocida* (May et al., 2001), *Mycobacterium avium* subsp. *paratuberculosis* (Li et al., 2005) and *Brucella abortus* (Halling et al., 2005) were among the first animal pathogens with genomes sequenced by researchers at NADC along with their collaborators. Microarrays constructed from pathogen sequence data have been produced using information from these genomes for transcriptomic and genomic diversity studies (Boyce et al., 2002, 2004; Marsh et al., 2006; Nicholson, 2007).

NADC is leveraging next-generation sequencing technologies by investing in the latest equipment and training researchers. With the rapidly developing power and lower cost of these technologies, metagenomic studies have become achievable. The first analysis of the avian intestinal metagenome in feed-deprived 3-week-old turkeys was accomplished using molecular techniques (Scupham, 2007). Data revealed a high percentage of *Papillibacter* in fasting turkeys, suggesting that these microbes may be specifically dividing in response to the environmental conditions.

Recently, NADC researchers and colleagues at Michigan State University applied metagenomics and quantitative PCR analyses to assess the impact of dietary antibiotics on the swine intestinal microbiome (Looft et al., 2012). These investigators demonstrated shifts in intestinal microbial populations, including elevated *E. coli* shedding, and increases in various metabolic and antibiotic resistance genes. The detection of bacteriophage carrying antibiotic resistance genes and likely capable of spreading the genes was also a discovery from these studies (Allen et al., 2011). Understanding the effects of antibiotics on intestinal microbes enhances our ability to monitor antibiotic use and discover antibiotic alternatives.

12. Animal health research response to the 2009 H1N1 influenza A virus outbreak

In early 2009, a novel pandemic H1N1 influenzae A virus (H1N1pdm09) emerged in the human population in North America. This antigenically distinct H1N1 quickly spread in the human population, and the World Health Organization declared on June 11, 2009, that the outbreak had reached pandemic phase 6. Although the sequences of the virus's eight gene segments were similar to those of corresponding genes from swine influenza A viruses from North America and Eurasia, no closely related ancestral influenza A viruses with this gene combination had been previously identified anywhere in the world. For the human population, the genome of the H1N1pdm09 virus contained novel forms of the matrix (M) and neuraminidase (N1) genes that rendered this virus antigenically distinct from previously circulating strains (Garten et al., 2009). Therefore, the global human and swine populations were potentially immunologically naïve to this virus, and diagnostic tests available at the time could not differentiate it from other influenza virus strains. Within the first few weeks of the 2009 pandemic, a team of NADC scientists led by Drs. Amy Vincent, Kelly Lager and Kay Faaberg developed a differential diagnostic test for the pandemic virus in swine and conducted a series of high containment pathogenesis, transmission, and vaccine experiments with the H1N1 virus in swine (Vincent et al., 2010, 2009).

In response to this outbreak, a number of key countries immediately closed their borders to U.S. pork exports citing potential concerns that the H1N1 virus could affect the safety of U.S. pork products. The pathogenesis studies performed at NADC were the first to demonstrate that the tissue distribution of the 2009 pandemic virus was limited to tissues of the respiratory tract and that the virus was quickly cleared from infected pigs. These results confirmed

that the H1N1 virus did not pose a food safety risk (Vincent et al., 2009) and that U.S. pork products were safe. This rapid research response enabled science-based decisions on the safety of U.S. pork and pork products during the early stages of the pandemic by providing data that was invaluable to U.S. and international pork producers. The U.S. government and the U.S. pork industry cited this research while engaging trading partners in a science-based conversation to maintain and re-open market access to over 27 countries that had banned or threatened to ban U.S. pork and pork products, costing the industry over $5.0 M per day.

13. Foodborne pathogens

In response to the needs of producers and consumers, a major research paradigm shift occurred at the NADC in the late 1990s. Investigators who previously focused on controlling enteric bacterial pathogens of farm animals (*E. coli*, *Salmonella*, and *Brachyspira hyodysenteriae*), adopted food safety research projects. They form the nucleus of the current Food Safety and Enteric Pathogens (FSEP) Unit. The FSEP Unit aims to reduce numbers of human foodborne pathogens and antibiotic resistant microbes in animals on the farm, before they get to humans. New chemical, biological, genetic, and immunological strategies are being explored, not only as control measures for human foodborne pathogens (and animal pathogens), but also as alternatives for reducing antibiotic use.

An early food safety intervention, from the labs of Drs. Tom Casey, Mark Rasmussen, and Iowa State University collaborator, Jacob Petrich, was the invention of a fluorescence detector for real time monitoring of animal carcasses for fecal contamination, a most important source of foodborne pathogens in meat products (Ashby et al., 2003). For this invention, these researchers were recognized by a national R&D 100 award for a top 100 invention of the year, a 'da Vinci' Award from the State of Iowa, and a Superior Service Honor Award from the U.S. Secretary of Agriculture.

14. Antibiotic resistance

An important concern in animal agriculture today is the widespread use of antibiotics in animal feed. The extent of antibiotic resistance among members of the microbiome of animals has only begun to be appreciated in recent years; this results in clinical issues pertaining to treatment of animal diseases caused by resistant bacteria. Furthermore, it generates concern over the spread of antibiotic resistant bacteria, especially foodborne pathogens from animals to humans. But mechanistically, how does resistance to antibiotics spread? Studies at NADC have recently shown that antibiotic resistance genes are present in bacteriophage from swine fecal samples (Allen et al., 2011). These authors further demonstrate that the presence of antibiotics in animal feed induces latent phages to activate a lytic infection providing a means for antibiotic resistance gene transfer.

Selective pressure from frequent antibiotic use can drive both the spread and the evolution of antibiotic resistance genes. Dr. Arthur Andersen and collaborator Dr. Dan Rockey were the first to demonstrate the presence of tetracycline resistance in swine strains of *Chlamydia suis* (Dugan et al., 2007, 2004; Lenart et al., 2001) and how readily new resistance is acquired through horizontal transfer and recombination events (Suchland et al., 2009). They showed the mosaic recombination of intraclass tetracycline resistance genes, which suggests the ease of transfer and intermingling of *tet*(C) alleles. Although the presence of antibiotic resistant chlamydia was initially controversial, tetracycline resistant strains are now widely accepted in the chlamydial field. NADC scientists also discovered the first example of interclass genetic recombination of tetracycline resistance genes, *tet*(O) and *tet*(W) alleles, in the strict anaerobe *Megasphera elsdensii*, a non-pathogen commensal bacterium, from the swine gut (Stanton et al., 2011).

15. Conclusion and future perspectives

While this review has focused on a select few highlights, in total NADC scientists have collectively published over 3000 research articles since the center opened in 1961. A selection of additional noteworthy accomplishments are listed in Table 1. Today, the national need for innovative high impact animal health and food safety research at NADC and elsewhere has never been greater. Of the 1415 species of infectious organisms known to be pathogenic in humans, 61% are zoonotic, and more strikingly, 75% of newly emerging human pathogens are zoonotic (Taylor et al., 2001). The recent 2009 H1N1 pandemic influenza outbreak illustrates just how quickly a zoonotic infection can emerge and spread globally. With the global population estimated to grow to over 9 billion people by 2050 (Lee, 2011), there will continue to be an ever-increasing demand for new technologies to produce more food more efficiently while assuring food safety. Research solutions that enable cost-effective production of healthy livestock and poultry will be a critical component in a comprehensive strategy to assure global food security to meet the nutritional needs of the future population base. As future population pressures on the environment increase, the resulting loss of habitat will lead to closer proximity of wildlife and livestock populations and increase the likelihood of disease transmission among these animal populations and perhaps between animals and humans. Continued research using a combination of wildlife and domestic livestock animal models will be crucial to mitigating the potential impact of wildlife reservoirs of zoonotic diseases to human and animal health. The NADC research community is proud of the pioneering efforts of their scientists to date. Building upon the foundation laid down during the past 50 years with newly constructed facilities and cutting edge technologies, the NADC is well-positioned to lead the nation to meet the current and upcoming animal health and food safety challenges in the years to come.

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