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**FAO/WHO Expert Consultation on the**

**Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish**

***Rome, 17–21 November 2003***

# REPORT

# Contents

# Executive summary

A joint FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish was held at the Headquarters of the Food and Agriculture Organization of the United Nations (FAO) in Rome from 17 to 21 November 2003. The objective of this Consultation was to provide scientific advice to FAO/WHO and their Member Governments on the safety assessment of foods derived from genetically modified animals, including fish (hereafter "GM animals"). The Consultation focused on discussing what strategies are appropriate and applicable to the food safety assessment of GM animals. Additionally, it addressed specific issues originating from the production of GM animals as well as environmental and ethical issues. The Consultation did not address all environmental issues but focused on the connection between environmental entry of GM animals and food safety. The Consultation also addressed ethical considerations that relate directly to the scientific assessment of foods derived from GM animals.

Potential benefits of GM animals might be realized in the near-to-medium term, such as improved animal production and product quality and novel animal products. Other applications that might be realized over the longer term include use of GM animals as bioindicators, for biological control, and for xenotransplantation.

Effort should be invested in making GM animals safer from the outset, e.g. by wise selection of breeding goals, improved techniques such as design of vectors, and avoidance of unnecessary DNA sequences such as marker genes that raise safety concerns.

The food safety assessment of GM animals and derived products can largely be performed along the lines that have already been established for the evaluation of GM plants and derived products on a case-by-case basis. This means that the initial step of the food safety assessment will be a comparative safety assessment of the GM animal with its conventional counterpart, including a food intake assessment, followed, where appropriate, by a full risk characterization.

Rigorous pre-market safety assessment of foods derived from GM animals should provide sufficient safety assurances. The use of post-market surveillance as an instrument to gain information on the potential long-term or unexpected adverse and beneficial effects of food either GM animal-derived or traditional should be further explored. Post-market surveillance could be useful in certain instances where clear-cut questions require, for instance, a better estimate of intake and nutritional consequence of foods derived from GM animals, or a better estimate of the environmental fate of GM animals and their transgenes.

Accessible databases on the natural variation in key compositional constituents in animal products are necessary tools in the assessment of the unintended effects of the genetic modification. There is a need for a worldwide accessible database, linked to ongoing efforts in this area, with information on detection and identification methods and reference materials for food products derived from GM animals on the market and in development.

There is a need for capacity building, particularly in developing countries, for food safety assessment and management of GM animals, including environmental and ethical aspects related to food safety.

The Consultation recommended participatory deliberation by all stakeholders and the general public, starting at an early stage, including communication about potential benefits, risks and uncertainties posed by the genetic modification of animals.

There is a need to develop a framework for the ethical consideration of animal biotechnology. This framework should make the assessment more transparent, methodical and amenable to quality assurance.

# 1. Introduction

A joint FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish was held at the Headquarters of the Food and Agriculture Organization of the United Nations (FAO) in Rome from 17 to 21 November 2003. A total of 18 experts, including the authors of working papers, participated in the Consultation. The complete list of participants is given in Annex 1.

Mr Hartwig de Haen, Assistant Director-General, Economic and Social Department of FAO, opened the Consultation on behalf of FAO and the World Health Organization (WHO).

In his opening remarks, Mr de Haen highlighted the importance of food safety issues for Member Governments as well for consumers, and the role of FAO and WHO in providing scientific advice and technical guidance to policy-makers and food safety regulators to improve overall food safety and enhance consumer confidence in the safety of the food supply.

Mr de Haen referred to the growing application of modern biotechnology in food production and to the potential benefits that this technology may have on food security, nutritional quality of certain staple foods and human health in general. He indicated, however, that despite the assurances given by scientists and regulators about the lack of any proof of negative effects on consumers' health of genetically modified (GM) products, the consumers in many countries of the world remain sceptical about these products in general and are demanding more transparency in conducting their safety assessment.

He stressed the importance of this Expert Consultation in providing further scientific guidance on the safety assessment of foods derived from GM animals, including fish. These products are under development in many parts of the world and it was timely to address their safety for the consumer as well as for the environment. Ethical issues surrounding the application of GM technology to the animal kingdom should also be considered.

Mr de Haen reminded the participants of their status as FAO/WHO experts, representing the international scientific community and participating in their personal capacities and not as representatives of their respective institutions or governments.

It was noted that declarations of no conflict of interest had been received from all the experts.

The Consultation elected Dr H. Kuiper as Chairperson and Dr A. Kapuscinski as Rapporteur.

# 2. Background

At its 23rd session in 1999, the Codex Alimentarius Commission established the Ad Hoc Inter-governmental Task Force on Foods Derived from Biotechnology and entrusted it with the task of developing standards, guidelines and recommendations on foods derived from modern biotechnology. To assist this Task Force in conducting its work, FAO and WHO convened a series of expert consultations on the safety and nutritional aspects of GM foods, which provided the scientific basis for the Codex Task Force deliberations. These expert consultations, while addressing issues closely related to the work of the Task Force, were completely independent of the intergovernmental negotiation process, and treated the subject from a purely scientific perspective.

Three Expert Consultations were organized, covering the following subjects:

- Safety aspects of genetically modified foods of plant origin (Geneva, 29 May–2 June 2000);
- Evaluation of allergenicity of genetically modified foods (Rome, 22–25 January 2001); and
- Safety assessment of foods derived from genetically modified micro-organisms (Geneva, 24–28 September 2001).

The outcome of these consultations has been extensively used by the Codex Task Force on Foods Derived from Biotechnology to develop principles and guidelines for the safety assessment of GM foods (see section 7).

The safety assessment of GM animal-derived foods has been addressed by a number of expert meetings such as the Organisation for Economic Co-operation and Development (OECD, 1992, 1993), FAO/WHO (1991, 1996, 2000), the Royal Society of Canada (2001), the United Kingdom Council of the Royal Society (2001), and the United States National Research Council (NRC, 2002). The OECD and FAO/WHO expert meetings dealt with the safety assessment of GM foods in general, while the other meetings addressed specifically the safety assessment of foods derived from GM animals and fish.

Experience in the safety assessment of GM animals is still very limited, although evaluators of GM animal-derived food products may benefit from experiences with GM plants as the basic approaches used for the assessment of GM plant materials may also apply to GM food animals.

## 3. Scope, including definitions

The Consultation addressed specifically GM animals, including fish. Hereafter in this report "GM animals" includes not only terrestrial but also aquatic species.

The genetic modification of animals is a set of rapidly developing technologies which have a number of interesting and promising applications. It can be used:

- in fundamental biomedical research to improve our genetic and physiological knowledge;
- to make models of human diseases;
- for the production of proteins or other substances for therapeutic aims;
- as an alternative source of cell tissues and organs for xenotransplantation;
- to obtain or to improve desired features of farmed animals including fish, such as disease resistance and food production.

The Consultation addressed mainly the last application of this technology, namely the foods derived from genetically modified animals.

The objective of the Consultation was to provide scientific advice to FAO/WHO and their Member Governments on the safety assessment of foods derived from genetically modified animals. The Consultation devoted most of its time to discussing what strategies are appropriate and applicable to the food safety assessment of GM animals and in particular fish. Additionally, it addressed specific issues originating from the production of GM animals as well as environmental and ethical issues. The Consultation did not address all environmental issues but focused on the connection between environmental entry of GM animals and food safety. The inclusion of ethical issues in the discussion was considered important in the scope of the Consultation because of the public concerns associated with the introduction of this new technology.

The Consultation did not fully consider the safety assessment of cloning, especially somatic cell nuclear transplants.

***Definitions.*** For the purpose of the Consultation, the following definitions have been used:

*Modern biotechnology* means the application of:

(i) *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles; or
(ii) fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.[1]

*Recombinant-DNA animal* means terrestrial and aquatic species in which the genetic material has been changed through *in vitro* nucleic acid techniques including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles.

*GM animals* and *transgenic animals* are used interchangeably to mean recombinant DNA animals.

*Transgene* means the recombinant DNA that has been integrated in the genome of the GM animal.

*Conventional counterpart* means:

- an unmodified terrestrial or aquatic animal from the same genetic source as the GM animal and with a known history of safe use in producing or processing food; or
- food produced using traditional unmodified animals for which there is an experience of establishing safety based on common use in food production.

## 4. State of the art in GM animal production

### 4.1 Introduction

A safety assessment of foods derived from GM animals must be grounded in an understanding of transgenesis methods, anticipated applications and possible outcomes from transgene integration and expression. Against this background, the Consultation considered the potential hazards of transgene expression on the animal and on human health-related environmental issues. The Consultation also discussed future perspectives on development, use and oversight of transgenesis for the purposes of food animal production.

The Consultation also noted that genetically modified insects are being produced, although not currently for food production. Although issues posed by genetically modified insects need discussion, they were beyond the scope of this Expert Consultation.

[1] This definition is taken from the Cartagena Protocol on Biosafety under the Convention on Biological Diversity.

## 4.2 Techniques and applications

### 4.2.1 Techniques

A number of techniques can be utilized for transferring genes into animals (Houdebine, 2003). They differ in their suitability for different classes of animals, in their efficiency of transformation, and in their implications for risk assessment.

Utilization of the gene transfer approach depends upon knowledge of a gene encoding a product conferring a trait of interest. The gene to be transferred is incorporated into an expression vector that also contains genetic elements to control its expression. The use of different types of expression vectors poses methodological advantages for different classes of animals, and also affects the likelihood of subsequent genetic or immunological hazards being realized. Biotechnologists may purposely transfer into a host a:

- Fusion gene – a gene encoding a product of interest with an element that will regulate its expression in the host.
- Transposon – a DNA element capable of excising itself from one location in the genome and inserting itself into another location, which has been modified to contain the fusion gene.
- Retrovirus – a virus that can integrate itself into the genome and become expressed through the host cell's replicative processes, and that has been modified to contain the fusion gene.

Many expression vectors contain marker genes. Some marker genes are simply reporters for successful gene transfer, while others encode gene products so that transgenic individuals can be selected for, e.g. by application of antibiotics.

Common methods for introducing an expression vector into the host include:

- Microinjection – direct injection of the expression vector into fertilized eggs or host cells using a fine glass needle.
- Electroporation – introduction of the expression vector into fertilized eggs or host cells by application of pulses of electricity to induce transient pores in the membrane of host cells.
- Particle bombardment – coating the expression vector on to gold particles, and introduction in host cells by bombardment with the particles.
- Cell transformation, followed by cloning – since it is more straightforward to add or knock out genes for cultured cells than for fertilized eggs, nuclei from successfully transformed cells can be transferred into enucleated eggs and implanted into surrogate dams to generate somatic cell cloned animals, which are also transgenic.
- Transformation of gametes – genes may be introduced into oocytes or spermatocytes, and the transformed gametes used for fertilization, generating a whole animal.

Application of any one of these methods will result in the successful transformation of a small percentage of the animals so produced. Transgenic individuals can then be identified and bred to develop a transgenic line.

### 4.2.2 Applications and their potential benefits

Transgenic animals expressing one introduced gene have been or might be developed for a variety of applications, posing a range of possible benefits to food production or human health (Table 1). Such animals are at various stages of development. Early applications for approval of

transgenic animals for food production involve several species of fishes expressing introduced growth hormone genes.

Production of transgenic agricultural mammals is challenging and expensive, especially because of their low reproductive rate and internal fertilization and development. Many transgenic founder individuals are mosaic for the transgene, i.e. they have it in some, but not all, of their cells. For these reasons, development of transgenic agricultural mammals has lagged. However, nuclei from transformed cultured cells or transformed cells from a mosaic animal can be used as donor material for somatic cell nuclear transfer-mediated cloning, producing individuals that are transgenic in all cells. This approach might eventually be used to produce transgenic lines for food production, as is already being applied for development of pigs intended for xenotransplantation, where several transgenes will have to be expressed and several host genes knocked out.

### 4.3 Food-related hazards associated with producing GM animals

The discussion below addresses hazards associated with transgenesis methods and the environmental release of GM animals that have a bearing on food safety. The possible hazards of transgenesis discussed below must be placed into perspective by considering their relative likelihood and the degree of harm they pose. We note that these hazards are not unique to transgenesis.

#### 4.3.1 Transgenics

Introduction of a transgene into an animal is not a precisely controlled process, and can result in a variety of outcomes regarding integration, expression and stability of the transgene in the host.

The desired outcome generally is stable integration of a single copy of the transgene into a single location in the genome, and not in a functional gene or a regulatory element. However, other outcomes are frequently observed, including integration of multiple copies of the transgene at one locus or insertion of the transgene at multiple locations in the genome. Insertion of the transgene into a host gene may turn the host gene off, sometimes affecting the viability or health of the host. Insertion of a transgene sometimes can affect expression of another gene(s). A transgene may become rearranged before integration, thereby becoming non-functional. During the process of transgenesis, undesired DNA sequences may become inserted into the genome, such as marker genes or selectable markers from the expression vector or contaminating bacterial DNA left over from vector production. Hazards stemming from insertional events or genetic instability can be identified by screening and managed by culling individuals that have undesired events during the course of development of the transgenic line.

Expression of the transgene ideally should have no undesired effects on the expression of other host genes or health of the host. Other outcomes, however, have been observed. The transgene can be silenced by methylation or through other mechanisms. Because expression of the transgene often is controlled by novel regulatory elements outside the host's normal homeostatic feedback mechanisms, expression of the transgene can have pleiotropic effects, that is, effects upon multiple traits of the host. Notable pleiotropies have been observed among animals expressing introduced growth hormone genes, and have included pigs, sheep and fish exhibiting a range of morphological or metabolic abnormalities. Other pleiotropies, such as increased carcass yield, may be positive. Ectopic expression of the transgene may occur in tissues, sexes or life stages where it is not expected, and may affect the health of the host and the safety of its food products. Hazards stemming from transgene expression can be identified by screening and managed by culling

individuals with undesired expression phenotypes during the course of development of the transgenic line.

The use of viral and transposon vectors poses the hazard that the transgene might subsequently move within the genome. Work with *Drosophila* suggests that transposons may have a greater probability of movement following crossing into a new background strain. Even though the vectors were engineered to lack all the DNA sequences needed to be packaged into virions or to transpose, there is a theoretical possibility that they could recombine with other DNA sequences in the genome, such as endogenous transposable elements, or with exogenous viruses or transposons, thereby gaining infectivity or mobility. Development and use of well-designed vectors will reduce the likelihood of these hazards.

The development of pigs for xenotransplantation involves knocking out expression of molecules that elicit immune response in humans and adding molecules that make the surface of pig cells more like that of human cells. This raises the possibility that pigs might become more susceptible to human viruses. This could provide an alternative host for spread of human disease, and could also give rise to a new evolutionary pathway for adaptation of pig viruses to humans. This hazard could theoretically be minimized by using pig breeds lacking known endoviruses for development of xenotransplantation lines and by maintaining such lines in strict quarantine.

### 4.3.2 Cloning

Cloning may be used to propagate GM animals and raises its own issues. The Consultation, however, did not address the risks associated with cloning *per se* (especially somatic cell nuclear transfer).

Somatic cell nuclear transfer-mediated cloning requires reprogramming of the genome from a differentiated cell to allow it to drive embryogenesis. This results in some degree of altered gene expression, especially early in the life of the cloned individual. The effects of altered gene expression and of reproductive manipulations needed for the cloning process may result in high rates of prenatal and postnatal mortality and of morphological or physiological abnormalities in cloned individuals, which may in turn affect animal health and food safety (National Research Council, 2002). Observation of the limited numbers of offspring of cloned animals produced to date suggests that they may be phenotypically normal.

### 4.3.3 Environmental considerations that can affect food safety

Different GM animals pose different potential environmental benefits and risks (National Research Council, 2002; Pew Initiative on Food and Biotechnology, 2003; Scientists' Working Group on Biosafety, 1998). This discussion does not address all environmental issues but, rather, focuses on the connection between environmental entry of GM animals and food safety. The potential spread of GM animals or their transgenes in the environment is an environmental hazard that provides a route for entering into the human food supply.

The potential entry of GM animals into the food supply via the environment will vary owing to different predispositions of the animals to enter the environment and spread, differences in the farming system's ability to reduce animal escape, and differences in whether humans hunt or fish for the same species. Some farmed animals are often transported and sold alive, posing additional routes for accidental entry into the environment. Escaped GM fish and shellfish, or their descendants, could be harvested without being detected and subsequently eaten by people. The current status of development of GM animals suggests that food safety managers might be faced

with this issue first for GM fish and shellfish, and somewhat later for some kinds of GM poultry such as ducks and quail.

Key species or taxa of GM animals can be ranked in terms of their ability to become feral, likelihood of escape from captivity, mobility and historical reports of ecological community disruption Such a ranking from high to low for North America (National Research Council, 2002). would consist of insects, shellfish, fish, mice-rats, cat, pig, goat, horse, rabbit, dog, chicken, sheep and cattle. On a regional scale, the relevance of this ranking to food safety will change depending upon whether these animals are widely eaten by humans. Furthermore, the rankings will vary among regions owing to different environmental conditions, but the same risk factors apply.

Assessment of the potential environmental spread of GM animals or their transgenes should be done case-by-case for each combination of integration event (i.e. transgenic line) and local environmental conditions. The assessment should compare the GM animal with its conventional counterpart, i.e. unmodified animals derived from the same genetic source. The assessment should estimate the probability of movement of the GM animal or its transgene(s) into the environment, given the estimated rate of escape. This involves assessing whether:

- the GM animal, compared with the conventional counterpart, has a lower, equal or higher potential for gene flow to any wild or feral relatives found in the receiving ecosystem. Recent research suggests that the transgene could be purged within a few generations or could spread through the natural population and possibly affect its abundance (Muir and Howard, 2001, 2002). For potential entry into the food supply, purging would be a safer outcome. However, these animals may still enter the food supply because the purging process is likely to take one or more generations;
- the GM animal, compared with the conventional counterpart, has a lower, equal or higher potential to invade and establish itself as an alien species, particularly when the receiving ecosystem lacks wild or feral relatives.

#### 4.3.3.1 Status of methods for estimating potential environmental entry

The best methods for reliably characterizing potential environmental entry have not yet been standardized. The net-fitness methodology (Muir and Howard, 2001, 2002) provides a systematic and comprehensive approach based on contemporary evolutionary and population biology (National Research Council, 2002; Pew Initiative on Food and Biotechnology, 2003). It involves a two-step process: (1) measuring fitness-component traits covering the entire life cycle for GM animals, their conventional counterparts or wild relatives, and crosses between the two; and (2) entering the fitness data from step 1 into a simulation model that predicts the fate of the transgene across multiple generations. There is a need to validate this method's predictions; initial experiments are under way towards this end. For example, a transgenic fish project is testing the validity of the net-fitness model's predictions (summary at: www.reeusda.gov/crgam/biotechrisk/biot00ls.htm). There is also a need to add stochasticity, elaborate additional features and improve the user-friendliness of the simulation model. The data needed to apply this methodology have yet to be obtained for most GM animals; efforts to gather such data have recently begun for a few cases of GM fishes.

#### 4.3.3.2 Confinement of GM animals

If the combined conclusions from the environmental hazard characterization (discussed above) and the food safety assessment (discussed in section 5) are that GM animals or their transgenes will spread in the environment to a degree that poses a risk to the human food supply, then risk managers should consider the need to apply confinement measures to prevent or reduce escape of GM animals or their viable gametes into the environment. The primary focus of these

measures should be to ensure that release does not occur. If this cannot be assured, then it can be complemented by the use of methods to ensure that any escaped individuals cannot reproduce.

Biological, mechanical and physical/chemical confinement measures are available for fish and shellfish produced in different aquaculture systems (Agricultural Biotechnology Research Advisory Committee, 1995; Scientists' Working Group on Biosafety, 1998; Kapuscinski, 2003). Biological confinement measures typically involve disrupting the animal's ability to reproduce, such as sterilizing fish and shellfish by induction of triploidy, i.e. resulting in individuals with three sets of chromosomes rather than the normal two sets. Mechanical confinement involves application of some kind of implement to prevent or reduce escape of animals from the aquaculture system (e.g. screens in effluent pipes of land-based fish tanks or ponds) and physical confinement involves making an aqueous escape pathway lethal by changing a physical attribute of the water (e.g. heat effluent water to lethal temperature, and then cool down before discharge). Other confinement systems could be developed for GM terrestrial animals.

In many cases, there is a need for multiple confinement measures because no single measure is fully effective. For instance, all-female triploid populations of salmon can be used to ensure that any individuals that might escape physical confinement are unable to reproduce in the wild. There is also a need for robust verification of confinement measures.

There is a need to develop and validate better methods for reliably inducing reproductive sterility of GM animals, in particular GM fish and shellfish. Improved methods could include repeatable protocols for induction of triploidy (applicable to animals other than birds and mammals) and new methods for inducing sterility via chemical treatments or gene transfer, for instance, by inserting anti-sense genes to disrupt key steps in the endocrine pathway controlling reproductive development.

#### 4.3.3.3 Monitoring for environmental entry and spread

In future, specific GM animals may gain approval for widespread production, either with or without approval to enter them in the human food supply. In such situations, it will be important to consider whether or not to apply post-market monitoring for unexpected environmental spread of the GM animals and their transgenes that pose food safety hazards. Methods for detection of such GM animals and their transgenes in the environment are likely to involve the application of two well-established bodies of scientific methodologies: (1) diagnostic, DNA-based markers and (2) sampling protocols that are adequate (in terms of statistical power) and cost-effective. However, there is a need to develop fully appropriate protocols for the application of these methods to post-market detection of environmental spread of GM animals and their transgenes. Monitoring can also be helpful to assure confinement of GM animals during research and development.

### 4.4 Future perspectives

Realizing the full range of potential benefits from use of GM animals will depend on advances in technical aspects of their production. For instance, innovative molecular methods will be needed in order to address current limitations with respect to low frequency and randomness of integration, gene silencing and epistatic and pleiotropic effects of transgenes. These innovations may include using improved expression vectors to target transgenes to specific places in the host genome or incorporating transgenes on to bacterial or yeast artificial chromosomes and their introduction into the host. Greater experience with anti-sense gene expression and homologous recombination-based gene knockout techniques will allow the turning off of targeted genes. Other advances, especially development of embryonic stem cells or primordial germ cells from additional species, will facilitate a greater range of genetic modifications of those animal species.

Identification and the transfer of genes will promote beneficial food uses, and also necessitate their assessment with respect to food safety and environmental impacts (e.g. insects with food safety implications, such as honey bees). Transfer of new genes and advances in gene transfer and cloning techniques will facilitate developments contributing to human health by means of new animal models of human disease, expression of pharmaceutical proteins and development of genetic lines for xenotransplantation. Although many potential benefits from GM animals can be anticipated, these will present more challenging conditions for risk assessment, risk management and risk communication.

TABLE 1. Examples of application of gene transfer to animals

| Application | Intended outcome | Example | Comments |
|---|---|---|---|
| Improved animal production | Increased yield by accelerated growth rate or improved feed conversion rate | Growth hormone gene in Atlantic salmon, common carp, and Nile tilapia | |
| | Improved disease resistance | Lactoferrin gene in carp cecropin gene in channel catfish | |
| | Increased tolerance of environmental conditions, such as low temperature | Antifreeze protein in Atlantic salmon and goldfish | Cold tolerance was improved in goldfish but not in salmon |
| | Improved digestibility of feed ingredients | Phytase gene in pig | Approach could also be used to adapt carnivorous fishes to a plant-based diet |
| Improved product quality | Change in nutritional profiles | Reduced lactose concentration in milk | |
| | Remove allergens from food | Knock out gene for allergenic protein in shrimp | |
| | Novel ornamental animals | Fluorescent protein genes expressed in zebrafish | |
| Novel products | Pharmaceuticals for human and veterinary use | Genes for monoclonal antibodies, lysozyme, growth hormone, insulin, etc., expressed in milk or blood of farm animals | |
| | Industrial products | Spider silk expressed in milk of goats | |
| Bioindicators | Sensors for pollution | Expression of reporter genes linked to metallothionein promoter in topminnows exposed to heavy metal ions | |
| Human health | Cells, tissues and organs for xenotransplantation | Knock out of galactosyl transferase gene in pig | Cloning may also be needed |
| Animal health | Prevention of transmissible spongiform encephalopathies | Knock out Prn-p gene of cattle and sheep | Prevention of mad cow disease and scrapie |
| Biocontrol | Pesticide-resistant beneficial insects | Introduction of pesticide resistance gene into predators and parasitoids | Ability to use both chemical and biological means of insect pest control |
| | Control transmission of disease | Introduce genes for resistance to Plasmodium parasite to Anopheles mosquito | Could reduce transmission of malaria |
| | Reproductive and sex control | Introduce anti-sense gene for GnRH or aromatase | Could be used to control invasive exotic species |

Sources: (NRC, 2002; Kapuscinski, 2003).

# 5. Approaches to the safety assessment of foods derived from GM animals

## 5.1 Introduction

The food safety assessment of GM animals and derived products can largely be performed along the lines that have already been established for the evaluation of GM plants and derived products for the consumer (Codex Alimentarius Commission, 2003). This means that the initial step of the food safety assessment will be a comparative safety assessment of the GM animal with its appropriate comparator, including a food intake assessment, followed by a full risk characterization.

## 5.2 General principles

### 5.2.1 Comparative safety assessment

Because of their history of safe use, it is generally acknowledged that traditional food products may serve as a baseline for comparison for the assessment of the safety of GM foods. This is generally referred to as the concept of substantial equivalence. The basic idea is that novel genetically modified organism (GMO)-derived food products should be at least as safe as the traditional products that they may replace in the diet.

Substantial equivalence is not a safety assessment in itself; rather it represents the starting-point which is used to structure the safety assessment of a GM food relative to its conventional counterpart. Since its inception, the concept has evolved (FAO/WHO, 2000). More recently, it has been suggested to replace it with the broader Comparative Safety Assessment (CSA) concept (Kok and Kuiper, 2003). The Consultation agreed that the CSA approach is equally applicable to GM animals as it is to GM plants.

The CSA is basically a two-tiered approach. The initial step comprises a thorough comparison with the closely related conventional counterpart to identify any differences that may have safety implications for the consumer. This comparison includes both phenotypic characteristics as well as a compositional analysis. The phenotypic analysis should also include comparative health parameters. The compositional analysis will focus on key substances in the animal products under scrutiny and will be subject to changes according to the latest scientific state of the art.

The second step of the CSA comprises the toxicological and nutritional evaluation of the identified differences between the GM animal and its conventional counterpart. As a result of this second step additional testing may be required and can result in an iterative process in order to obtain all relevant information for the final risk characterization.

In the initial step the information that should be considered includes:

- the transformation process of the genetic modification, including the sequence of the inserted material before and after the transformation event;
- the copy number and site(s) of insertion;
- sequence analysis of the site(s) of insertion, i.e. flanking regions;
- stability of the integration (multiple generations);
- the safety of any newly expressed proteins, including assessment of allergenicity;
- occurrence and implications of unintended effects;

- the role of the new GM animal food in the diet; and
- the potential influence of processing or spoilage on the new GM food product.

More precise criteria for the molecular characterization are dealt with in the Codex guidelines (Codex Alimentarius Commission, 2003) and are currently being discussed for further elaboration within the OECD.

In terms of classical risk assessment, the CSA approach means that for complex food products, including GM animal-derived products, it will in general be necessary to do both hazard identification and characterization as well as the food intake assessment in order to be able fully to characterize the risk.

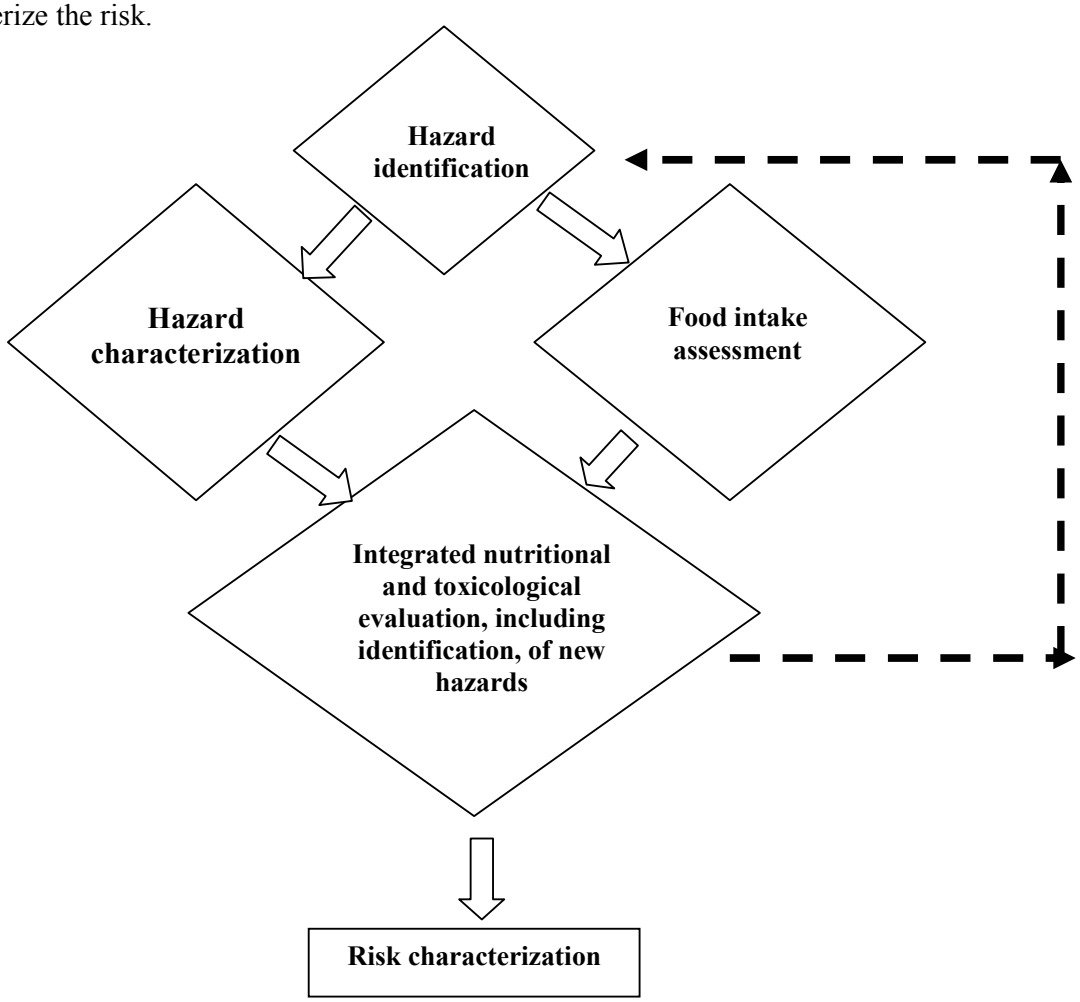


FIGURE. Schematic overview of the risk assessment process

### 5.2.2 Hazard identification and characterization

Hazard identification and characterization are typically the first steps in any risk assessment. Any differences found as a result of the CSA serve as comparable to the hazard identification and hazard characterization steps in a traditional risk assessment paradigm. However, for complex GMO-derived foods, the hazard identification and characterization steps will not be as readily completed as in the case of well-characterized single chemical compounds because of the variety and magnitude of unintended effects that may occur when testing complex food products.

#### 5.2.2.1 Molecular characterization

An extensive molecular characterization of the inserted genetic material construct will generally be required, both before and after the insertional event. The molecular characterization should furthermore comprise an analysis of the copy number and a sequence analysis of the flanking regions of the place of insertion in order to identify any unintended effects.

#### 5.2.2.2 Safety of the gene product

The safety of the gene product must be assessed on a case-by-case basis. Depending on the knowledge of the expressed product, the assessment may range from a limited evaluation process of the available data on the protein, such as amino acid sequence and expression rates in different tissues, to, in the case of less well-documented proteins, extensive toxicity testing including animal studies. In theory, production of GM animals may lead to the introduction of many new proteins without a history of safe use into the human diet. The assessment of the novel proteins should be based on current knowledge of toxic substances, including a search for sequence homology with known toxins, and the function of the novel protein. In the case of unknown proteins, a full classic toxicological safety assessment procedure will form part of the evaluation.

In this regard, a distinction should be made between GM animals developed for food purposes and GM animals developed for pharmaceutical, xenotransplantation or industrial purposes. While all GM animals and their derived products in the latter category will not be intended for food purposes, such animals may enter the food supply either directly or indirectly and therefore their hazards should be assessed.

So far, the number of different genes that is used for the production of GM food animals is still rather limited when compared with plants, but this situation may change with the progress of genome sequencing programmes that are likely to provide a wealth of data on important animal physiological pathways.

#### 5.2.2.3 Allergenicity

In the case of newly expressed proteins in the GM animal, the allergenic potential of the protein will need to be assessed. For the production of specific well-characterized proteins by the GM animal, it needs to be established whether post-translational modifications are comparable to the same substances being produced by more traditional sources in order to assess potential altered toxicological or allergenic properties of the newly synthesized proteins.

It has been recognized that there is no single parameter that can predict the allergenic potential of a substance. Recently, a strategy to assess allergenicity of biotechnology products has been formulated (FAO/WHO, 2001; Codex Alimentarius Commission, 2003), which relies on the following parameters: source of the gene, sequence homology, serum testing of patients known to be allergenic to the source organism or to sources distantly related, pepsin resistance, the prevalence of the trait and assessment using animal models.

The Consultation agreed that the strategies and methodologies for the allergenicity testing in GM animals will not differ fundamentally from those currently in use for the assessment of GM plants. It was recognized that animal models for allergenicity testing, even those that are not yet validated, may be of value to identify potential allergens. It is recommended that additional efforts should be directed to the further development and validation of these models.

#### 5.2.2.4 Gene transfer

The DNA construct used to change the genetic make-up of the animal should be considered within an assessment, especially if the gene or its promoter is derived from a viral source, since horizontal transfer or recombination may occur. Additionally, bacterial host-derived materials may include additional sequence fragments unrelated to the target gene (National Research Council, 2002). Inadvertent introduction of such sequences into the germline of a GM animal not only has the potential for creating unintended genetic damage but can also contribute by recombination to the generation of novel infectious viruses. A well-known example is the generation of a replication-competent murine leukaemia virus (MLV) during the growth of a vector containing a globin gene (Purcell *et al.*, 1996).

There is also potential for horizontal transfer of the gene construct: food-ingested foreign DNA may not be completely degraded in the gastrointestinal tract of mice and pigs (Chowdhury *et al.*, 2003; Schubbert *et al.*, 1997; Schubbert *et al.*, 1998). For the food safety assessment, it is prudent to assume that DNA fragments may survive the human gastrointestinal tract and be absorbed by either the gut microflora or somatic cells lining the intestinal tract.

Assessment of the safety of the genetic construct should include marker genes. Commonly used marker genes are genes that code for antibiotic resistance. Risk assessment of these selectable genes should focus on gene transfer to micro-organisms residing in the gastro-intestinal tract of humans or animals. However, as the potential of this gene transfer cannot be completely ruled out, the safety assessment should also consider information on the role of the antibiotic in human and veterinary medical uses.

In general, the Consultation advocated avoiding the use of any unnecessary DNA sequences including marker genes in the genetic construct.

#### 5.2.2.5 Unintended effects

Potential unintended effects represent a significant concern with GM animals and these effects highlight the difficulty of establishing generic considerations instead of case-by-case considerations. Unintended effects can be divided into insertional effects, related to the place of insertion of the transgenic fragment, and secondary effects, related to the nature of the expression products of the introduced genes. The major approach to detect any unintended side effects in the GM animal is phenotypical, including a compositional analysis to compare the new food organism with the conventional counterpart.

In general, the compositional analysis should be performed on the basis of validated scientific methods. Strategies for the compositional analysis of food products derived from GM animals will not differ fundamentally from those of plants, where key substances are identified and analysed per species. Furthermore, in order to be able to interpret the data from the compositional analysis of individual animal products adequately, insight into the natural variation in the relevant macro- and micronutrients and antinutrients, if present, will be required.

A special case is hemizygous GM animals that are intended for marketing. If the trait is inherited in a recessive way, so that it is expressed only in a recessive homozygote, it may be prudent to assess both the hemizygote as well as the homozygous animal for potential deleterious effects of the specific trait.

In future, compositional analysis may also be based on unbiased profiling of the GM food product and the conventional counterpart. Techniques for the profiling approach are now under

development and can be divided into three subsections: genomics, proteomics and metabolomics to screen for differences in the GM animals in relation to the gene transcription products, proteins and metabolites, respectively. At the moment, however, none of these techniques is yet validated and ready for routine use in risk assessment.

### 5.2.3 Food intake assessment

Whereas traditional risk assessment uses "exposure assessment" to indicate exposure to hazards, the Consultation agreed that "food intake assessment" is a more appropriate term for the case of food products. Food intake assessment addresses complex foods and not individual chemical compounds, and their entry into the food supply can affect diets and also overall consumption patterns.

The goal of a food intake assessment is to assess the amount of food or food ingredient an individual or population group may consume. No exact criteria have been formulated so far for the factors that need to be considered in a pre-market intake assessment of a complex novel food product. Some food intake paradigms make assumptions based on per capita production while others use per capita distribution. An intake assessment may also consider the cooking and food preparation process used. Some governments have instituted tracking of animal-derived food and from this data set post-market consumption data may be determined. Food intake assessments will also include an estimate of the extent to which current food products will be replaced by the GM animal-derived novel food product. Thus, the accuracy of the intake assessment for GM animal-derived foods is dependent upon the available data on consumption patterns of consumer groups of interest and the validity of the underlying parameters. Specific consumer groups may refer to different age groups, but also to more vulnerable groups such as pregnant or lactating women or specific patient groups.

Food intake assessment will be based not only on available consumption data, but also on our knowledge of the bioavailability in the gastro-intestinal tract of specific food components under investigation. Probabilistic mathematical models for integrating food consumption and distribution may in specific cases be used in a comparative approach to estimate future intakes more precisely.

### 5.2.4 Integrated toxicological evaluation

Following the phase of hazard identification, hazard characterization and food intake assessment, an integrated toxicological evaluation will combine all the information in relation to the food safety of the complex GM animal-derived food product. This integrated toxicological evaluation needs to identify food safety issues that may require additional investigation, including traditional toxicity testing.

In general, it will not be possible to test complex animal products by classical toxicological animal studies in the way they are routinely used to test single compounds. Classical studies measuring physiological responses relative to dose are complicated if the laboratory animal is receiving doses of the GM animal's edible tissue. If the genetic modification would result in the expression of novel proteins or if the compositional analysis revealed an alteration in an endogenous protein product or metabolite, the traditional toxicological approach would require the concentration of the product to be elevated in the laboratory animal's diet to the extent that the diet will often become unbalanced. This might result in toxicological observations that are unrelated to the product under investigation. The limitations of standard toxicity testing applied to whole foods have also been discussed (Codex Alimentarius Commission, 2003).

On occasions where the genetic modification results in an increase in a specific (exogenous) protein, for instance directly derived from the gene construct, traditional testing would still be valid to assess that protein. Alternatively, there may be instances wherein endogenous protein levels in the GM food are increased well above the physiological level in the given animal species and it might be prudent in specific cases to (also) test this elevated protein in animal studies.

### 5.2.5 Integrated nutritional evaluation

In order to identify nutritional issues that need further investigation, an integrated nutritional evaluation will need to combine all the information related to the nutritional aspects of the complex GM animal-derived food product. This has to be done in addition to the integrated toxicological evaluation.

The nutritional analysis should focus on the potential replacement of nutritionally important food products by the novel GM animal-derived food products with possibly altered characteristics. The information for the nutritional analysis will largely be derived from the initial CSA, including the compositional analysis (especially macro-, micro- and antinutrients) and the estimated consumption rates. Detected alterations in the GM animal-derived food products compared with the traditional counterpart will be assessed by evaluating the significance of the compositional differences for the consumer in general and also, in specific cases, for specific consumer groups. Nutritional aspects of GMO-derived foods may become of increasing significance when the number of compositionally altered food products on the market increases. Therefore, the nutritional assessment of GM animal-derived food products is dependent on current consumption data of animal-derived food products in distinctive consumer groups and with respect to geographical and demographical differences. Special consumer groups perhaps worthy of consideration include children, pregnant or lactating women, elderly persons and the immuno-compromised.

Micronutrients are vitamins and minerals that are essential for normal physiology and biochemical functioning. Both deficiency and excess of a micronutrient can cause health problems which emphasizes the importance of this class of compounds. Macronutrients include dietary lipids, proteins and carbohydrates and these classes of compounds are present in the food and diet in substantial quantities. Assessment of the replacement factor of important animal-derived sources of micro- and macronutrients by GM animal products in the event of altered composition with relation to these nutrients is therefore of major importance. Bioavailability of the important micro- and macronutrients from GM animal-derived tissues is also of significant importance in this respect.

### 5.2.6 Risk characterization

Risk characterization is the final step of the risk assessment process and involves integrating the outcomes from the full toxicological and nutritional evaluations in order to reach an overall conclusion about the safety of the food.

The baseline for the safety of novel food products derived from GMOs, including GM animals, in all cases will have to be the assessment that the novel GM animal-derived food products is at least as safe as its conventional counterpart. If any questions remain after the initial CSA with respect to the safety of the GM animal-derived food products, additional tests may be required, including animal studies with the whole product or selected tissues/extracts. If, after a full safety assessment, the safety standard, i.e. as safe as its conventional counterpart, cannot be satisfied, the GM animal-derived product should not be approved for marketing. This risk characterization should be established on a case-by-case basis for food products derived from GM food animals.

### 5.3 Post-market surveillance

In general, potential safety issues should be addressed adequately through a rigorous pre-market assessment, as the feasibility of post-market studies is very limited at present.

However, post-market surveillance may be an appropriate risk management measure in specific circumstances. Its need and utility should be considered, on a case-by-case basis, during risk assessment and its practicability should be considered during risk management.

The use of post-market surveillance as an instrument to gain information on the potential long-term or unexpected adverse and beneficial effects of food, either GM animal-derived or traditional, should be further explored. Post-market surveillance could be useful in certain instances where clear-cut questions require, for instance, a better estimate of food intake and/or nutritional consequence of a GM animal-derived food.

For GM animal-derived medicinal substances, existing pharmacovigilance schemes will apply to monitor any unforeseen unintended side-effects of the isolated medicinal substances. The same would apply in a veterinary sense with respect to the GM animal itself when modified with respect to the production of hormonal or disease-prevention substances: pharmacovigilance schemes could help to detect unintended side-effects of the introduced expression product to the GM food animal that were not detected in the pre-market phase. To this end, the GM animals should then be included in such pharmacovigilance schemes on the basis of "internal" administration of the specific veterinary substance.

It is important to note that product tracing and related control systems may be less straightforward in the case of chimeric organisms as different parts of the food animal will have different genetic constitutions and this may severely complicate analytical control of product tracing systems.

Depending on the questions and risk management needs underlying the establishment of post-market surveillance systems the product information conveyed to the consumer may, however, require adjustment. In order to enable consumers to relate potential adverse, e.g. allergenic, effects to a GM animal-derived food product, it may be necessary not only to label the product as GM animal-derived, but also to provide information on the specific GM animal source, for instance by including on the label the unique identifier code specific for a single integration event.

For the establishment of adequate product tracing systems and in order to distinguish safety evaluated products from unevaluated ones, it will be necessary to have the information on the sequence of the insert and on the flanking regions as well as reference materials of the transgenic animal and its conventional counterpart. It is recommended to use a relatively small size sequence for detection which is expected to be detectable in all kinds of products, including processed products.

## 6. Specific food safety issues of foods derived from animal biotechnology

### 6.1 Introduction

This section deals with specific issues that are frequently raised with regard to the safety of genetically modified foods. These issues include phenotypic analysis, sampling, compositional analysis and post-market surveillance. The discussion which follows provides an evaluation of

existing knowledge about these topics and elaborates scientific approaches that may be used to assess possible health risks.

### 6.2 Phenotypic analysis

The selection process of the initial founders will be very limited compared with the plant breeding situation where thousands of GM calluses are screened for incorporation of the transgenic fragment and subsequently monitored for their phenotypic characteristics. This means that the information on the variation range between animals with the same genetic modification will be rather limited and that detected differences between individual animals will be difficult to interpret.

#### 6.2.1 Phenotypic characteristics

Phenotypic analysis will relate to compositional analysis, but also to general performance parameters (such as growth rate, feed conversion efficiency, reproduction, clinical parameters), disease resistance and, depending on the animal and the genetic modification, the colonization and shedding of pathogens that may have food safety implications.

In specific cases, phenotypic analysis may also be advisable after processing or, for fish, during the various stages of spoilage. For example, adverse biogenic amines can be formed during spoilage in salmon, tuna, herring and other fish species. Similarly, formaldehyde may be formed in spoiled shrimp, cod, hake and many other species.

#### 6.2.2 Sampling

For individual animal species the number of GM animals and conventional counterparts required for a compositional analysis needs to be determined in order to result in statistically reliable results, i.e. perform a power analysis. Furthermore it will need to be decided which edible tissues and products should be analysed in the different animal species.

It is clear that, in the case of GM fish and other aquatic species, more individuals are likely to be available for a compositional analysis compared with, for instance, large farm animals. In order to obtain statistically meaningful results in both cases it will be necessary:

- to have information on the natural variation in the different tissues;
- to apply standardized experimental conditions to the GM animals and conventional counterparts; and
- to have standardized conditions for harvesting tissues and other animal products, for instance, with respect to developmental stage, age or market weight.

An example is the GM fish that has incorporated a growth hormone gene into its genome. In this case, sampling for the compositional analysis may be based on market weight rather than age.

#### 6.2.3 Compositional analysis

For GM animal-derived food products the same basic approach for the compositional analysis should apply as for plants. Similar to the GM plants, the key constituents of the tissue would have to be established. This will include key nutrients as well as those compounds that may have adverse effects on human health, such as thiaminase in fish (Kleter and Kuiper, 2002) and wax esters in butterfish (Nichols, Mooney and Elliot, 2001). The list of key constituents per tissue will have to be flexible and may have to be adjusted based on the current state of the art in an ongoing process.

It is important to generate background data on the natural variation for the individual constituents in different tissues. Existing databases on the composition of animal food products need to be evaluated as to whether their data are of sufficient quality to be of value in a comparative compositional analysis.

### 6.3 Post-market surveillance – product tracing systems

Post-market surveillance requires food intake data and may require the establishment of adequate product tracing systems. In this respect the food animal sector has advantages over the crop plant sector where basic product tracing systems are still virtually lacking. In the animal production sector, such systems are already well established for some animal food production chains in some countries and many other initiatives are ongoing in this field. It will, however, require further elaboration and adjustment before these systems can be used for the purpose of post-market surveillance.

### 6.4 Future developments

As a result of ongoing genome programmes, the potential of genetic modification in animal production will increase. The variety of genes that can be used will increase and it may also become more feasible to transfer entire metabolic pathways. It may be anticipated that the number of GM animal-derived products with improved health characteristics may increase, for instance pigs with a nutritionally improved meat composition or shrimp with reduced allergenic potential.

Based on our increased knowledge of the physiology of food animals, the number of unpredictable secondary effects of the genetic modification that cannot be analysed in a targeted analysis may decrease, theoretically reducing the number of unexpected effects of a transformation event.

Further development and validation of profiling methodologies in the field of genomics, transcriptomics, proteomics and metabolomics may provide additional insight into the unintended effects of a transformation event.

Improved product tracing and information transfer systems may make the application of post-market surveillance systems more feasible to assess the long-term effects of complex food products, including food products derived from GM animals.

## 7. International regulatory instruments

### 7.1 Codex Alimentarius

In July 2003, the Codex Alimentarius Commission adopted the following texts:

- *Codex Principles for the Risk Analysis of Foods Derived from Modern Biotechnology*

The purpose of these principles is to provide an overarching framework for undertaking risk analysis of the safety and nutritional aspects of foods derived from biotechnology. The “tracing of product” is referred in the text as a specific tool to facilitate risk management measures.

The key elements of the principles are:

- there should be a pre-market food safety assessment, on a case-by-case basis, for foods derived from biotechnology. The assessment should be based on sound science, obtained using appropriate methods and analysed using appropriate statistical techniques. The data and information used in this assessment should be of a quality that would withstand scientific peer review;
- the food safety assessment is based on a comparative analysis with a "conventional counterpart" to ensure that the resulting biotechnology food is no less safe than the foods normally consumed by the population;
- risk management measures should be proportional to the risks identified in the safety assessment and may include measures such as labelling, post-market monitoring and product tracing; and
- the definitions used in the Principles for the [Food Safety] Risk Analysis for Foods Derived from Modern Biotechnology are the same as those in the Cartagena Protocol on Biosafety (CPB), so that the Codex texts on food safety and the CPB text on biosafety and environmental protection are mutually compatible and supportive.

- *Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants*

This guideline, which is based on the above "Principles", describes the methodology for conducting a safety assessment specifically for foods derived from recombinant-DNA plants. The basic approach for the safety assessment is the comparative approach based on the concept of "substantial equivalence", thus focusing on the difference between foods derived from recombinant-DNA plants and their conventional counterpart. It pays special attention to the question of allergenic potential of new genetically modified (GM) plant varieties. An annex outlining the evaluation of allergenicity was also agreed.

- *Codex Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms*

Based on the above "Principles", this guideline describes the methodology for conducting safety assessment specifically for foods derived from recombinant-DNA micro-organisms. The basic approach is similar to the guideline of recombinant-DNA plants, however, elements peculiar to micro-organisms were highlighted.

The key elements of the guidelines are:

- a detailed step-by-step guidance on how to undertake a safety assessment, including the nature of the data to be collected and the elements in the decision-making process that allows food produced using recombinant-DNA micro-organisms to be considered suitable for human consumption;
- they allow comparison of the safety assessments undertaken by different national authorities;
- they allow national authorities that do not wish to do their own (rather expensive) safety assessments to use the safety assessments of other government authorities provided that these assessments are in line with the Codex Guidelines;
- they provide a basis for future food safety assessments that may be undertaken by FAO and WHO, if FAO and WHO decide to undertake case-by-case safety assessments.

### 7.2 Cartagena Protocol on Biosafety

The Cartagena Protocol is a legally binding international instrument that regulates the transboundary movement of living modified organisms (LMOs) resulting from modern biotechnology with the objective of protecting the environment. The backbone of the Protocol is the advance informed agreement (AIA), requiring consent prior to the shipment and introduction of an LMO into the environment of an importing country.

The Protocol establishes a harmonized set of international rules and procedures designed to ensure that countries are provided with the relevant information, through the "Biosafety Clearing-House". This Internet-based information system enables countries to make informed decisions before permitting the import of LMOs. The Protocol also ensures that LMO shipments are accompanied by appropriate identification documentation. The Protocol entered into force on 11 September 2003. It is important to note that, at present, there are no internationally agreed frameworks for considering ethical aspects relating to the use of modern biotechnology.

## 8. Ethical aspects

### 8.1 Introduction

The production of genetically modified animals raises a variety of legitimate ethical concerns. The need to address these concerns openly and without prejudice is further amplified by sections of a critical public that question some of the achievements of modern biotechnology. Responsible decision-making and policy needs to integrate ethics among the salient factors in the preparatory stages of risk analysis.

Ethics is rooted both in the world religions and in secular philosophies, while a sense of morality and moral value is common for everybody. Ethics comprises both a positive dimension relating to our conceptions of the good life/society, and a negative dimension relating to our judgements of what is morally wrong. For instance, owing to religion-based food practices relating to eating pork, the utilization of genetic material from pigs could present problems.

### 8.2 Environmental ethics and animal welfare

In large parts of mainstream Western ethics, the objects of our moral concerns have been human beings. With the advance of our knowledge, many people have come to realize that there is ample reason to extend the realm of moral concern to animals and perhaps even to ecosystems. This has led to discussions on the moral status of animals, as well as to increased attention being given to animal welfare issues, also related to transgenic animals. For instance, one set of early experiments with growth enhanced salmon showed some individuals with cranial deformities (Devlin *et al.*, 1995). As a general, but not unexceptional, rule the intended use of GM animals for food production bespeaks the interest of the producer to ensure or improve the health of animals and good animal welfare. Therefore, aspects of animal welfare of transgenic animals need to be evaluated on a case-by-case basis by competent bodies.

### 8.3 Uncertainty

Ethically responsible decision-making demands, *inter alia*, both the utilization of the best available knowledge and an awareness of the relevant uncertainties involved. While it is widely acknowledged that good risk assessment demands a measure of uncertainty, the common instruments to make these uncertainties visible are still limited. However, research on this topic has made significant progress during the last decade, and valuable and useful instruments to represent

the relevant uncertainties are now available (Walker *et al.*, 2003). This is ethically significant because, in some cases, the uncertainties relate to our state of knowledge (thus often indicating the need of more research) but, in other cases, the uncertainties relate to inherent characteristics of the system under study, e.g. chaos or complexity, or multiple states of equilibrium without linear and deterministic state change. In the latter cases of inherently limited predictability, we have to adopt a responsible scheme for the management of these uncertainties. This point is important both for the use of precaution in risk management and for the provision and presentation of scientific findings as the basis for such management. Precaution does not assume an unrealistic notion of zero-risk. Sometimes the best precautionary action is carefully controlled, monitored and stepwise development. There is a need to address explicitly the uncertainties involved in our assessments, and to adopt schemes for their responsible management.

### 8.4 Transparency and public deliberation

The recognition of consumer autonomy and the right of free and informed market choices is an aspect of responsible management. Another aspect relates to the worry in sections of the public that the new genetic technologies may not be used for the "right" or ethically justified ends. The distribution of risks and benefits may be morally problematic, and the scope of benefits may be wanting. At present, even the lack of data on such distributions is a concern. Similar concerns relate to the technological divide and the unbalanced distribution of benefits and risks between developed and developing countries. Often the problem becomes even more acute through the existence of intellectual property rights and patenting that places an advantage on the strongholds of scientific and technological expertise. Equity and fairness issues are thus obviously important. All these considerations point towards the positive dimension of ethics, i.e. a discussion of purpose, benefits and risks. There is a societal need to address these issues upfront, and in the early stages of development (Sagar, Daemmrich and Ashiya, 2000; Kapuscinski *et al.*, 2003). Proactive assessment is indicated, and the need for scientific data to inform such assessments should be described. Risk managers and decision-makers should shoulder this task in collaboration with stakeholders.

### 8.5 The role of ethical principles in assessments

In relation to human health and medicine there is already a tradition of carrying out practical ethical assessments. Four principles have been established as fundamental in the biomedical field: respect for autonomy, beneficence, non-maleficence and justice (Beauchamp and Childress, 2001). These principles seem to be widely accepted, represent important ethical theories and cover most of the problems appearing in the biomedical field. Within the field of genetically modified animals a similar framework needs to be introduced if ethics is indeed to become an integral part of regulation and guided policy advice. Extensions of the principle approach in biomedicine to other technological and environmental issues have been carried out e.g. in the ethical matrix approach (Mepham, 1996; Kaiser and Forsberg, 2000; Schroeder and Palmer, 2003). The basic idea in this framework is to combine the use of a variety of principles with the interest-related perspectives of the various stakeholders and other potentially affected organisms and their environment. A schematic version of one such approach is presented in the next paragraph. The rationale of these frameworks and approaches is to make ethical assessment more transparent and more methodical, and thus amenable to quality assurance.

### 8.6 A schematic ethical assessment

Assuming that we want to assess the ethical aspects of a certain genetic modification of a fish species for food production in a region, following the ethical matrix approach we would first address the issue of who the relevant stakeholders are. We also need to agree on potentially affected organisms and their components of the environment, for example fish and other biota. A proper set

of ethical principles then needs to be established, for instance, justice/fairness, dignity/autonomy and welfare considerations as comprising both the elimination of negative welfare and the increase of positive welfare. Once a common understanding of these principles is ensured, it is important to specify the principles for each interest perspective. Through the presentation of an example ethical matrix (see Table 2) it becomes clear that some of the cells in this table (indicated in grey) relate directly to the scientific description in the safety and benefit assessments of GM animals. Thus there is an overlap between the ethical assessment and the risk assessment and management. A description of specific consequences of the new technology as well as uncertainties in our knowledge is now possible within the matrix. This enables a broader evaluation of the issues.

TABLE 2. Simplified ethical matrix (for illustrative purposes only – grey cells in the matrix also relate directly to the scientific description of safety and benefit assessment of GM animals)

| **Ethical matrix for GM-fish:** | Welfare as eliminating negative utilities | Welfare as promoting positive utilities | Dignity/autonomy | Justice/fairness |
|---|---|---|---|---|
| Small producers | Dependence on nature and corporations | Adequate income and work security | Freedom to adopt or not to adopt | Fair treatment in trade |
| Consumers | Safe food | Nutritional quality | Respect for consumer choice (labelling) | General affordability of food product |
| Treated fish | Proper animal welfare | Improved disease resistance | Behavioural freedom | Respect for natural capacities (telos) |
| Biota | Pollution and strain on natural resources | Increasing sustainability | Maintenance of biodiversity | No additional strain on regional natural resources |

## 9. Conclusions

1. Potential benefits of GM animals might be realized in the near-to-medium term, such as improved animal production and product quality and novel animal products. Other applications that might be realized over the longer term include use of GM animals as bioindicators, for biological control, and for xenotransplantation.

2. There may be a variety of genetic and immunological hazards owing to transgene integration, expression or instability. Anticipated results of ongoing research and development work on vector design (including use of insulating or boundary elements and elimination of antibiotic resistance genes) provide the opportunity to prevent or reduce some safety concerns and thereby proactively design and produce GM animals that are safer from the outset.

3. Xenotransplantation poses benefits for human recipients of cells, tissues and organs, but also poses hazards to those recipients and to the human population. These hazards stem from the possibility that pigs and humans might more easily transmit diseases to one another, and that pigs might serve as hosts for the evolution of new human pathogens. There is also the possibility that products from animals developed for xenotransplantation could enter the human food supply, posing food safety hazards.

4. The likelihood of GM animals entering and persisting in the environment will vary among taxa, production systems, modified traits, and receiving environments. The spread and persistence of GM fish and shellfish – or their transgenes – in the environment could be an

indirect route of entry of GM animal products into the human food supply. This is because escaped individuals or their descendants could subsequently be captured in fisheries for those species. Similar mechanisms might apply for poultry such as ducks and quail that are subject to sport or subsistence harvest. Live transport and sale of GM fish and poultry poses another route for escape of GM animals and their entry into the environment.

5. When there is a food safety hazard and a high likelihood of entering the food supply through the environment, confinement of the GM animals is necessary. However, current confinement standards for research with GM animals do not address the commercial production of GM animals.

6. Sterility eliminates the potential for the spread of transgenes in the environment, but does not eliminate all potential for ecological harm. Monosex triploidy is the best existing method for sterilizing fish and shellfish, although robust triploidy verification procedures are essential.

7. Methodologies exist for post-release detection of GM animals in the environment, but protocols for applying them need to be developed and validated. A diversity of ecological methods could be applied for post-release determination of whether or not GM animals cause environmental harm, but are very challenging to apply.

8. The food safety assessment of GM animals and derived products can largely be performed along the lines that have already been established for the evaluation of GM plants and derived products for the consumer. This means that the initial step of the food safety assessment will be a comparative safety assessment (CSA) of the GM animal with its appropriate comparator, including a food intake assessment, followed by a full risk characterization.

9. As every GM (founder) animal will have a different genetic constitution with respect to the integration of the genetic construct, the safety evaluation should be carried out on a case-by-case basis, even if the same genetic construct was used for the genetic modification. If improved genetic technologies (e.g. homologous recombination and insulated insertions) should reduce the possibility of insertional effects in the future, it may become more feasible to come to more generic approaches for the safety assessment of GM animals and products thereof.

10. A few major differences can be seen when comparing the GM animal to the GM plant situation. First, the numbers of GM animals derived from a single GM founder animal will in general be much lower, aquatic species being the exception, compared with GM plant genetic modification events and numbers available in subsequent plant generations. This could result in fewer animals being available for the comparative safety assessment and therefore more background data will be required for the safety assessment of animals in comparison with plants where more background data already exist. Data on the natural background variation in animal tissue constituents will therefore have to be generated. Second, an additional difference is the omnipresence of natural toxins in plant products and the very few cases of animal products that have proved to contain antinutritional substances for the consumer. On the other hand zoonotic diseases and human pathogens of animal origin are a concern in the case of GM animals and need to be taken into account.

11. A rigorous pre-market safety assessment of foods derived from GM animals should provide sufficient safety assurance. The use of post-market surveillance as an instrument to gain information on the potential long-term or unexpected adverse and beneficial effects of food either GM animal-derived or traditional should be further explored. Post-market surveillance could be useful in certain instances where clear-cut questions require, for instance, a better estimate of food intake, and the nutritional consequences of foods derived from GM animals or a better estimate of the environmental fate of GM animals and their transgenes are required.

## 10. Recommendations

1. Effort should be invested in making transgenic animals safer from the outset, e.g. by wise selection of breeding goals and improved expression vector design. There is a need to develop improved vector/transformation systems (e.g. homologous recombination and insulated insertions) that reduce the random nature of gene insertion and, therefore, may decrease unintended effects. The Consultation recommended avoiding the use of unnecessary DNA sequences in the genetic construct, including marker genes.

2. It is recommended that the approach for the molecular characterization should be further standardized to include the flanking regions.

3. The establishment of databases on the natural variation in key compositional constituents in animal products, including fish products, will be an important item in order to be able to assess unintended effects of the genetic modification.

4. The Consultation agreed that the strategies and methodologies for the allergenicity testing in GM animals will not differ fundamentally from those currently in use for the assessment of GM plants. It was recognized that animal models for allergenicity testing, even those that are not yet validated, may be of value to identify potential allergens. It is recommended that additional efforts should be directed to the further development and validation of these models. More research efforts should be devoted to the elucidation of mechanisms of allergenicity.

5. There is a need to improve the accessibility and interconnectivity of existing databases or to establish a centralized database on allergenic linear and conformational epitopes and tools for screening transgenes for allergenic potential.

6. There is a clear need to continue the development of improved genomic, proteomic, metabolomic profiling tools and instrumentation for the detection of unintended effects.

7. There is a need for a worldwide accessible database, linked to ongoing efforts in this area, with information on detection and identification methods and reference materials for food products derived from GM animals on the market and in development.

8. Case-by-case environmental risk and benefit assessment of GM animals should assess each transgenic line (i.e. individuals with a single transgenic genotype) with regard to local conditions of the environment, farming system and human food system. It is essential to assess the whole life cycle of the animal, for instance, by estimating net fitness, to predict the likelihood of environmental spread of the GM animal or its transgenes. Established principles of contemporary evolutionary biology, population biology and ecology should be applied to risk analysis and safety verification.

9. There is a need for better predictive models and data sets for environmental risk assessment. Methods used to generate data must be validated, and data sets must be generated to fill key gaps in current knowledge.

10. Standardized methods for the confinement of genetically modified animals should be developed and validated to manage risk for cases where environmental spread of GM animals or their transgenes poses food safety risks. Redundant measures may be needed for confinement to prove reliable. There is also a need for improved methods of sterilizing certain genetically modified animals and for robust verification regimes for all species.

11. There is a need for capacity building, particularly in developing countries, for food safety assessment and management of GM animals, including environmental and ethical aspects related to food safety.

12. The Consultation encouraged strengthening coordination among national government and intergovernmental agencies responsible for food safety, environment, agriculture and trade when it comes to assessing and managing the risks posed by GM animals. This is also essential for addressing the unintended entry of GM animals that are not intended for human food into the human food supply.

13. The Consultation recommended participatory deliberation by all stakeholders and the general public, including communication about potential benefits, risks and uncertainties posed by the genetic modification of animals in order to promote public knowledge and trust. Participatory deliberation should occur at an early stage of product development and at key points in the decision-making process.

14. Since no universal framework for the practical assessment of ethical aspects of animal biotechnology has yet been widely embraced by various parties, it is recommended that WHO and FAO together with other relevant bodies seek to work out relevant frameworks for this task. These frameworks should make ethical assessments more transparent and more methodical, and thus amenable to quality assurance.

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**ANNEX 2**

# List of documents

**Benfey, Tillmann**
Environmental impacts of genetically modified animals

**Dunham, Rex**
Status of genetically modified (transgenic) fish: research and application

**Hallerman, Eric**
Hazards associated with transgenesis methods

**Houdebine, Louis-Marie**
Generation and use of genetically modified farm animals

**Kaiser, Matthias**
Ethical issues surrounding GM-animals/GM-fish production

**Kok, Esther Jeannette and Jones, Wendelyn**
The food safety risk assessment of GM animals

**Report of a Joint FAO/WHO Expert Consultation**
Allergenicity of Foods Derived from Biotechnology 22–25 January 2001
Evaluation of allergenicity of genetically modified foods

**Food Safety Programme, World Health Organization**
20 questions on genetically modified (GM) foods

**Report of a Joint WHO/EURO–ANPA Seminar**
Release of Genetically Modified Organisms in the Environment: is it a Health Hazard?
7–9 September 2000, Rome, Italy

**Report of a Joint FAO/WHO Expert Consultation**
Safety aspects of genetically modified foods of plant origin
29 May–2 June 2000, WHO Headquarters, Geneva, Switzerland

**Report of a Joint FAO/WHO Expert Consultation**
Safety assessment of foods derived from genetically modified micro-organisms
24–28 September 2001, WHO Headquarters, Geneva, Switzerland

**Codex Alimentarius**
Codex Principles and Guidelines on Foods Derived from Biotechnology
CAC/GL 46-2003