Bio-based and Applied Economics 1(3): 313-329, 2012

Factors Affecting the Adoption of Genetically Modified Animals in the Food and Pharmaceutical Chains

Cristina Mora[1]*, Davide Menozzi[1], Gijs Kleter[2], Lusine H. Aramyan[3], Natasha I. Valeeva[3], Karin L. Zimmermann[3], Giddalury Pakki Reddy[4]

[1] Department of Food Science, University of Parma, Italy
[2] RIKILT, Wageningen University & Research Center, The Netherlands
[3] LEI, Wageningen University & Research Center, The Netherlands
[4] Agri Biotech Foundation, India

Abstract. The production of genetically modified (GM) animals is an emerging technique that could potentially impact the livestock and pharmaceutical industries. Currently, food products derived from GM animals have not yet entered the market whilst two pharmaceutical products have. The objective of this paper is twofold: first it aims to explore the socio-economic drivers affecting the use of GM animals and, second, to review the risks and benefits from the point of view of the life sciences. A scoping study was conducted to assess research relevant to understanding the main drivers influencing the adoption of GM applications and their potential risks and benefits. Public and producers' acceptance, public policies, human health, animal welfare, environmental impact and sustainability are considered as the main factors affecting the application of GM animal techniques in livestock and pharmaceutical chains.

Keywords. Genetically modified (GM) animals, socio-economics, life sciences, acceptance, sustainability

Jel Codes. Q57, Q18, D11.

1. Introduction

The production of genetically modified (GM) animals is an emerging technique that could potentially impact the livestock and pharmaceutical industries. Most GM animals have been developed for research in private or University laboratories; rodents, but also rabbits and pigs, are genetically modified to study action and function of gene mechanisms. Apart from those GM animals developed for recreational purposes (e.g., the first GM animal commercialized was GloFish®, a GM Zebra fish with a fluorescent gene to glow in the dark under UV light), some GM animals are also being produced to improve livestock production, such as those developed to increase growth, to be disease resistant or to increase the quality of their products (meat, milk, etc.). Other applications, such as Enviropig™, were created to reduce the environmental impact of farming (e.g., reduc-

* Corresponding author: cristina.mora@unipr.it.

ISSN 2280-6180 (print)
ISSN 2280-6172 (online)

www.fupress.com/bae

ing phosphorus pollution). Finally, genetic engineering can be used for bio-medical and human health applications, like GM livestock (cows, goats, sheep, pigs, chickens or rabbits) developed for producing pharmaceutical proteins from milk, egg white or other fluids (e.g., blood), human antibodies, animal tissue or organs for use in human transplants, or xenotransplantation (Houdebine, 2009; Laible, 2009; Murray *et al.*, 2010; Vàzquez-Salat *et al.*, 2012).

Although the economic analyses of potential costs and benefits of GM crops are widely described and used, there is little analysis of GM applications in the animal and pharmaceutical chains. This is because genetic modification of animals has proceeded much slower than crops, for a variety of reasons, such as socio-economic, technical, human health, environmental and animal welfare factors. This paper examines the main drivers affecting the development and adoption of transgenic animals from a socio-economic and life science point of view. A scoping study was conducted to assess research relevant to understanding the main drivers influencing the adoption of GM applications.

Europe has had a leading role in the development of cloned and GM animals throughout the '90s. Notable examples include Dolly, the sheep that was the first animal created by cloning through transfer of a cell nucleus from a differentiated cell to an egg cell at the Roslin Institute in Scotland. Another example is Herman the bull, developed by the Dutch biotechnology company Gene Pharming Europe. Genetic modification was applied so that subsequent generations of female offspring would produce the protein lactoferrin through their milk, which can be used for food, nutraceutical, and pharmaceutical purposes. Other experimental animals have been developed at European institutions, including genetically modified fish and chicken, with specific advantages and benefits to food production and other areas of application.

Despite considerable European innovations occurring in the area of GM animal technology, many of the current activities in the field of GM food animals take place outside the EU, in particular regions like the Far East, North and South America, and Australia-New Zealand. It can be envisaged that some of these animals will possibly find their way into the European food supply chain through imports from overseas, in particular given that the EU is the world's largest international trading block for food commodities.

In a more general sense, improvements in animal biotechnology (including but not limited to genetic modification of animals) are expected to result in economic benefits for farmers, processors and consumers. For instance, the development of GM fish species growing faster than non-GM ones is expected to reduce farming costs, e.g. feeding costs, while providing economic advantages for consumers in terms of lower prices (Menozzi *et al.*, 2012). However, the distribution of these benefits depends on many factors like the type of technology (cost reducing or quality enhancing applications), market structure and competitiveness (concentration ratio, suppliers' market power, etc.), information transparency (labelling and traceability programs, etc.), price elasticity, consumer acceptance, etc. Besides the direct economic effects, other externalities should also be considered in the overall economic evaluation. In particular, transgenic animals could provide substantial benefits to consumers in the form of safer food produced by healthier livestock, improved products including food with additional health benefits, and, in a more general sense, a cleaner environment through reduction of the environmental footprint of livestock farming (Laible, 2009). On the other hand, the application of animal biotechnology should be

properly controlled so as to prevent unintended environmental damage or increased risks to human health, as well as animal health and welfare.

The objective of this paper is twofold: first it aims to provide insight into the socio-economic drivers affecting the adoption of genetically modified (GM) animals in the food and pharmaceutical production chain (feed industry, breeding industry, primary sector, processing industry, and pharmaceutical industry). Second, it aims to review the risks and benefits from the point of view of the life sciences on issues like public health, animal health, animal welfare, environmental safety, sustainability, and agro-biodiversity.

2. Material and Methods

Scoping studies aim to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available (Arksey and O'Malley, 2005). Scoping study guidelines have been developed to provide suggestions on how to identify relevant papers (keywords, journals, web sources, etc.) for the socio-economic dimensions. Strict limitations on the use of search terms were avoided in these guidelines in order to identify relevant studies more clearly and study a selection at the outset and reporting stages. The process is not linear but iterative, requiring researchers to engage with each stage using reflection and, where necessary, to repeat steps to ensure that the literature was covered comprehensively.

The kind of terms that it was appropriate to search for was a key question for which all partners involved in the scoping study were asked to provide feedback. An initial list was provided as suggestions (Table 1), and new terms were added iteratively.

Table 1. Keywords applied in the socio-economic search

Biotechnologies-related keywords	Methods-related keywords	Animals-related keywords	Use-related keywords
GM animals GE animals Transgenic animals Clone GM food Traceability Labelling Identity preservation Animal welfare Intellectual property rights Stem cell DNA Nucleus transfer Biotech Genetic trait	Revenue Cost, Benefit Price Economic effects Cost-benefit analysis Supply chain analysis Willingness to pay Added value Food safety costs Livestock economics Net present value	Fish, Salmon, Carp, Tilapia Pig, Sow, Swine Sheep, Goat Cow Horse Rabbit Chicken Bees	Food Meat Feed Milk Pharmaceutical Vaccine Medical Nutraceutical

Several sources were considered in the analysis of the literature: electronic databases, reference lists, key journals and existing networks. The search strategy for electronic databases (e.g. internet, CD-Rom, etc.) was developed from the research questions and definitions of keywords and key concepts. It was important to check the reference lists and bibliographies of studies found through the database searches to ensure they had been included in the scoping exercise. Another important step was the hand-searching of key journals; this helped to identify studies missed in database and reference list searches. Finally existing knowledge and networks could generate information about research. Contacting relevant national or local organizations working in the field, EU projects and/or EU support researches with a view to hand-searching libraries and/or identifying unpublished work thus improved the analysis. Papers in English were preferred in the study; however, relevant publications in other languages (e.g., Italian, Dutch, Spanish, etc.) were included in the research as well, provided there was an abstract in English covering the main information included in the paper (subject, method applied, main results, etc.) or, alternatively, the main information had been translated into English for charting and reporting.

A "data charting form" was defined to collect and standardize all the information of the relevant papers. This form included general information about each study (e.g., year, aim of the study, source, etc.) and specific information (e.g., genetic modification, economic effects, governance issues, methodology applied, main results, factors affecting the adoption of GM technologies, geographical location, outcome measures, data source, secondary results, etc.). In this way, the main characteristics of each study analyzed were shown in the form of a table or graph. These data formed the basis of the analysis. A total of 145 studies were collected from different sources.

3. Socio-economic factors affecting the introduction of GM animals

A third of the selected studies involved food chains and only in a relatively smaller proportion pharmaceutical chains (30%); about a half of the studies were reviews of transgenic applications and only one third empirical or econometric analysis. This shows the large number of reviews about potential applications of GM animals, rather than actual economic data. Many studies were published between 2002 and 2003 (30%), as well as in more recent years (25% after 2007). The type of animals involved was mostly bovine (44% of the studies), fish (30%) and swine (30%), showing a marked interest of research in these species.

The review of methods to evaluate the economics of GM animals shows that, although there is great potential of GM applications to improve the performance of animal production chains and pharmaceutical products in theory, the applications ready for the market are very limited (Mora *et al.*, 2011). Empirical research on economic factors, such as costs and benefits, affecting the introduction of GM applications in animal and pharmaceutical products compared to GM crop products is substantially lacking. For GM applications in animals, most of the economic analyses are focused on GM applications related to introduction of GM hormones or GM vaccines in animals. The economic analysis of GM applications in animals themselves (e.g. introducing foreign DNA into germline) are lacking to a great extent. Besides, most of the studies are not at the chain level, but at the farm or laboratory level. A wide variety of methods and techniques are used to

analyze the economic advantages and disadvantages of GM applications including quantitative economic models, scenario analysis with simulation models, econometric analysis, and qualitative telephone interviews.

From the literature studied, the main factors affecting the (future) application of GM animals techniques to livestock and pharmaceutical chains range from public and producers' acceptance to public policies. Other factors, such as environmental sustainability, human health effects, animal welfare and ethical concerns are also involved and will be analysed in the following sections.

3.1 Public acceptance

Public acceptance is generally considered as a "condicio sine qua non" for any development of transgenic animals in food and pharmaceutical chains. The uncertainty of consumers' reaction is the largest issue in assessing the potential of animal biotechnologies worldwide (Caswell *et al.*, 2003). The framework suggested for adopting technology, therefore, takes the consumer as a starting point. Consumers' attitude (positive vs. negative) and concerns (health, food safety, unnaturalness, ethical, environmental, animal health and welfare, etc.) are fundamental factors to understanding GM adoption and public perceptions of GM technology. These issues have been the focus of several studies (Novoselova *et al.*, 2007; Frewer *et al.*, 2011).

Many studies show that public acceptance of GM application is lowest where food or animals are involved (Gaskell *et al.*, 2000; Aerni, 2004). The fact that plant applications received higher support than animal applications has been reported by a research carried out in the U.S. (Knight, 2006). A FAO global pool reports that 62% of all respondents worldwide opposed the application of biotechnology to increase farm animal productivity. Another example is a survey performed for the Pew Initiative on Food and Biotechnology, which indicates that 65% of consumers disagree with the idea of creating transgenic fish to improve efficiency of production (Logar and Pollock, 2005).

The end-user acceptance of biotech varies considerably by application area and by world geography. Medical and pharmaceutical biotechnology related to GM animals is generally accepted by most, due to perceived personal benefits for patients carrying strong interests and willingness to take high risks. So in the pharmaceutical sector the level of acceptance for GM animal applications is higher, ranging from 83% in developing countries to 70% in Japan (Devlin *et al.*, 2009), because of the expected advantages and the different array of political actors (Vàzquez-Salat and Houdebine, 2013). The final user of GM animal food-related applications is the consumer. In countries where food security is not a priority, consumers acceptance of GM animals is expected to be lower, especially for those applications offering economic advantages, like accelerated growth. Only a few applications, such as Enviropig^{TM} or pigs with omega-3 fatty acids, offer non-economic advantages (Vàzquez-Salat and Houdebine, 2013). Fish biotechnology shows the lowest acceptance rate. The low tolerability for GM fish may stem from several factors, including environmental concerns. If geographic differences are considered, consumers' acceptance is higher in developing countries where the requirement for enhanced food production might be met by application of this technology (Devlin *et al.*, 2009). Different cultural values were also reported for GM animals resistant to common diseases, such as mastitis.

American animal welfare organisations believed that application of GM would result in a welfare improvement for mammals, whilst their European counterparts consider it to be an excuse to worsen housing conditions and veterinary interventions, with a negative impact on animal welfare (Vàzquez-Salat and Houdebine, 2013). Another study shows that disease-resistant animals were the most accepted among livestock-derived products by U.S. consumers, while the least accepted were animals producing tastier and tender meat, those producing human organs for xenotransplantation, and those providing increased outputs (Knight, 2006).

Some empirical studies analyze consumer acceptance of specific GM products, e.g. reporting a higher consumer preference of conventional over GM pork (Novoselova *et al.*, 2005). In this case, the negative perception of GM pork may be compensated by improvements in quality, increased animal health and welfare (Greger, 2011), a lower impact on the environment, less residues and a price discount (Novoselova *et al.*, 2005). Increased animal welfare has the most positive effect on consumer choices, whereas improvement in environments receives the lowest utility. This means that, according to this study, consumers trade off GM applications with significant benefits, included price discount. In other words, they have an interest in GM products as long as they bring them different benefits and they are substantially cheaper. The amount of monetary compensation is also dependent on GM application (Novoselova *et al.*, 2005).

Price discount is the most quoted personal benefit for accepting GM salmon (Kuznesof and Ritson, 1996, Grunert *et al.*, 2001, Bennet *et al.*, 2005). Other benefits associated with GM salmon consumption are health benefits, resulted from higher omega-3 intake (Lutter and Tucker, 2002; Qin and Brown, 2006; Smith *et al.*, 2010) and environmental benefits, from reducing the need for chemical usage (Bennet *et al.*, 2005) or using less fodder (Grunert *et al.*, 2001). Low consumer acceptance results in high price discounts required by consumers to buy GM salmon, or premium price to avoid this product (Kaneko and Chern, 2005, Chen and Chern, 2004, Chern and Rickertsen, 2004, Grimsrud *et al.*, 2002). Consumer acceptance in the U.S. is higher than in Europe, which leads to a lower price discount required than for European consumers (Chern and Rickertsen, 2004). Other important factors, like environmental sustainability, human health effects, animal health and welfare and ethical concerns may also affect consumer acceptance of GM fish.

In this context, a study conducted within the PEGASUS project analysed 71 papers containing data on public perceptions of agri-food applications of genetic modification (Frewer *et al.*, 2013). These papers were published between 1994 and 2010, reporting on data collected between 1990 and 2008, and were amenable to formal meta-analysis. The results indicate that consumer intention to use the products of GM animals was lower than for GM plants or for GM applications in general, independent of region. Among Europeans, there was less intention to purchase and a lower acceptance for the products derived from GMOs than in Asia and North America. Similarly, results show that North American and Asian consumers had more positive attitudes to GM applied to agri-food production compared to Europeans. North Americans perceived more benefits associated with GM overall when compared to Europeans and Asians. However, benefit perception increased with time in all of the regions for which analysis was possible. This effect occurred independent of whether the target of the application was focused on GM animals, plants or generic applications. North American, South American and Asian participants perceived fewer risks than Europeans. Risk percep-

tion increased with time, almost equally compared to benefit perception increase, independent of region and of target organism. In contrast, ethical and moral concerns were greater in North America and Asia compared to those in Europe.

3.2 Producers' acceptance

Like consumers, producers may also have concerns about the adoption of a new technology. Uncertainty surrounding the way the technology will perform in the future, concerns related to increased dependency on input suppliers, expectations of higher input prices, problems related to coexistence at the production stage and segregation along the supply chain, uncertainty of the results and of the likely consumer acceptance, are among the main producers' concerns cited in the literature reviewed (Melo *et al.*, 2007; Novoselova *et al.*, 2007; Areal *et al.*, 2012). It is also clear that producer acceptance will depend on the benefits expected from the GM application (reduction of feeding costs, increase yields, etc.) and on how costs and benefits are distributed across the chain. It is often argued that the costs of technology adoption occur in one stage of the chain, while the benefits are perceived in another stage (Novoselova *et al.*, 2007).

Initially, the methods for animal transgenesis, such as microinjection technology (i.e. DNA transfer via direct microinjection into a pronucleus or cytoplasm of embryo), were highly inefficient, but recent scientific advances have overcome many of these technical difficulties (Houdebine, 2009). However, it has been suggested that GM animal applications for food production are more technically difficult to develop than the pharmaceutical ones, mostly because of difficulties in selecting the appropriate target genes and because of increased welfare concerns, especially regarding growth-related transgenesis (Vàzquez-Salat and Houdebine, 2013). Moreover, the long reproductive cycles of large animals, such as cows, is considered as a major limiting factor, since projects involving such animals require significant investment over extended periods of time (Vàzquez-Salat and Houdebine, 2013). Compared to mammals, avian species are easy to raise and have short reproductive cycles and high egg production; they are therefore particularly suited to more efficient production of commercially valuable and biologically active proteins in egg white for pharmaceutical and industrial use (Li and Lu, 2010). Similarly, the high research attention placed on transgenic fish is explained by technical factors, i.e., a higher production of eggs that can be more easily manipulated (Aerni, 2004), as well as by economic reasons, since fish farming is a rapidly growing market (Menozzi *et al.*, 2012).

It has also been suggested that existing structural differences in different production chains will also have an effect in the adoption of GM animals. The strong vertical integration and the powerful role of multinational companies in sectors like pharmaceuticals may facilitate the adoption of a new application (Vàzquez-Salat and Houdebine, 2013). The commercial release of transgenic animal products into food chains may also require new boundaries, e.g., segregation and other handling measures required to guarantee coexistence (Areal *et al.*, 2012). This implies additional costs on the production chains while also creating new objects of governance requiring specific regulatory attention (Bloomfield and Doolin, 2011). The production of high-value products from transgenic livestock, e.g. lactose-free milk, could also affect the structure of agricultural industry with new niches and segmented markets (Melo *et al.*, 2007).

In the specific case of aquaculture, it has been suggested that a company that produces a new growth-enhanced salmon may not just face scepticism from consumers, but may also be shunned by the fishery industry itself. American aquaculture producers have been described as reluctant to accept GM fish, and aquaculture producers' association in Norway reassured the consumer that they will not use GM salmon in their farms (Vazquez-Salat and Houdebine, 2012). Established local fish producers might fear new competition from transgenic fish and a radical change in the market structure of the sector. If transgenic fish become widely grown because of their higher efficiency, and if special broodstock are required to produce fry for on-growing to adults, which cannot be used as broodstock, a dependency on input suppliers is created. Depending on the arrangements made for seed supply, this dependency may become more or less oppressive for fish farmers (Beardmore and Porter, 2003). In turn, retailers, who wield most market power in the food business and value consumer concerns more strongly than producers' innovative strategies, may be unwilling to buy transgenic fish and run the risk of being ostracized by their customers. Companies may also be afraid of anti-GMO campaigns by activist groups which might negatively affect the public image of the brand (Aerni, 2004).

The picture varies considerably if we consider the pharmaceutical sector. Biopharming is the production of pharmaceutical compounds in plant and animal tissue in agricultural systems and it is considered as the next major development in both farming and pharmaceutical production (Kaye-Blake *et al.*, 2007). For biomedical applications, GM animal technology not only enjoys the greatest public acceptance due to perceived personal benefits – such as obtaining cheaper drugs produced more quickly – overriding other ethical concerns (Devlin *et al.*, 2009), but also commands supreme economic incentives. For pharmaceutical firms the use of transgenic animals for producing proteins and other pharmaceutical compounds in milk and other animal tissues, promises a method for reducing production costs and increasing yields. However, due to the high costs, the production of transgenic animals such as pig, goat, sheep and cattle must bring an elevated profit in order to be an economically feasible investment. Drugs produced by animal bioreactors, although highly valuable, are often targeted to a small community of patients which makes these applications less attractive to multinational companies' investment (Vàzquez-Salat and Houdebine, 2013). Nonetheless, the production of high-value pharmaceutical substances is the principal and most promising application for animal transgenesis (Melo *et al.*, 2007). So it is not surprising that the recombinant protein ATryn® (human antithrombin-III) produced in transgenic goats' milk was approved in the EU in 2006 (Houdebine, 2009) and the Ruconest™ (Rhucin® outside the EU), a recombinant C1-inhibitor produced by a GM rabbit, in 2010 (Vàzquez-Salat and Houdebine, 2013).

3.3 Policy implications

Public policies affect the profitability of private R&D investment through mechanisms that include direct public funding of research, intellectual property rights legislation, regulatory policies, financial and tax policies, education policies and other policies covering the environment and industry (Caswell *et al.*, 2003). Several documents have been produced to provide insights into the governance of products derived from transgenic animals (Gavin, 2001; Kleter and Kok, 2010). Food safety and environmental risk

assessments are considered fundamental steps to deal with these new technology applications. Recently, a review was carried out on behalf of the European Food Safety Authority (EFSA) to define environmental risk assessment criteria for GM fish to be marketed in the EU (Cowx *et al.*, 2010). It has also been argued that, as decisions made by one country may affect the others, different approaches towards decision-making should be harmonized as much as possible (Le Curieux-Belfond *et al.*, 2009).

Intellectual property rights (i.e. patents, trademarks and copyrights) influence a firm's incentive to invest in R&D by enhancing a firm's ability to capture rent and profits resulted from the innovation (Caswell *et al.*, 2003). In the case of biotechnology and transgenic animal in particular, this is a very difficult issue. The transgenic animals' patent debate is not confined to technical and legal arguments and has extended over ethical and political issues, including public opinion. Many products of nature (like specific antibiotics, microorganisms, protein etc.) have been successfully patented protecting the innovators right to reproduce. But it is debatable whether a naturally occurring substance can be patentable, as it lacks novelty and inventive steps. However, if a product of nature is enriched, purified or modified in an industrially useful format, it is then patentable. Biological materials which previously existed in nature are patentable provided they are purified from their natural environment and confirm to the general patentability principles regarding novelty, non-obviousness, utility and sufficiency of disclosure (Daneshyar *et al.*, 2006).

The future of private industry funding for biotechnology R&D will be influenced by the regulations in force. For instance, multinational companies in the pharmaceutical industry were believed to be unwilling to invest in GM applications until they are accepted by regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (Vàzquez-Salat and Houdebine, 2013). In particular, environmental and food safety regulations are expected to affect the profitability of R&D by i) increasing the costs of developing new technology by: extending the time necessary to bring a product to market and ii) increasing the cost of meeting stricter standards (Caswell *et al.*, 2003). Regulatory policy and industry practices associated with transgenic livestock must be transparent and effectively communicated to achieve consumer acceptance (Kochhar and Evans, 2007). Strict control of an animal or a herd starts at the level of identification. Reliable and permanent identification is already available in the livestock industry in many forms, such as ear tags, ear tattoos, external electronic transponders, subcutaneous electronic transponders, etc. (Gavin, 2001). Segregation measures along the supply chain to guarantee coexistence of GM and non-GM animals and derived products may impact producers' willingness to adopt the technology (Areal *et al.*, 2012). Therefore, the impact of heavy regulatory procedures may be stronger in the breeding sector, where the abilities of small and medium enterprises to efficiently comply with it can be limited, than in the pharmaceutical sector, where the market is highly harmonised and shaped to absorb the administrative regulatory burden (Vàzquez-Salat and Houdebine, 2013).

Labelling and information policies could be a solution in helping consumers to make a deliberate choice and in helping producers to differentiate their products. Assuming that GM animals and derived products will be properly labelled in the EU once approved and commercially available, it is unclear whether the food obtained from GM animals will have to be labelled on other markets. The U.S. FDA is now debating whether GM salmon should be labelled (U.S. Food and Drug Administration, 2010), mostly for environmen-

tal and allergenicity reasons, although this would lead to a different solution compared to food from GM crops. Labelling regulations will lead to extra costs, including the costs of traceability (Novoselova *et al.*, 2007). Monetary costs associated with tracing and labelling biotech-derived animals and their products have to be taken into account, especially in countries like U.S. where such regulations are not in force for GM crops. Other costs that might be necessary to meet the regulatory requirements (e.g., segregation with physical containment for GM fish) will also have to be considered. The costs of complying with regulations will likely reduce the private profitability of the technology, but the public will benefit from reduced risk. Thus, the balance between the costs and benefits of the regulation will determine the social cost-effectiveness of the regulation (Caswell *et al.*, 2003).

Finally, it has been argued that GM animals will likely face similar regulatory challenges in the U.S. and EU for their strict regulations in both pharmaceutical and food sectors. However, it is not clear yet if these regulations will also be applied in other countries where investment is high (e.g., Argentina and China), or if a more favourable regulatory framework will offer a competitive advantage (Vàzquez-Salat and Houdebine, 2013). In this context, China, where regulatory requirements for the approval of GM animals and derived products are already in place, is expected to take the lead thanks to a favourable policy environment and steady investments in this field.

4. Life science factors affecting the adoption of GM animals

As explained above, the PEGASUS project also explored the factors of GM animals producing food, feed or pharmaceuticals which have an advantageous or disadvantageous impact from a life science perspective. The outcomes were summarized in a project report (Kostov *et al.*, 2011). From a general, overall review of the literature and risk assessment guidance documents [including the Codex alimentarius and scientific panels of the European Food Safety Authority (EFSA)], different categories of factors were identified. These were human health, animal health and welfare, the environment, sustainability and agro-biodiversity.

Human health considerations include the potential effects on consumers of GM animal-derived foods as well as humans, such as farmers, coming into contact with the animals. For the safety of foods produced from GM animals, internationally harmonized guidelines have been published by the FAO/WHO Codex alimentarius (Codex alimentarius, 2009). This is an international organization representing nations of the world which sets internationally recognized standards and codes of conduct for food quality and safety. The scientific panels of EFSA on genetically modified organisms and on animal health and welfare recently published guidance on the assessment of food and feed safety as well as animal health and welfare, which expands upon the Codex alimentarius' (EFSA, 2012). A central role in the approach recommended by Codex alimentarius and the EFSA GMO Panel is the comparative assessment of GM products with conventional non-GM counterparts with a history of safe use, in addition to the molecular characterization of the introduced genetic material. The focus of the additional tests is on the differences identified by this comparative analysis. Commonly considered items include the occurrence of unintended effects alongside targeted modification, potential toxicity and allergenicity (of the introduced or altered components), nutritional value, and horizontal gene transfer.

Additional considerations include, for example, the potential transfer of zoonotic pathogens from the animal (acting as a reservoir) to humans and the safety of the vectors used for the transformation of the GM animal (e.g. viruses) (Codex alimentarius, 2009; EFSA, 2012). Among the advantages identified are the ability to produce enhanced quantities of food (food security) or food with increased quality characteristics, as well as new or ameliorated pharmaceuticals for the cure of patients. As a disadvantage, potential human health impacts linked to the use of this technology have to be assessed before the product can be marketed (Kostov *et al.*, 2011).

The impact on the health and welfare of the GM animals themselves are also a focus of attention. This includes the health of founder animals, selected further for desirable traits and absence of other adverse symptoms and used for commercial production as well as the first generations after genetic modification. The approach is comparative in this case too, and compares the impact of the genetic modification of the GM animal versus the health and welfare of non-GM animals. Moreover, health and other phenotypic characteristics of the GM animal compared to a non-GM animal may also serve as an important indicator for potential adverse effects on both consumers and people coming into contact with the animal. Welfare includes the ability of the animal to express its normal behaviour, among other things, and is linked to animal health. An advantage of the use of GM technology in animals is the ability to enhance resistance against parasites and diseases, while the disadvantages include possible suffering of the animals during the genetic modification process (including that of surrogate dams) as well as potentially adverse effects on the offspring (Kostov *et al.*, 2011).

The potential environmental impact of GM animals straddles a wide range of issues, of which two important ones are 1) the possible effects on wild populations, such as introgression or replacement (once the GM animal is released into the environment) and 2) the impact on the eco-system as a whole. These effects can be caused by either or both of two factors; the behaviour of the GM animal itself once released into the environment (e.g. after escape) and the production systems used for raising the GM animal as compared to conventional systems. The possible advantages identified include the decreased environmental burden of more efficient production systems as well as diminished requirements for space and inputs (e.g. for rapidly growing farmed fish). The possible disadvantages identified include possible disruption of ecosystems and loss of biodiversity of wild populations (Kostov *et al.*, 2011).

With regard to the issues of sustainability, this relates to the ecological footprint of the production system for raising the GM animal (and whether this has changed as compared to conventional production). Agro-biodiversity relates to the animal breeds that are available to breeders for creating new breeds with desirable characteristics. A possible advantage of GM animals in this respect is that this technology widens the genetic resources available to the breeders for improvement of animal characteristics (such as disease resistance). On the other hand, there may be a loss of agro-biodiversity of commercially used breeds (e.g., if less competitive than GM animals) as well as issues related to the privatization of genetic resources (e.g., patenting) (Kostov *et al.*, 2011).

The advantages and disadvantages from life science perspectives have been further explored in depth in three case studies, growth-enhanced salmon, dairy cattle producing human lactoferrin through their milk, and rabbits producing humanized polyclonal

antibodies. These case studies include aspects of terrestrial and aquatic animals, as well as food and pharmaceutical applications (Kostov *et al.*, 2011).

Growth-enhanced GM salmon, which is to be used in aquaculture, does not grow bigger than conventional cultured salmon but reaches its marketable size within a shorter time span. The possible advantages identified include nutritional benefits for consumers if fish becomes more affordable and hence is consumed in greater amounts by certain segments of the population (leading to increased uptake of omega-3 fatty acids). Another envisaged advantage is decreased environmental burden caused by aquaculture systems employing GM fish owing to less feed inputs required and less waste for the same outputs. Possible disadvantages are animal health issues, such as skeletal deformations observed in some studies on experimental GM fishes and enhanced stress under oxygen-deprived conditions caused by increased need for oxygen. An environmental issue, and a possible disadvantage, which has received a lot of attention surrounding the potential market introduction of growth-enhanced salmon, is the effect of escape of such fish into the wild on natural salmon populations. Because of this, one company seeking market approval in the USA has proposed to grow this salmon in tanks in land-locked facilities instead of the conventional aquaculture practice employing pens in open waters (Kostov *et al.*, 2011).

With regard to the recombinant human lactoferrin protein (naturally occurring in human mother's milk) produced through the milk of GM dairy cattle, it is noted that this product may have different purposes. For example, lactoferrin's antibacterial properties may strengthen the animal's defence against certain bacterial infections, such as mastitis. Because of its antibacterial properties, it may also find applications in human medicine, after purification from the bovine milk. Moreover, because of its iron-binding capacities, the bovine form of lactoferrin has been used as an ingredient for baby and infant foods. The human version of this protein could help consumers to avoid allergic reactions. Depending on the application chosen, the products could thus fall under different categories, each covered by a different legislation (besides GMO regulations), such as dietary supplements, human or veterinary medicine, or foods for medicinal or particular nutritional uses. A possible advantage of the GM dairy cattle producing recombinant human lactoferrin is the improved health of humans and animals, while possible disadvantages include animal health and welfare effects on the first generation of offspring and their dams (so-called "large offspring syndrome", which may occur at high frequencies as a result of cloning techniques for creating the GM animals) (Kostov *et al.*, 2011).

With regard to the production of humanized polyclonal antibodies in rabbits, this aims at the application of antibodies for "passive immunization" of human subjects against the antigens, such as pathogens, with which the rabbits have been challenged so as to trigger the production of antibodies neutralizing the antigen. These antibodies contain a range of molecules with slightly different structures that recognize distinct parts on the antigen, to which they bind, forming an antibody-antigen complex that can be further neutralized by specialized cells of the host's immune system. Replacing the rabbit's own polyclonal antibodies with a humanized version helps to prevent possible reactions against rabbit-derived proteins when antibodies purified from serum of immunized GM rabbits are used in human subjects. A wide range of antigens can be used to challenge the GM rabbits so as to trigger the production of antibodies recognizing these antigens. This provides a flexible production platform that can be employed against a great variety of dis-

eases to be treated with passive immunization, and is also envisaged as a possible advantage for human health. A possible disadvantage is the environmental consequences of a hypothetical escape of these animals into the wild. It is considered that GM animals used for production of pharmaceuticals will have to be kept in highly contained facilities under disease-free conditions, so that the animals would be unlikely to be able to cope with natural conditions in the hypothetical event of escape (Kostov *et al.*, 2011).

The case studies above show that a number of generalizations are possible on potential issues relating to food and feed safety, animal health and welfare, environmental safety, sustainability and agro-biodiversity. But at the same time each specific case also raised case-specific concerns and envisaged benefits from the life-science perspective.

5. Conclusions

The production of transgenic animals, which could potentially have a big impact on the livestock and pharmaceutical chains, has proceeded much slower than genetic modification of crops. Improvements in animal biotechnology are expected to result in economic benefits for farmers, processors and consumers. Beside the direct economic effects, other externalities, both positive and negative, should be considered in the overall evaluation.

The interest in GM development in aquaculture is stronger than for terrestrial animals. There are several reasons for this; faster growth rates in fish and improved feed conversion rates that may result in a cost reduction, and thus lower market prices, which also explain why the economic impact of the introduction of GM fish could be significant. The case of growth-enhanced GM fish shows that benefits for producers, arising from increased growth rates and food conversion rates, may lead to a reduction in costs and, without a full transmission of these advantages to consumers, to an increase in gross margin. At the same time, environmental and human health risks should be considered in depth in the overall evaluation of the transgenic fish introduction. In fact, serious ecological concerns associated with GM fish farming may make necessary physical containment strategies, which may potentially limit the economic attractiveness of GM fish.

Biopharming is a new territory for the agricultural and pharmaceutical industries, and presents novel challenges for government regulators and others. Due to the high cost, the production of transgenic animals such as pig, goat, sheep and cattle must bring an elevated profit in order to be a feasible economic investment. For this reason, the production of high-value pharmaceutical substances, which correspond to a market worth billions of dollars, is currently the principal and most promising application for animal transgenesis. However, the financial commitment required during the protracted development phase has halted many attempts at commercial exploitation and, at present, only two drugs produced in this way have reached the market.

Given the rapid development of these technologies and the intense GM debate of the 1990s, some governments are beginning to produce a regulatory response to the marketing of GM animals. Experts argue that the distinction between the U.S. and EU approaches, which in the past accompanied the development of GM crops, might be less marked in the case of GM animals (Vàzquez-Salat *et al.*, 2012). Both players are going to face stakeholders' adversity, e.g. from animal welfare organizations, and a lower positive pressure from multinational companies. The regulatory strategy adopted by these global play-

ers will affect their ability to exploit the commercial potential of biotechnologies as well as international trade. In this context international bodies, such as FAO, World Health Organization (WHO) and World Organization for Animal Health (OIE), will have an important role in providing forums for neutral discussion and encouraging harmonization in the food sector (Vàzquez-Salat *et al.*, 2012).

A review of these issues in general and for the three case studies in particular (growth-enhanced salmon, dairy cattle producing recombinant human lactoferrin, rabbits producing humanized polyclonal antibodies) shows that at present it is not possible to make generalizations on the possible advantages and disadvantages of GM animals from a life science perspective. So should one of these be introduced for possible marketing in Europe, a case-by-case approach will need to be followed for the assessment of these issues.

Acknowledgments

An earlier version of this paper was presented at the 1st AIEAA Conference 'Towards a Sustainable Bio-economy: Economic Issues and Policy Challenges'. 4-5 June, 2012, Trento, Italy. This research has been supported by the PEGASUS (Public Perception of Genetically modified Animals – Science, Utility and Society) project which is funded by the European Commission through the Seventh Framework Programme (grant agreement n. 226465). The following people contributed to the research described in this paper: P. Rüdelsheim, G. Smets (PERSEUS, Belgium); G. Dimov, T. Dzhambazova, K. Kostov (AgroBioInstitute, Bulgaria); L.M. Houdebine (INRA, France); A. Merigo, S. Pancini, G. Sogari (University of Parma, Italy); J. Bartels, M.J. Reinders, I. van den Berg, X. Zhang (LEI, the Netherlands); J. van Dijk, M. Groot, M. Noordam (RIKILT, the Netherlands); I.A. van der Lans, A.R.H. Fischer (Wageningen University, the Netherlands); S. Bremer, M. Kaiser (University of Bergen, Norway); G. Rowe (Institute of Food Research, U.K.); B. Salter, N. Vàzquez Salat (King's College of London, U.K.); M. Brennan, L.J. Frewer, M. Raley (University of Newcastle, U.K.); K. Millar (University of Nottingham, U.K.). In particular, we gratefully acknowledge leadership and coordination of Prof. Lynn Frewer. The information contained in this paper reflects only the authors' opinions and the sole responsibility lies with the authors. The European Commission is not liable for any use of the information contained therein.

References

Aerni, P. (2004). Risk, regulation and innovation: The case of aquaculture and transgenic fish. *Aquatic Sciences* 66: 327-341.

Areal, F.J., Riesgo, L., Gómez-Barbero, M. and Rodríguez-Cerezo, E. (2012). Consequences of a coexistence policy on the adoption of GMHT crops in the European Union. *Food Policy* 37: 401-411.

Arksey, H. and O'Malley, L. (2005). Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 8: 19-32.

Beardmore, J.A. and Porter, J.S. (2003). Genetically modified organisms and aquaculture. Rome, Italy: FAO Fisheries Circular No. 989.

Bennett, B., D'Souza, G., Borisova, T. and Amarasinghe, A. (2005). Willingness to consume genetically modified foods – the case of fish and seafood. *Aquaculture Economics & Management* 9: 331-345.

Bloomfield, B.P. and Doolin, B. (2011). Imagination and technoscientific innovations: Governance of transgenic cows in New Zealand. *Social Studies of Science* 41(1): 59-83.

Caswell, M.F., Fuglie, K.O. and Klotz, C.A. (2003). Agricultural biotechnology: an economic perspective. New York: Novinka book.

Chen, H-Y. and Chern, W.S. (2004). Willingness to pay for GM foods: results from a public survey in the USA. In: Evenson, R.E. and Santaniello, V. (eds.), Consumer acceptance of Genetically Modified Foods, London: CABI Publishing, 117-129.

Chern, W.S. and Rickertsen, K. (2004). A comparative analysis of consumer acceptance of GM food in Norway and the USA. In: Evenson, R.E. and Santaniello V. (eds.), Consumer acceptance of Genetically Modified Foods, London: CABI Publishing, 95-109.

Codex alimentarius (2009). Foods derived from modern biotechnology (2nd edition). Rome: Codex alimentarius Commission, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization. ftp://ftp.fao.org/codex/Publications/Booklets/Biotech/Biotech_2009e.pdf

Cowx, I.G., Bolland, J.D., Nunn, A.D., Kerins, G., Stein, J., Blackburn, J., *et al.* (2010). Defining environmental risk assessment criteria for genetically modified fishes to be placed on the EU market. Scientific/Technical Report submitted to EFSA, Parma: EFSA.

Daneshyar, S.A., Kohli, K. and Khar, R.K. (2006). Biotechnology and intellectual property. *Scientific Research and Essay* 1: 20-25.

Devlin, R.H., Raven, P.A., Sundstrom, L.F. and Uh, M. (2009). Issues and methodology for development of transgenic fish for aquaculture with a focus on growth enhancement. In: Overturf, K. (ed), Molecular research in aquaculture, Ames (Iowa): Wiley-Blackwell publishing, 217-260.

EFSA (2012). Guidance on the risk assessment of food and feed from genetically modified animals and on animal health and welfare aspects. *EFSA Journal* 10: 2501 [43 pp.] http://www.efsa.europa.eu/en/efsajournal/doc/2501.pdf

Frewer, L.J., Bergmann, K., Brennan, M., Lion, R. Meertens, R., Rowe, G., Siegrist, G. and Vereijken, C. (2011). Consumer response to novel agri-food technologies: Implications for predicting consumer acceptance of emerging food technologies. *Trends in Food Science and Technology* 22: 442-456.

Frewer, L.J., van der Lans, I.A., Fischer, A.R.H., Reinders, M.J., Menozzi, D., Zhang, X., van den Berg, I. and Zimmermann, K.L. (2013). Public Perceptions of Agri-food Applications of Genetic Modification – A Systematic Review and Meta-Analysis. *Trends in Food Science and Technology*.

Gaskell, G., Allum, N., Bauer, M., Durant, J., Allansdottir, A., Bonfadelli, H. *et al.* (2000). Biotechnology and the European Public. *Nature Biotechnology* 18: 935-938.

Gavin, W.G. (2001). The future of transgenics. *Regulatory Affairs Focus* May 2001: 13-18.

Greger, M. (2011). Transgenesis in animal agriculture: addressing animal health and welfare concern. *Journal of Agricultural and Environmental Ethics* 24: 451-472.

Grimsrud, K.M., McCluskey, J.J., Loureiro, M.L. and Wahl, T.I. (2002). Consumer attitudes toward genetically modified food in Norway. American Agricultural Economics Association Annual Meeting, July 28–31, Long Beach, California.

Grunert, K.G., Lahteenmaki, L., Nielsen, N.A., Poulsen, J.B., Ueland, O. and Astrom, A. (2001). Consumer perceptions of food products involving genetic modification – results from a qualitative study in four Nordic countries. *Food Quality and Preference* 12: 527-542.

Houdebine, L.M. (2009). Production of pharmaceutical proteins by transgenic animals. *Comparative Immunology Microbiology and Infectious Diseases* 32: 107-121.

Kaneko, N. and Chern, W. (2005). Willingness to Pay for Genetically Modified Oil, Cornflakes, and Salmon: Evidence from a U.S. Telephone Survey. *Journal of Agricultural and Applied Economics* 37: 701-719.

Kaye-Blake, W., Saunders, C. and Ferguson, L. (2007). Preliminary Economic Evaluation of Biopharming in New Zealand. Agribusiness and Economics Research Unit Report 296, Lincoln (New Zealand): Lincoln University.

Kleter, G.A. and Kok, E.J. (2010). Safety assessment of biotechnology used in animal production, including genetically modified (GM) feed and GM animals – a review. *Animal Science Papers and Reports* 28: 105-114.

Knight, A.J. (2006). Does Application Matter? An Examination of Public Perception of Agricultural Biotechnology Applications. *AgBioForum* 9: 121-128.

Kochhar, H.P.S. and Evans, B.R. (2007). Current status of regulating biotechnology-derived animals in Canada-animal health and food safety considerations. *Theriogenology* 67: 188-197.

Kostov, K., Dzhambazova, T., Dimov, G., van Dijk, J., Groot, M., Kleter, G., Noordam, M. Smets, G. and Pakki Reddy, G. (2011). Report on scenario development of GM animals and food, WP4 – "Life Science Dimension", Deliverable 4.1, PEGASUS project. http://www.pegasus.wur.nl

Kuznesof, S. and Ritson, C. (1996). Consumer acceptability of genetically modified foods with special reference to farmed salmon. *British Food Journal* 98: 39–47.

Laible, G. (2009). Enhancing livestock through genetic engineering – Recent advances and future prospects. *Comparative Immunology Microbiology and Infectious Diseases* 32: 123-137.

Le Curieux-Belfond, O., Vandelac, L., Caron, J. and Séralini, G.-É. (2009). Factors to consider before production and commercialization of aquatic genetically modified organisms: the case of transgenic salmon. *Environmental Science & Policy* 12: 170-189.

Li, J-J. and Lu, L-Z. (2010). Recent progress on technologies and applications of transgenic poultry. *African Journal of Biotechnology* 9(24): 3481-3488.

Logar, N. and Pollock, L.K. (2005). Transgenic fish: is a new policy framework necessary for a new technology? *Environmental Science & Policy* 8: 17-27.

Lutter, R. and Tucker, K. (2002). Unacknowledged Health Benefits of Genetically Modified Food: Salmon and Heart Disease Deaths. *AgBioForum* 5: 59-34.

Melo, E.O., Canavessi, A.M.O., Franco, M.M. and Rumpf, R. (2007). Animal transgenesis: state of the art and applications. *Journal of Applied Genetics* 48: 47-61.

Menozzi, D., Mora, C. and Merigo, A. (2012). Genetically modified salmon for dinner? Transgenic salmon marketing scenarios. *AgBioForum* (3): 276-293.

Mora, C., Menozzi, D., Aramyan, L., Valeeva, N., Pakki Reddy, G. and Merigo, A. (2011). Report on Production chain context. Deliverable 3.1, PEGASUS project. http://www.pegasus.wur.nl.

Murray, J. Mohamad-Fauzi, N., Cooper, C.A. and Maga, E.A. (2010). Current status of transgenic animal research for human health applications. *Acta Scientiae Veterinariae* 38(Suppl 2): s627-s632.

Novoselova, T., van der Lans, I.A., Meuwissen, M.P.M. and Huirne, R.B.M. (2005). Consumer acceptance of GM applications in the pork production chain: a choice modelling approach. EAAE Congress, August 23-27, 2005, Copenhagen, Denmark.

Novoselova, T.A., Meuwissen, M.P.M. and Huirne, R.B.M. (2007). Adoption of GM technology in livestock production chains: an integrating framework. *Trends in Food Science & Technology* 18: 175-188.

Qin, W. and Brown, J.L. (2006). Consumer opinions about genetically engineered salmon and information effect on opinions. A qualitative approach. *Science Communication* 28: 243-272.

Smith, M.D., Asche, F., Guttormsen, A.G. and Wiener, J.B. (2010). Genetically modified salmon and full impact assessment. *Science* 330: 1052-1053.

U.S. Food and Drug Administration (2010). Public hearing on the labeling of food made from the AquAdvantage Salmon. Background Document, August 2010.

Vàzquez-Salat, N. and Houdebine, L-M. (2013). Will GM animals follow the GM plant fate? *Transgenic Research* 22(1): 5-13.

Vàzquez-Salat, N., Salter, B., Smets, G. and Houdebine, L-M. (2012). The current state of GMO governance: Are we ready for GM animals? *Biotechnology Advances* 30(6): 1336-1343.