Genetically Modified Animals from Life-Science, Socio-Economic and Ethical Perspectives: Examining issues in an EU policy context

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Running head

Genetically Modified Animals - Evidence for EU Policy

Abstract

The interdisciplinary EC consortium (the PEGASUS project) aimed to examine the issues raised by the development, implementation, and commercialisation of genetically modified (GM) animals, and derivative foods and pharmaceutical products. The results integrated existing social, (including existing public perception) environmental and economic knowledge regarding GM animals in order to formulate policy recommendations relevant to new developments and applications. The use of GM in farmed animals (aquatic, terrestrial, and pharmaceutical) was mapped and reviewed. A foresight exercise was conducted to identity future developments. Three case studies (aquatic, terrestrial, and pharmaceutical) were applied to identify the issues raised, including the potential risks and benefits of GM animals from the perspectives of the production chain (economics and agri-food sector) and the life sciences (human and animal health, environmental impact, animal welfare, and sustainable production). Ethical and policy concerns were examined through application of combined ethical matrix method and policy workshops. The case studies were also used to demonstrate the utility of public engagement in the policy process. The results suggest that public perceptions, ethical issues, the competitiveness of EU animal production, and risk-benefit assessments that consider human and animal health, environmental impact, and sustainable production need to be considered in EU policy development. Few issues were raised with application in the pharmaceutical sector, assuming ethical and economic issues were addressed in policy, but the introduction of agricultural GM animal applications should be considered on a case-by-case basis.

Key words

Genetically modified animals, Pharmaceutical, Food, Societal acceptance, Economic impact, Risk-benefit assessment.

Highlights

- Public perceptions of GM animals are generally more negative than towards GM plants.
- GM animals are perceived more negatively if used for food rather than for pharmaceuticals.
- A case-by-case assessment of the risks and benefits of GM animals is warranted.
- EU governance systems are reasonably well-prepared.
- Clarity is needed on how different publics are engaged in GM animal technology.
- Public and stakeholder engagement exercises can be useful tools for informing policy development.

1. Introduction

Food products derived from genetically modified (GM) animals have not yet entered the European market. None-the-less, the on-going discussion about GM crops [1], and the developing debate about the safety and ethics of foods and pharmaceutical products produced by both GM animals and plants, have provoked varying views across different sectors of society (*e.g.*, see [2]; [3]; [4]). At the time of writing, while no GM animals have been approved for food use in Europe or the US (see also [5]), this is not the case for pharmaceuticals derived from GM animals ([6]; [7]; [8]). Medical application is more widespread internationally, with research focusing on applications of GM animals in the study of gene function and human diseases [6], or as a source of therapeutic human antibodies [9].

The use of GM animals in agriculture may potentially present greater challenges than process and products, the relative value of the product is less within the agricultural sector, and animal welfare concerns related to farmed animals may arise. In addition, production of GM animals for agricultural purposes is a less efficient process than is the case for medical applications (*e.g.*, [10]; [11]; [12]; [13). These potential barriers to commercialisation have frustrated many scientists keen to bring applications to the commercialisation stage ([14]; [15]). Independent of whether a specific application of GM animal is licenced for use in a particular region or country, regulators may also need to consider the possibility that agri-food applications of GM animals may enter the food supply chain through imports from overseas [16]. For example, the EU is the world's largest international trading block for food commodities [17]. Importing goods from countries and regions which operate different regulatory approaches to commercialisation of GM animals [8] may result in accidental or fraudulent inclusion of GM animals in the European food supply chain. Progress in reducing or eliminating potential inconsistencies across jurisdictions, and harmonising international regulations, is slow. Despite this, commercialisation of the products of GM animals, whether applied to agriculture or pharmaceutical production, is fast becoming a reality. Appropriate evidence-based governance frameworks, which take account of all relevant factors, are required, and these need to be contextualised by understanding of societal responses to emerging technologies such as GM animals used in agricultural and pharmaceutical production. This information is needed to optimize and regulate strategic development of, and communication about, GM animals, as well as to develop and refine commercialisation strategies associated with specific GM products (see, *inter alia*, [18]; [19]). The issue of whether alternative technological approaches can be applied to reach the same goals also needs to be considered [19].

An overview of the current European regulatory framework for GM animals is provided by [8]. In summary, guidance for specific risk assessments for food/feed applications and the environment is provided by the European Food Safety Authority (EFSA), whereas those for pharmaceutical applications fall within the remit of the European Medicines Agency (EMA). In addition, DG SANCO has a central role in governance, in particular with respect to risk management, with the addition of animal specific legislation in the framework of the Community Animal Health Policy (CAHP) including animal welfare legislation. Partly in response to societal negativity towards GM technology within Europe, the European Commission has adopted a more precautionary approach to introductions in agriculture [20],

including mandatory labelling of GM food products [21]; [22]. This has, in turn, resulted in implications for international trade [23]; [24].

The objective of the Pegasus project was to provide support for European policy regarding the development, potential implementation, and commercialisation of GM animals, both terrestrial and aquatic. The research drew on the results of research originating within both the life- and socio-economic sciences, which assessed the potential risks and benefits of the development and application of GM animal technology. In addition, ethical analyses were applied to ensure that such evidence is provided for policy development. The research synthesised this evidence into concrete and actionable suggestions for policy outcomes relevant to Europe, as well as considering policies relevant to the EU's major trading partners. To the authors' knowledge, this is the first time interdisciplinary evidence relevant to European policy development has been collated in the area of the use of genetically modified animals for food and pharmaceutical developments. The issues raised by the development and use of GM animals will now be considered from both life science and socio-economic perspectives. Ethical issues and policy dimensions will also be considered. Future policy implications will be identified from the synthesis of these different perspectives.

Background

The definition of “genetic modification” (“GM”) aligns with that provided by Directive 2001/18/EC [25]. This definition includes techniques for introduction of recombinant DNA, transfer of heritable material through various artificial ways, and fusion of cells of different organisms that cannot be crossed in nature. In addition, there are various techniques for cloning animals, including embryo splitting, and the transfer of a nucleus from a donor cell into an enucleated oocyte. These techniques are not usually included in the same category as genetically modified organisms (GMOs) by European regulators. This is not necessarily the case in other regulatory frameworks (*e.g.*, the cloning of organisms new to New Zealand from imported cell materials [26]).

The potential risks and benefits of GM animals, whether applied to food production or to other areas of application, such as pharmaceutical “farming”, have been recognised by governments, industry and non-governmental organizations (NGOs) as an important determinant of their potential future development (*e.g.*, [27]; [28]; [29]; [30]; [31]). Substantial resources have been invested in national and regional initiatives relating to research and safety assessment of GM animals with the aim of managing human and animal health risk, and environmental impacts ([32]; [5]; [33]; [34]). Resources have also been dedicated to the analyses of activities which focus on the ethical dimensions of using GM animals in the food production ([35]; [12]) and pharmaceutical [6] sectors. As in any novel area of science, progress in the field of GM animals - from basic research, through the experimentation and testing phases, to the positioning of the final application in the marketplace and the development of the associated commercialisation strategy - is dependent on both the *safety* and the *cultural acceptability of the processes and the products* concerned [36].

An extensive literature regarding public perceptions and other socio-economic aspects of GM animals applied to food production and other areas of application is available. Similarly, there are many scientific publications relating to technological advances and potential economic impacts. This information cannot be translated into concrete policy support unless different disciplinary perspectives can be integrated into a coherent evidence base from which policy can be developed. The Pegasus projects adopts multidisciplinary approach, drawing on expertise from both the social and life sciences, to integrate scientific information into evidence for policy development, which can then be translated into policy options. Ethical dimensions and insights into the evolving international policy landscape must be taken into account in this process.

The potential risks and benefits of GM animals from a life-science perspective

Realistic scenarios representing technological applications of GM that may enter the market in the future were developed through a combination of literature review, data mining activities, and expert consultation with industry and academic specialists. Data sources included the scientific literature, and data from patents, and experimental permits [37]. The results suggested that the techniques available to generate GM animals have improved considerably, and so development costs are no longer represent a major barrier to the development of transgenic animals. In particular, the cost of genetically modifying larger animals is no longer prohibitive, as was the case in the past. For example, models for the study of human diseases can now utilise GM pigs as well as GM mice, allowing for more sophisticated analysis ([12]; [37]; [38]). GM animals have also been used to develop organs for xenotransplantation to humans, although these are not yet licensed for use [39].

Advances in research into GM farm animals have resulted in foods derived from these animals having enhanced quality or production yields [12], or improved nutritional value (*e.g.*, [40]; [41]). A major problem in conventional breeding remains that of animal diseases, which results in animal losses, animal welfare problems and threats to human health. Chickens which do not pass on influenza virus to other chickens [42], and (potentially) pigs resistant to Aujeszky disease ([43]; [44]) provide good examples of breeding improvements resulting from animal GM. Foods may be changed to meet the needs of individuals with specific dietary requirements, such as the modification of milk fat composition to enhance fatty acid content [45]. Developments are frequently intended to improve food security or human health, although the benefits and long-term impacts on agricultural sustainability are difficult to predict [46]. The most technologically advanced projects are related to the expression of bioactive compounds such as human lactoferrin in bovine milk ([47]; [48]), and the production of meat enhanced with omega-3 fatty acids through the expression of roundworm desaturase gene in transgenic pigs [49]. The most direct application of GM animals, which may bring benefits to public health, is the production of therapeutic recombinant proteins ([6]; [9]). For example, GM animals have been used for production of specific proteins for treatment of various health problems such as blood disorders (thrombosis and haemophilia), hereditary angioedema, osteoporosis, and emphysema [50].

The production of pharmaceuticals from GM animals is relatively efficient, but rarely applied in a commercial context by pharmaceutical companies. This, in part, may be a consequence of industry concerns about the societal acceptance of GM animals. However, there may be other commercial reasons underlying this observation. Pharmaceutical companies can potentially be in competition to produce pharmaceutical proteins. For this reason, individual companies may be disincentivised regarding the promotion of the production of pharmaceutical proteins by GM animals, which may broaden competitors' access to the same compounds. Despite this, there is greater investment in the use of GM animals in the medical and pharmaceutical sectors compared to the food sectors, with three major countries leading developments (China, Argentina and the USA) [15]. In comparison, the EU is less advanced scientifically [8]. The technical potential and scientific resources for the production of GM animals in the EU is high, but the number of supported projects remains very low compared to those on other regions of the world.

Some animal welfare issues associated with GM animals have been identified, which may militate against development of GM animal technology. These include reproduction problems originating from *in vitro* procedures such as large offspring syndrome, (although it should be noted that uncertainties in the risk assessment arise from the limited number of studies available, the small sample sizes investigated and the absence of a uniform approach to allow all the relevant issues to be addressed [51]), and requirements for special feeding and restricted rearing conditions [52]. Some welfare issues are particularly problematic, e.g. those related to animal welfare requirements such as free rearing, mating and access to feed [53]. Agrobiodiversity may be potentially reduced as breeding will involve fewer species and breeds. A further concern relates to the possible privatisation of genetic resources due to the application of intellectual property rights. Improved food security through increased production efficiency may be facilitated by the development of GM animals, assuming this is not compromised, by, for example, reduced availability of genetic resources.

A further issue relates to environmental impact (*e.g.*, unintended environmental release of animals) which may be less controllable for high profligacy species such as fish [51]. In the areas of both pharmaceutical and food production, contained production facilities may be required to prevent such occurrences. In addition, the implementation of effective traceability systems is required to ensure that GM animals and their products can be identified within supply chains. The production of recombinant proteins is regulated under conventional pharmaceutical guidelines [54].

The main risk assessment concern, which can be identified when considering the use of any GM organism for food or feed production is food safety, is the potential for introduction of allergens or toxins [5]. Risk assessment should be conducted on a case-by-case basis using a comparative approach, and due consideration should be taken of differences between different types of animals and their putative area of application. Thus not all assessments would apply to all cases, at least not in the agri-food sector [55].

A broad range of relevant issues were assessed in the context of the three specific case studies, based on GM animals relatively close to commercialisation (Table 1). The cases were selected to represent aquatic *versus* terrestrial GM animals, and drawn from animals used for food *versus* pharmaceutical production.

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There are differences in the amount of data available to assess risks and benefits within cases. For example, the available data suggest that the contained farming of GM salmon poses limited environmental risks [56], whereas there are fewer data available regarding the GM rabbit case (e.g., associated with potential environmental impact following deliberate or accidental environmental release [52]). In addition, there are no data on health and welfare issues specific to the case of GM rabbits used for production of polyclonal antibodies. This is problematic given concerns related to the large numbers of animals sacrificed, the procedures such as caesarean section required in reproductive processes, and actions such as handling and restraint that can cause distress.

Public perception of GM animals and the food and pharmaceutical products derived from them.

A systematic review of the published literature on public perceptions of GM animals was conducted. This resulted in two subsequent analyses. In the first, a meta- aggregated published data[1] on public perceptions of GM animals and plants, allowing changes in perceptions and attitudes in time, and in different regions, to be identified [10]. Seventy papers yielded data of appropriate quality to be included in this meta-analysis. In summary, it was found that both risk and benefit perceptions increased with time (from the early 1990s until 2011), independent of the region in which the data were collected. Ethical concerns, and perceptions of unnaturalness, were found to influence societal and/or consumer acceptance. However, not all these dependent variables were included in all studies reviewed. As a consequence, an aggregated analysis of the impact of ethical concerns and unnaturalness on risk and benefit perceptions was not possible, although trends in time and between regions within dependent variables could be analysed. In addition, trust (both in regulatory institutions and in information about GM animals) was identified by researchers as being highly relevant to acceptance. In this case, the application of different methodological approaches applied to measuring trust made it inappropriate to integrate research results using meta-analytic approaches, to the extent that statistically significant differences between regions and trends in time could not be reliably assessed. Other important results related to comparisons between different sectors of application. Medical applications were consistently better accepted than those related to food production. Regional differences were observed, such that perceptions of risk were higher, and benefit perceptions lower, in Europe compared to North America and South-East Asia, while the converse was true of ethical concerns, which were lower in Europe. (See [10] for details of the quantitative analysis and significance tests).There were few data available from BRIC countries[2] (Brazil, Russia, India, China), nor South America and Sub-Saharan Africa.

The second analysis focused on all papers identified in the systematic review which included data on consumer perceptions of GM animals, *independent* of whether these yielded data suitable for meta-analysis [11]. Forty-two such papers were included[3]. The main findings of the papers were collated and coded according to superordinate themes. Most data were collected in North America (in particular the US) and Europe, with some data being collected in South-East Asia and Australia. Two papers reported on consumer attitudes in either China or India. As was found in the meta-analysis, attitudes were less positive towards GM applied to animals compared to plants, and for GM animals applied to food relative to other sectors. Higher perceptions of benefit tended to offset risk perceptions, in both the food and medical sectors. Attitudes towards GM fish applied in the agricultural sector (specifically salmon as no other public perception data were identified through the paper selection process used in the review) were more positive than towards other types of animal.

[1] For practical reasons, only English language peer reviewed publications were included.
[2] The authors suspect that such a literature may be available in local languages, for example in China. However these publications were not available for pragmatic reasons related to language and limitations of the data bases accessed (Scopus and Web of Science).
[3] The results of the systematic reviews conducted within Pegasus are published in [10] and [11]. The reader is referred to these documents for a full list of the papers contributing to systematic reviews.

The economic dimension of GM animals in production

The economic implications of GM animals and their applications from a production chain perspective (i.e. feed industry, breeding industry, primary sector, processing industry, and pharmaceutical industry) were considered. It should be noted that relevant economic data were difficult to obtain, given that the products of GM animals have yet to be commercialised within either the pharmaceutical or agri-food sectors. In the course of the project, one pharmaceutical product from GM goats, ATryn®, was released onto the market [57], which may provide relevant data for follow-up economic studies. An initial scoping study identified key issues from the literature [58]. Broad consensus emerged insomuch as developments in GM animals were expected to result in economic benefits for farmers, processors and consumers, in particular, but not exclusively, in the area of pharmaceutical production [59]; [60]; [61]. However, empirical data were not available to substantiate these claims. For this reason, scenario analysis was applied, which permitted assessment of the economic impacts of potential 'futures' associated with different applications of GM animals. Scenario analysis has been widely used to deal effectively with the many uncertainties that surround the future of strategic decision-making [62], including that associated with technology assessment [63].

The scenario analysis was applied across the case studies. Analogies were identified across the different case studies, even if the products considered were very different [64] (see table 1).

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The results of the analysis suggest that production costs will decrease as a consequence of the use of GM animals in both food and pharmaceutical production, which will potentially increase producers' and consumers' acceptance and subsequently increase global production. However, consumer acceptance of products, in particular food products, will act to increase production costs. Given that public acceptance of pharmaceutical products is likely to be higher than for food, economic advantage is most likely to be associated with the pharmaceutical sector. It was concluded that policy makers should explicitly consider taking socio-economic aspects associated with the introduction of GM animals into the evaluation and authorisation processes linked to new applications. In addition, care should be taken to ensure that the socio- economic benefits of GM animals are distributed equitably across countries and populations. Small to medium enterprises which do not (or are unable to) adopt GM animal technologies may need to be protected, not least in order to protect the autonomy of consumer choice.

Analysis of stakeholders' positions and ethical judgements

The ethical issues raised by the development and application of genetic modification were considered through a process of stakeholder consultation utilising dedicated workshops in order to identify values and principles underlying the stakeholder's perceptions of GM animals. Five stakeholder workshops were convened, involving policy, industry, producer, and NGO representatives. All workshops were entitled "Examining the social and ethical issues raised by genetically modified animals; Examining the key issues". The first three workshops focused on mapping stakeholder views and were held in three European countries, (Germany, N=6 stakeholders (see [65]); Norway, N=9 stakeholders (see [66]); and

the UK, N=12 stakeholders (see [67]). A fourth workshop had a less diverse stakeholder membership, involving 7 participants with an EU policy profile, and was held in Brussels (see [68]). The final workshop was held in Hyderabad, India, and provided a non-EU perspective in a country which represents an important trading partner for the EU, and where there is also controversy associated with GM animals. Seventeen stakeholders were involved the Hyderabad event. The Ethical Matrix approach was selected as an appropriate method to consult stakeholders [69]. This has been demonstrated to be a successful approach to understanding stakeholder ethical issues associated with GM animals in previous investigations (e.g. [70]; [71]). In brief, this approach is intended to support individuals when making ethical decisions, particularly regarding ethical issues associated with new technologies. Four ethical principles are normally addressed. These are *to do good* (beneficence), *to do no harm* (maleficence), the principle of *autonomy* (providing the freedom of choice) and *justice* (ensuring the equitable distribution of costs and benefits). It was not feasible to invite stakeholders to discuss all three cases in great detail within the workshops, given specific circumstances and the amount of information pertaining to each. Deliberation needed to be initially limited to one application, although broader questions were raised in the final discussion sessions. A decision was made to use the workshops to explore and map ethical issues arising from the use of GM salmon. This was pertinent because the European Food Safety Authority (EFSA) appeared to be most advanced with its policy preparations for GM fish [72], and the high-profile application to allow the commercialisation of a GM salmon was being considered by the USA's Food and Drug Administration at the time the workshops were being held [73].

Most of the issues discussed relative to GM salmon were deemed to be equally relevant to other species of GM animals [74], and were identified across the different workshops. These will now be briefly discussed. The notion of a single instance of the technology acting as a 'door-opener' to future technology development and commercialisation was identified as relevant, irrespective of species modified. Some participants suggested that each application should be 'treated individually,' with particular regard to its purpose; for example, applications intended to enhance food security may be regarded as more necessary and ethically justifiable than those applied for ornamental purposes (*e.g.*, the "Glofish"[4]). It was argued that GM fish present fundamentally different issues to terrestrial animals, because (a) they present a higher risk of escape, and are almost impossible to contain once they are in the external environment and (b) society tends to have relatively fewer animal welfare concerns for fish. However, welfare concerns were prominent across all species of animal considered. The discussions suggested that what is deemed to be acceptable is informed not only by scientific data, but also by ethical boundaries (*e.g.*, what level of potential suffering is deemed acceptable). Many workshop participants highlighted and discussed the knowledge gaps and uncertainties related to research and use of GM animals, for example in relation to animal welfare, environmental, and socio-economic implications, as well as uncertainty associated with these. Participants indicated that future interdisciplinary research is required to address these gaps in knowledge, acknowledging the relevance of the precautionary approach. Participants also felt it was important that the burden of proof associated with technology assessment in order to make a judgement on a licensing decision should lie with the relevant industry, and this should be supported by independent audit of industry information.

[4] A GM zebrafish altered to exhibit fluorescent colours.

Whilst acknowledging the need to encourage industrial innovation in food production, in line with EU policies, some participants suggested that any collective decision-making process should not be rushed according to the 'politics of urgency.' It was felt that 'Europe' has time to consider properly any decision to permit the introduction and or commercialisation of GM animals. If individual consumer autonomy is deemed to be important then the specifics of labelling requirements will be a central element of any licensing conditions, an observation in line with consumer perceptions and expectations, as well as a prerequisite for economic success. Stakeholders also suggested that it may be important to first reconsider conventional practices and alternative technological approaches to reach the same objectives, together with the wider management and use of natural resources [18]. In general, stakeholders did not appear to express intrinsic objections towards GM animals *per se*. The general focus of the discussions was on the purpose and the placement of any technology within a production system, in particular agri-food production. The primary question related to what might be the best form of technical investment, in line with the results of the economic analysis. Many stakeholders also expressed the view that consideration of socio-economic impact should be, an integral part of any technology assessment process. Finally, stakeholders suggested that more data is needed to support a number of statements about GM animals. For example, when considering the 'grand challenges' for modern society, such as the need to improve food security, a notable number of participants across all the five workshops felt that GM salmon technology would not address global food security needs because it is a niche product for more affluent consumers. Other technological options, or GM species, need to be considered in this respect.

Policy implementation and development

Methodological details of policy data-gathering are provided in [8]. In summary, the data were gathered through literature review of peer-reviewed journals and policy reports, internet searches and media stories complemented by face-to-face and phone interviews with key stakeholders. In total, 28 semi-structured interviews were conducted with participants drawn from scientific, regulatory, industry and consumer groups [15] drawn from Europe and the US. Workshops were held in collaboration with the Ethical Matrix consultations described in the previous section in order to discuss with stakeholders various policy-related issues associated with the introduction of GM animals and to identify policy gaps and policy options that need to be considered. Various policy-related issues, including regulatory needs, were discussed in order to address the aspects of the GM animal cases.

An initial scoping exercise (internet and desk-based study) was used to construct a model of the main policy parameters. This theoretical framework provided the background from which the interview schedule was developed. To further understand the politics surrounding the governance of GM animals, the range of existing policy at national, (pan-) European and USA (international) levels relevant to the regulation of the GM animal field was reviewed [8]. The key national regulatory bodies and other agencies involved in the governance of GMOs were then identified. Stakeholders within these organisations were approached and interviewed regarding the complexities of GMO governance mapped. In parallel, the international organisations that have a role in GMO governance (at the risk assessment

and/or risk management stages) were identified and key stakeholders interviewed regarding governance practices associated with GM animals.

The results suggest that, at the regulatory stage in the EU, existing governance structures are reasonably well prepared for GM animals. In the area of research and development, the regulations were perceived by stakeholders to be adequate, but the situation was quite different at the commercialisation stage. The level of risk communication with European citizens considered was insufficient, although there were disagreements on *what* to communicate and *who* should do it. The majority of the interviewees believed that the European Commission should lead any communication strategy on GM animals. The situation for the pharmaceutical sector was seen to be stable at the international level, but the future of GM animals in the agrifood sector varied regionally. The most significant change was seen in the USA, (which has historically been a strong proponent of GM plants). The cultural attitude of the American consumer towards GM animals (in particular in relation to ethical concerns) appeared to trigger a retreat from the food industry in its support for GM animals in production. At the same time, emerging economies, particularly China, are encouraging development in this sector. It is therefore likely that the international landscape for GM animals will differ significantly from that of GM plants.

In addition to interviewing policy makers, the utility of an approach to public consultation regarding policy development, the 'citizens' jury,' was assessed as a potential process to facilitate public engagement with the policy process. The consultation process utilised a 'citizens' jury' approach, with jurors being drawn from participants from various backgrounds [75]. The need to engage the public in the development of science and technology policy is recognised [76], and has included public engagement associated with GM policies [77]; [78].The vogue for public engagement has been criticised [79], in part due to frequent lack of goal orientation regarding how public engagement might *inform* policy impact, and absence of processes or mechanisms to assess the *impact* on policy development. This is despite such exercises being frequently commissioned with the stated aim of informing policy [80]. The result is that there has been a lack of evaluation of both the process and policy impact [79] of public engagement exercises.

The main goal of the citizens' juries was to demonstrate 'best practice' in public engagement in future policy regarding innovation in the area of GM animals. Two public engagement activities were conducted, in Newcastle, UK and Parma, Italy [81][5]. Fifteen jurors participated in the Newcastle event, and 16 in the Parma event. They were drawn from a wide range of socio-economic backgrounds. The juries were both held over a two day weekend. Jurors were able to 'cross-examine' the expert witnesses (drawn from researchers in the project consortium), and were requested to develop a report making specific policy recommendations regarding an innovation strategy for GM animals applied in the pharmaceutical and food production sectors. Expert witnesses presented a "lay" version of the scientific activities of the project, together with draft policy implications. In addition, and in accordance with best practice, an independent evaluation of both the process of conducting both juries, and the impact on the final policy recommendations, was conducted [79].

[5] Citizens' juries have been used in the UK and Italy previously. See, for example, (http://www.parliament.uk/documents/commons/lib/research/briefings/snpc-04546.pdf), accessed 20th January 2013 for the UK, and [82] for Italy.

Overall, the jurors approved of existing governance structures within Europe (for example, separation of medical and food-related GM animal governance to the European Medicines Agency, EMA, and European Food Safety Agency, EFSA, respectively). However, this observation cannot be extrapolated to all EU Member States, which may have very different socio-historical contexts associated with governance structures and implementation, and highlights the need to conduct such exercises in all areas where a particular set of policies are to be implemented. The attitudes of jury members towards GM animals applied to food production and pharmaceuticals were broadly in line with the conclusions of the public perception analysis. These results validated the use of the citizens' jury approach as a tool to engage citizens and solicit information about their opinions regarding GM animals.
The evaluation process was based on short-term participant observation during the citizens' jury events themselves, and involved observation of the proceedings of the events as well as formal and informal discussions with witnesses, convenors and jurors. The focus for this evaluation was on the issues arising that are of relevance to an understanding of the extent to which the citizen's juries approach fulfils the intended objectives, and, in particular, to comment on their role as a useful tool for informing policy development.

The jurors in the UK perceived that the majority of the expert witnesses to be pro-GM and felt they would have liked to hear a more strongly articulated anti-GM argument. This may reflect the jurors' expectation of being presented with two different 'sides' of the argument, and subsequently being asked to make a decision between them. Instead, the citizens' jury was presented with the potential risks and benefits of GM animals, which, while allowing the jurors to come to their own mediated position, did not necessarily require an outright ascription to one extreme position or another. This may reflect a pre-existing "bias" on the part of the jurors towards controversy associated with this subject, which may have increased the intensity of the jurors' discussions. There was a sense from the citizens' juries that formulating policy recommendations was a particularly difficult task for the jurors. Temporal limitations restricted the time available for jurors to consider and construct policy recommendations. In addition, jurors themselves were interested to know the use of any outputs in terms of policy impact which could not be provided as the activities were designed to demonstrate the utility of the approach, not deliver evidence upon which policy could be based.

Discussion

Taken together, the integrated results imply that GM animals need to be considered on a case-by-case basis, independent of whether risk assessment, socio-economic impacts, or ethical issues are being considered. Due consideration should be taken of differences between different types of animals and the reasons for their modification. Not all assessments would apply to all cases, at least not for those within the agri-food sector. For example, research is needed which will enable examination of the welfare issues associated with handling and manipulating GM animals in general, although a case-by-case approach will be required as different types of animals and genetic modification may raise different welfare issues. Ensuring there is clarity regarding ethical 'boundaries' of decision-making processes may be an important element of any future GM animal licensing / policy process. As part of this more research into the socio-economic dimension of GM animal commercialisation, and how this contrasts with alternative approaches, may be required in order to optimise food chain and pharmaceutical benefits from innovations using both GM

and non-GM animal technologies. Issues of social equity were also identified. Risk-benefit assessments should consider the impacts on all producing countries to ensure developed countries, (for example, EU member states), do not reap the benefits of animal GM technologies, while exporting any health, environmental or socio-economic risks to other countries, in particular those which are economically developing.

In order to promote scientific and regulatory leadership in this area, the results indicate that it is important that the EU supports research to improve techniques for the generation of GM animals and the evaluation of the potential impacts which simultaneously take due account of the preferences of European citizens. It is suggested that, as a recommendation for best practice, this may also be relevant internationally. The results suggest this may translate into prioritisation of medical applications of GM animals, at least in the initial stages of an implementation and commercialisation trajectory. Given the reticence of pharmaceutical companies and other industry stakeholders to engage in research utilising GM animals, it may be useful to initially develop innovation through public funding if pharmaceutical applications are deemed a public good. Alternatively, such research might be advanced through facilitation of public-private partnerships.

An important conclusion was that the development, implementation, and (possible) commercialisation strategy for GM animals would need to assess what benefits of products are perceived to be substantial enough to outweigh perceived risks and negative attitudes. This may require research to identify information about what the public perceives to constitute a desirable benefit early enough in development to influence the design of the final product. In this context, attitudes may crystallise following the implementation of EU or international legislation, or following the commercialisation of the products of GM animals intended for consumer purchase, (in particular in the food sector, where public concern is greatest). Further tracking of perceptions and attitudes is warranted. In addition, greater understanding of consumer and/or citizen reactions to GM food and pharmaceutical products in potential markets (e.g. in BRIC countries) and in capacity building partner countries is important in order to refine trade and capacity building agreements developed between Europe, and international trading and development partners.

Labelling and consumer choice emerged as an important issue in relation to food in all regions where data were available. Although attitudes towards food related applications of GM animals appeared more positive in South-East Asia, the requirement for effective traceability and labelling was also high in this region. Following on from this, a certification system is needed to distinguish the products of GM animals from non-GM counterparts. This is a complex issue for regulators, specifically in terms of what labelling conditions and verification systems would be needed, but reflects societal expectations, and the conditions which will lead to successful economic exploitation of GM animals, in particular applied to food production. In line with current European legislation regarding other food products produced using GM, it is suggested that labels should indicate that a specific product has been produced using GM animals. Mechanisms to ensure effective traceability (e.g., through RFID tagging or other traceability testing) may be needed to develop and maintain consumer trust. It is also important to develop a labelling strategy in line with the WTO agri-food sector agreements [83]. However, GM-animal-free labelling might emerge as a private initiative adopted by some companies. Labelling should also be applied to export products to countries where there is particular consumer demand for such traceability, such as South-

East Asia. Traceability systems should enable labelling to be easily applied to pharmaceutical products may also be relevant, if societal demand suggests that this is appropriate. However, the societal requirement for the introduction of stricter regulations related to traceability and labelling systems for products obtained from GM animals will act to increase production costs, which will be offset by decreased production costs overall. Price reductions have potential to increase producers' and consumers' acceptance, (assuming the reduction in price is passed on to the final consumer).

Increased consumer acceptability is also contingent on consumers identifying personal benefits to be associated with GM animals (such as those related to health) compared to benefits to the business sector. Thus monoclonal antibodies produced using GM rabbits may be viable economically, as public acceptance of pharmaceutical products developed using GM animals will be more positive than those applied to food production.

Two issues relating to socio-economic economic impact and issues of equity were identified. The first relates to small and medium enterprises (SMEs), identified as essential elements in European economic competiveness and provision of employment [84], as well as important generators of income in other parts of the world [85]. As a consequence of the introduction of foods produced using GM animals reducing the prices of associated products in regional or international markets, businesses which do not adopt the technology may become non-competitive, unless they were able to charge a premium for non-GM derived equivalent products. Under these circumstances, financial or informational support to SMEs that could potentially suffer economic losses might be important to preserve the SME sector and maintain consumer choice [86]. The second relates to developing and maintaining economic equity between developed and developing countries. Specifically, the EU and other regions where GM technology is relatively highly advanced should define appropriate tools to support high-quality GM animal pharmaceutical products to be available for therapies and treatments in developing countries, in particular in relation to patent enforcement and capacity building [64]. Similar policies might apply to knowledge transfer regarding GM animals and food production. The successful implementation of such policies would require societal acceptance of pharmaceutical and food products derived from GM animals in both producer and end-user communities. Data are not available to assess local stakeholder and consumer concerns and priorities in many developing regions, research into citizen priorities and preferences within these communities may be required. If GM animals are adopted internationally, international organisations will be required to take a leading role in promoting the global harmonisation of relevant regulatory structures, in particular regarding the handling of the trade disputes that are expected to emerge may also be the responsibility of international organisations.

In terms of science, the EU might encourage the definition of different baseline scenarios for various GM animal species that could be debated and agreed by the National Competent Authorities. These could be used during the risk assessment process by the European Food Safety Authority (EFSA) or the European Medicines Authority (EMA). Duplication of effort across different EU Member States could be averted through the systematic collection of research data across Europe, and promotion of collaboration among existing research groups to maximise efficiency and the development of common research portfolios. When applicable, the specialisation of particular research teams with a common sharing of resources might be relevant, in particular within the pharmaceutical sector in the production

of GM animals that improve the drug innovation process (e.g., disease models). Researchers should be encouraged to consider the minimum number of animals required for a study and whether existing GM animals could be used instead of developing a new GM animal line, in line with existing 3Rs policy (i.e. reduction, refinement, and replacement) of animal use in research [87]. Such policies may also be relevant internationally. The pharmaceutical industry and medical sector generally should be encouraged to collaborate in the development of strategies to enable the benefits of pharmaceutical innovation to be delivered, perhaps through establishing private-public partnerships.

With respect to governance, stakeholders indicated that the EU should maintain its effort to harmonise regulation. Where regulatory implementation is difficult (e.g., the GMO comitology procedure - see [88]), procedural changes should be explored. For example, inclusion of socio-economic factors in the European comitology procedure would potentially improve the transparency of dialogue with stakeholders and, consequently, the discussion between national competent authorities. Advisory bodies such as EFSA only report on the scientific risks of a given GM animal; and empowering institutions to provide information on the possible benefits, in addition to the possible risks, in their assessments (including GM animal applications) is important in the facilitation of innovation processes. Such changes in regulation within Europe would, of course, need to remain sensitive to the international context (i.e. WTO) and where appropriate work towards global harmonisation of regulations.

The need to involve the public in the debate about implementing and commercialising GM animals and their products is recognised, and public engagement mechanisms such as the citizens' jury, and other deliberative processes, will potentially represent a useful approach to fine-tuning policy relating to GM animals. The 'deliberative space' created by the citizens' jury methodology facilitates the kind of group interaction and depth of discussions needed to inform policy. However, a more geographically extensive application of the methodology is required, in order to include differences in countries and regions with different socio-historical approaches to technology regulation, and allow comparative analysis between these. The approach is better suited to the discussion of pre-formulated and realistic policy scenarios or options which are compatible with existing systems of policy making. For example, if the results are to be used explicitly to assess the relative merits of different policy outcomes or alternatives, these need to be translated from scientific outcomes to different policy options. An analysis of policy impact is needed in order to justify and optimise citizen engagement within the policy process. As a *de minimis*, the process by which such policy outputs are anticipated to have an impact on local, national, regional or international policy should be described, both in terms of process (i.e. how is the information to be translated and delivered to decision-makers) and practice (i.e. what is the impact of such information on the policy process). This is in line with current thinking regarding the impacts of other forms of consultation on policy processes, for example in the context of expert consultations [89].

Conclusions

The results have delivered data relevant to support policy with the development of an innovation strategy, taking into account the range of issues associated with GM animals from a life and social science perspective. As for any emerging area of technology, potential risks and benefits can be identified, and, in the case of GM animals, the evidence suggests that these require a case-by-case analysis. This is demonstrated by the different issues raised by

the three case studies (Table 2) and the extrapolation to other examples of GM animals currently under development (Table 3).

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Table 3 about here

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One issue is that, as a result of the research being conducted by a European research consortium, with the aim of supporting European Policy development, many major events, works and issues that have emerged in the US have not been addressed. Discussion of these is beyond the scope of the current paper, and indeed these have been discussed extensively elsewhere (e.g., see [90]). However, the international dimension merits further analysis in a global policy context, in particular in relation to regulatory harmonisation. A deciding factor regarding whether, and under what conditions, GM animals are to be introduced and commercialised will be societal acceptance, which will be contingent not only on risk perceptions or other value-based attitudes, but also the perceived benefits offered by specific applications. The issue of consumer choice (and implementation of effective traceability and labelling strategies) will also be important, in particular in relation to agri-food applications. In addition, equitable distribution of socio-economic benefits between producers and consumers, and between affluent and disadvantaged countries and regions is important.

Assuming appropriate risk assessments have been conducted (including those related to animal welfare and the impact of environmental release and/or escape), there appears to be little evidence that the introduction of GM animals for pharmaceutical production will be problematic from a societal perspective. Developing applications of GM animals for food use will be successful only if benefits align with public preferences. Communication about, and public engagement with, emerging policy is important, providing the goals of such activities are well thought through and the policy impact of such public engagement activities are explicitly assessed. In addition, harmonisation of European research activities is an important priority to avoid duplication of effort and unnecessary sacrifice of animals, as is global harmonisation of regulatory activities regarding international trade and development.

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Case study	Type	Method	Driving forces	Type of experts' consultation	Scenarios identified
Growth-Enhanced GH Transgenic Salmon	Qualitative and quantitative	Cross-impact analysis → logic-verbal technique Production and firm-based cost model	15 driving forces divided in 4 categories: 1) Production 2) Market 3) Public/Consumption 4) Regulatory framework	Questionnaire web + telephone interviews	A- GM fish banned B - GM salmon for dinner C - GM salmon doesn't take off
Recombinant Human Lactoferrin (rhLf) in the Milk of Transgenic Cows	Qualitative	Intuitive logic →Focused interview (structured questionnaire with open ended questions)	Main driving forces: 1) cost-effectiveness 2) human health Other relevant driving forces: 1) Production 2) Market 3) Consumer/producer Acceptance 4) Regulatory framework	Questionnaire+ Face to face , telephone, e-mail interview	A-rhLf adopted outside the EU B- rhLf adopted also in the EU C- rhLf is not adopted worldwide
Polyclonal Antibodies (pAbs) from Transgenic Rabbits	Qualitative	Intuitive logic with personal interview and structured questionnaire	Driving forces are: 1) Proprietary knowledge and patents 2) Public policy 3) Consumer behaviour 4) Risk factors	Direct and indirect contacts of different stakeholders (personal interview)+ Structured questionnaire e-mails	A - pAbs from GM Rabbits a reality with limited access B - pAbs from GM animals unrealistic C - pAbs from GM rabbits may take off with wider access

Table 2 . Scenario analysis settings for the three case studies

Genetically modified animal under consideration	Advantages from a life science perspective	Disadvantages from a life science perspective	Advantages from an economics perspective	Disadvantages from an economic perspective	Public/citizen perceptions	Ethical aspects
Transgenic Salmon with increased growth rate and/or increased disease and stressor resistance	-Improved human nutrition (increased availability of omega-three fatty acids) -Potential for improved - resistance to environmental stressors and pathogens	-Potential for the introduction of allergens into the human food chain -Strong environmental impact potential (although data suggest this is not the case if containment is sufficient) * -100% sterility not achievable	-Increased gross margins (profits) for producers -Reduction of retail prices for consumers -Costs of producing safety dossiers / claims dossiers for regulators will be high and bourn by the industry -	-Increased costs from building aquatic containment facilities -Increased dependency of farmers from suppliers -Negative impacts on SMEs -Labelling and traceability required -Equity of distribution of benefits to different countries and across populations needs to be considered	-Transgenic fish more acceptable than transgenic terrestrial animals applied to food production -Consumer benefits need to be concrete and visible (i.e. reduced cost) -Non-medical applications are less acceptable -Effective labelling, traceability and animal welfare policies essential for consumer acceptance	-Welfare issues not well defined -Alternative technologies need to be considered -Effective labelling and traceability policies essential for consumer choice -Socio-economic impacts (e.g. negative impacts on small producers) need to be considered -benefits for developing countries not well defined -Labelling and traceability required to preserve consumer autonomy - Does the application delivery increased global food security or only reduce price for developed countries? -
Transgenic cattle produce lactoferrin in milk, for use in infant formula	-Improved human nutrition (infant formula) -Appropriate species to produce large amounts of protein for human consumption	-Generation through cloning or lentiviral vectors -Slow reproduction -Susceptible to prion diseases -Reduction in agro-biodiversity	-Slow rate of reproduction reduces efficiencies in the supply chain -Costs of producing safety dossiers / claims dossiers for regulators will be high and bourn by the industry -Economic efficiencies in production chain	-Potentially high margins if public assume that this is a medical product and/or a functional food -Labelling and traceability required to preserve consumer autonomy -Equity of distribution of benefits to different countries and across populations needs to be considered	-Potentially higher acceptance if perceived as medical application -Product designed for consumption by infants may trigger concerns -perceived potential to introduce of prion diseases to human food chain -Further case study based analysis required	-Animal welfare issues associated with reproduction, quality of life etc -Alternative production options may be available, -Labelling and traceability required to preserve consumer autonomy
Rabbits modified to produce polyclonal oclonal antibodies (pAbs) for human therapeutics	-PABs produced using genetically modified animals have high titers -Note polyclonal antibodies produced using GM animals may be associated with increased immunogenicity -Relatively high rate of reproduction	- Requirements for special feeding and restricted rearing conditions	-Equity of distribution of benefits to different countries and across populations may involve knowledge transfer and capacity building -The production cost is expected to be acceptable for treatment of patients. At the present time, alternative methods are not available as the only available human pABs come from immunized persons. -Other candidate producer animals (pigs and cows) will occur.		- If a clear need is established, acceptance is likely to be high as this will be perceived as a medical application -Little data available regarding consumer preferences for pharmaceutical labelling but stakeholders suggest this will be required. -Labelling and traceability	-Limited data regarding animal welfare -Large numbers of animals required means high levels of animal sacrifice -Alternative technologies may be available if research is resourced.

				is also establish for pharmaceutical applications	

Table 1. Summary of the issues raised by the GM animal cases.

* 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(2), 170-189. See also Van Eenennaam and Muir, 2011 [51] in reference list.

Category	Application time scale	Examples	Ethical issues	Economic issues	Public perception and attitude	Results of citizens' juries	Policy	Life science Benefits	Life science risks	Research needs	
Disease models	The most common form of GM animal currently used	Rodents, rabbits and pigs used to - Model human diseases - Test therapeutics	-Animal welfare issues associated with the high numbers of animals sacrificed, such as duplication of effort -Animal alternatives may be feasible -Ethical requirement to reduce animal and human suffering associated with disease	- Cost is reducing enabling larger animals to be used as more accurate models	-Generally positive as medical benefits are both tangible and desirable	Medical research is essential, although improved animal welfare and reduced animal sacrifice required if possible (e.g. through elimination duplication of effort across the EU)	-Duplication of effort in research capacity across Europe suggest the need for harmonisation of research activities	-Acceleration of medical research	-Risk of unintended environmental release not well understood -Animals kept in confined areas	-Can alternatives to the development of animal models be identified?	An ap
Bioreactors -GM animals producing therapeutics in their milk or eggs	Application is current, less advanced or extensive than animal disease models	Current examples include Atryn (goat), Rhucin or Ruconest (rabbits)	-Animal welfare issues associated with the high numbers of animals sacrificed and technique. -Alternative approaches may be feasible -Will all citizens , including those in developing countries, have equitable access to products?	-Pharmaceutical Industry "buy-in" is poor owing to IPR concerns - Cost of pharmaceutical products could reduce for the consumer -potential advantages for poorer countries assuming capacity building is adequate	-Positive regarding pharmaceutical production -Ethical and religious objections are not severe but could potentially arise	-Medical research important but are alternative approaches available? Improved Animal and reduced animal sacrifice are important if possible. Labelling and traceability systems required to support informed choice.	-Public financial support essential -Public-private partnerships should be encouraged -Knowledge transfer to developing countries a priority --At the present time, production costs (and hence retail costs) are in gen ral not reduced by utilisation of genetically modified animals, although exceptions can be identified. -. Uptake by pharmaceutical sector is limited because of concerns about competition.	-Increased rate of pharmaceutical production should improve public health -Some proteins (e.g. Human Albumin) can only be produced in sufficient amounts by use of GM animals or plants	-Introduction of unintended health risks -Unintended release into the environment may have uncertain impacts, in particular for high profligacy species	-Consumer research needed to understand if pharmaceutical products derived from GM animals would be labelled as such? -More data is needed regarding animal welfare issues	-Sh be res
Animals genetically altered to improve foods	Application is current, but not commercialised widely (for example, no applications are licenced in Europe or North America.	Aquabounty Salmon -Environpig (research transferred from Canada to China)	-Animal welfare issues need to be examined and contextualised by comparison with production systems -Animal welfare may be improved in some cases (fro example, through increased resistance to diseases) -Are the benefits substantial enough to justify the concerns	-Efficiency in the production chain much lower than for pharmaceutical applications -GM Labelling essential if commercialisation is to be successful -Consumer prices will reduce -Potential threats to SMEs and smaller producers	-Generally negative but each case should be examined with respect to potential benefits -Perceptions are species dependent (Transgenic fish are more acceptable than terrestrial animals) -Not clear whether nutriceuticals will be perceived as medicine or foods. -GM Labelling essential	-Generally negative as little perceived need for food related applications and lack of clarity over the possible benefits it would deliver to the end consumer, but more positive for cases associated with the cases which boarder food and medical/pharmaceutical application -Where clear 'need' and concrete benefits could be demonstrated, acceptability of agri-food applications may rise.	-Risk-benefit assessment required -Assessment of socio-economic and ethical issues, as well as health and environmental impacts, required within risk analysis process.	-Improved public health through improved nutrition and food security	-Reduced or increased agribiodiversit eith unknown impacts. -products may not meet the demands of societal challenges as claimed (e,g, food security)	-More data needed regarding perceptions of consumer in the BRIC countries -Societal attitudes developing countries not well understood -Consumer inputs into the design of beneficial food products will facilitate their introduction	Th foo ani att be pe ass ap -Gi pu en de des ap ap

Table 2. Summary table -The issues for GM animals. Despite attempts to extrapolate broad policy issues to different category of application, it is important that a case-by case approach to regulation is applied. This table seeks to highlight issues which may be of particular relevance to the different categories. The table highlights prominent applications, but it excluded the use of genetically modified animals to produce organs for xenotransplantation as such applications were not systematically in the analysis conducted within this work. Similarly companion animals were not included. Note that for both Xenotransplantation and genetically modified companion animals there is little data regarding either the economic advantages and disadvantages, nor public perceptions of the risks and benefits.