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COGEM TOPIC REPORT
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GENETICALLY MODIFIED ANIMALS: A WANTED AND UNWANTED REALITY

INDEPENDENT SCIENTIFIC ADVICE AND INFORMATION FOR THE DUTCH GOVERNMENT

COGEM TOPIC REPORT
CGM/120111-01

GENETICALLY MODIFIED ANIMALS: A WANTED AND UNWANTED REALITY

COGEM
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COGEM provides scientific advice to the government on the risks to human health and the environment of the production and use of GMO's and informs the government of ethical and societal issues linked to genetic modification. (Environmental Management Act §2.3).

To the State-Secretary for
Infrastructure and the Environment
Mr. J.J. Atsma
P.O. Box 30945
2500 GX The Hague

DATE	11 January 2012
REFERENCE	CGM/120111-01
SUBJECT	Topic report 'Genetically modified animals: a wanted and unwanted reality'

Dear Mr. Atsma,

I would hereby like to present you with the monitoring report 'Genetically modified animals: A wanted and unwanted reality' (CGM/120111-01).

SUMMARY

Due to developments abroad, through either import requests or permit applications for market admittance, Europe will be faced with genetically-modified (GM) animals and animal products in the future. This raises the question of whether the legislative framework and procedures in the Netherlands and Europe are equipped to deal with these developments and whether the present assessment framework is adequate for this purpose. This was why COGEM undertook to investigate the nature of these developments and the possible problems which they may raise.

In this report COGEM examined four topical and representative cases. In order to substantiate and augment the arguments which have been put forward, COGEM organised an international symposium on 25 October 2011 entitled 'GM Animals: Perspectives and Perceptions' in which a number of case studies were presented and discussed with a wide audience. The symposium findings have been included in this report.

Among its findings COGEM noted the following:

- the present system of assessment of GM animals in Europe is aimed mainly at environmental and food safety issues, while a wider set of arguments applies to the developments surrounding cloned and GM animals.
- it is unclear whether or not ethical considerations should form part of the assessment procedure related to the import of GM animal products.
- under the present European admittance procedures the inclusion of alternatives, or of ethical or societal considerations, could be perceived as too narrow in the future.
- with regard to future field tests with GM insects it is unclear whether an ethical assessment will also be necessary in the Netherlands, who should undertake this assessment, how it should be carried out and where it should be placed in the broader framework of considerations.

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- in an international context, ethical arguments may not be sufficient to restrict the import of cloned animals in the event of a WTO conflict. The report further notes that it would appear to be difficult to enforce a potential ban on the use in the food chain of the offspring of cloned animals.
- a pledge on labelling which cannot be fulfilled could have an adverse impact on consumer and public confidence in government and the companies concerned in the food chain and that alternatives to this should be considered.

It is recommended that the Netherlands and the EU reflect on a position concerning the matters raised in this report which also takes into account what the consequences of certain decisions might be in terms of what is feasible in the international context.

A draft version of this report was submitted to Professor Egbert Schroten for comments, as an external expert.

The complete report is enclosed herewith as an attachment.

Yours sincerely,

Professor Bastiaan C.J. Zoeteman
Chairman COGEM

SUMMARY

Europe takes a negative view of genetic modification and animal biotechnology. Public resistance to the genetic modification of animals, based on social and 'in principle' objections, has significantly curtailed the development of genetically modified (GM) animals. Outside Europe, work is continuing on the development of GM animals and products resulting from this are beginning to come onto the market. These developments abroad will in future lead to Europe being confronted with GM animals and GM animal products, for example via applications for import and placing on the market. This raises the question of whether the legislation and procedures in the Netherlands and Europe form an adequate response to these developments and whether the current assessment and review framework is still appropriate. This study by COGEM set out to throw more light on the topic by identifying the relevant developments in the field, which aspects could play a role in the discussion and what problems might arise.

The developments in genetic modification appear to be taking place in a diverse and international context and go beyond applications for increasing the efficiency of food production or for biomedical research. The EU agencies appear to be (partly) aware of the developments taking place abroad and are taking preparatory measures. The European Food Safety Authority (EFSA) is preparing guidelines for the environmental risk assessment of GM fish, GM mammals and birds, and GM insects. The European Commission has obtained (confidential) advice on the legality or otherwise, within the framework of the World Trade Organization (WTO), of imposing restrictions on cloning animals based on non-safety considerations. It appears that the possibilities for taking ethical and social considerations into account in the assessment and authorisation of specific cases of GM animals, such as for placing on the market or import, are limited. It would be advisable for the Netherlands and the EU to consider adopting a standpoint on the issues raised in this report and to take stock of the possibilities and impossibilities of certain choices from an international perspective.

1. COGEM observes that the current assessment of GM animals in Europe focuses primarily on environmental and food safety issues, whereas a broader range of arguments are relevant to developments in the cloning and genetic modification of animals.

Worldwide development of GM animals

An initial inventory of worldwide developments in the field of GM animals clearly shows that the animals being developed are not limited to attempts to raise or

improve the efficiency of food production, but that the applications are much more varied. They include research into the contribution that can be made by genetic modification to increasing disease resistance in animals, producing medicinal compounds and human proteins, improving livestock quality and production, and controlling human infectious diseases. A number of these developments in the US and South America are at an advanced stage or are already commercially available. In Brazil, Malaysia and other countries, field trials are taking place with GM mosquitoes to control the infectious disease dengue fever, while similar techniques are being used to control malaria. The use of GM insects to control agricultural pests is in the pipeline. In Canada, a GM pig has been developed that is less environmentally polluting, and in the US a fast-growing GM salmon is in the final stages of the authorisation process. In China, an extensive research programme has been set up for the genetic modification of animals for the purposes of improving disease resistance, producing valuable compounds and raising productivity.

This diversity of applications means that the arguments and considerations in the debate are also diverse and that a generic evaluation or assessment of GM animals is not possible. The developments prompt the need for a further elaboration of the Dutch 'no, unless' policy and raise the question of what role the various arguments can and should play in a European assessment procedure. To draw up an inventory of the relevant arguments and considerations, COGEM presents four current and representative cases in this report that critically examine both the development in question and the context of the development. To verify and deepen the arguments, COGEM organised an international symposium in 2011 on 'GM Animals: Perspectives and Perceptions', in which three cases were presented and discussed with a diverse audience. The findings of the symposium have been integrated into this report.

Genetically modified salmon

Fifteen years ago the Canadian company Aquabounty developed a salmon for aquaculture that achieves its final weight twice as quickly as conventional fish of the same species. Using this fish offers the prospect of higher fish production per unit time, which could provide a solution, or partial solution, to the problem of overfishing and the growing worldwide demand for animal protein for consumption. During the marketing authorisation procedure in the US, which has already taken more than ten years, it has become clear that the issues are not limited to food and environmental safety, but include other aspects as well. The arguments in the discussion about GM salmon also highlight the problems in conventional aquaculture, such as the need to include fishmeal in fish feed (which in turn requires intensive fishing of the world's seas) and the escape of breeding salmon into the environment. Questions related more specifically to GM salmon are about coexistence and the labelling of products obtained from the salmon. The likelihood that applications will be made for permission to produce

these salmon in Europe appears to be small, because Europe imports most of its salmon from Norway. However, imports of food products from GM salmon (e.g. in tins) cannot be ruled out.

Genetically modified pig

The University of Guelph in Canada has developed a GM pig that is better able to digest phosphate from feed, reducing the phosphate dose needed in the ration. As a result, the pig excretes less phosphate in its faeces, which reduces its environmental impact. This must be seen against the background of the growing environmental problems in areas of intensive agricultural production caused by the accumulation of phosphate and nitrogen in soil and water from the application of manure and fertilisers. The GM pig is in the initial stages of the marketing authorisation procedure. One of the biggest objections made to the GM pig, however, is not so much to do with environmental or food safety, but the role it could play in encouraging further intensification of livestock farming. Many people object to intensive livestock farming and associate it with poor animal welfare and an excessive instrumentalisation of animals. As the GM pig puts less of a burden on the environment, this may actually reduce the sense of urgency in finding other solutions. Critics of the GM pig say the solution to the phosphate problem should be found elsewhere, for example through a reduction and better spatial distribution of pig production or a change in the composition of animal feed. In many Western countries, though, pig farming is a highly rationalised sector driven mainly by economic factors, which makes such adaptations less likely because they involve higher costs. The Netherlands is one of the European countries with a relatively large pig farming sector, which is highly concentrated in certain regions. Eutrophication is an increasing problem in these areas too. Applications for the placing on the market of the GM pig in Europe cannot therefore be ruled out.

Genetically modified mosquitoes

The British company Oxitec has been working for some years on the development of sterile GM mosquitoes to reduce the transmission of infectious diseases such as dengue fever and malaria. The same technology is also used to control agricultural pest insects. This report discusses a GM mosquito used to control the spread of the dengue virus. Sterile male GM mosquitoes are released into the environment. When they mate with female mosquitoes the progeny are not viable and the larvae die at an early stage of development. This suppresses the population and checks the spread of the virus. The chosen strategy is self-limiting and so the effect in the environment is temporary; effective control depends on the repeated release of the GM mosquitoes. Field trials with the GM mosquito have already been held in several countries. The objections put forward relate to a range of arguments, varying from environmental safety and biodiversity to freedom of choice, the right of the local population to be involved in the decision-making and the independence (or lack of it) of developing countries.

Here again, the discussion touches on the question of the availability and desirability of alternatives. The dengue virus does not occur naturally in the Netherlands, which makes the introduction of these specific GM mosquitoes unlikely. However, work is underway on GM agricultural pest insects, which could be relevant.

Cloned animals

Lastly, the report discusses the cloning of animals. Although cloning is not genetic modification, there are close links between the technologies and their applications, and most people consider them to be much the same. Cloning is used to increase the quality and production of meat for food and to maintain valuable breeding stock. Several companies in the US and South America already offer a commercial animal cloning service. These companies often also work with other reproductive techniques used in the animal breeding industry, such as embryo transplantation and artificial insemination. The high costs and health complications of cloned animals are currently slowing down developments in this area. It is expected that in future the technology will be further refined and optimised.

Various countries (including the US, Japan, Australia and New Zealand) have concluded that the products of cloned animals are safe for consumption. Although in 2008 the EFSA, in line with other countries, also concluded that food products obtained from cloned animals are safe, it noted that there are ethical objections to the use of the technology, including the health problems suffered by cloned animals. Accordingly, a temporary prohibition on cloning animals for food production purposes was subsequently proposed, but negotiations on the details of such a prohibition broke down in March 2011. At the moment there is no specific legislation in Europe on the cloning of animals.

It should be noted that cloned animals can only be detected in certain limited situations. It is possible to distinguish a cloned animal from the original if both parent animals are known, but the progeny of the cloned animal cannot be identified, except through certification and herdbook registration. In the US there is a voluntary moratorium on the use of clones in food production, but this does not apply to their progeny. Some companies maintain a registration system for cloned animals, but others do not. Cloned animals and their progeny are also reared in the Netherlands and elsewhere in Europe. A French company is active in cloning valuable sport horses. In the summer of 2010 it became known that several offspring of cloned cows in the United Kingdom entered the food chain by mistake.

The case studies threw up a number of issues that could in time pose problems for national and international legislation and their enforcement.

Imports: Importing products of GM animals into Europe requires a permit, for which the product is assessed for safety. Moreover, in Europe all products of GM animals

must be labelled. COGEM points out that it is not clear whether an ethical review of products from GM animals to be imported is considered desirable. The existing EU directives appear to leave room for ethical and social considerations, but it is not clear what part these could play in the authorisation procedure. A general advice by the European Group on Ethics (EGE) may be taken into consideration in the assessment, but may not carry full weight as an independent input to the decision-making process. There are no existing procedures within the EU that provide for a case-by-case review of ethical aspects that can be incorporated into the decision-making process.

2. COGEM observes that it is not clear whether it is considered desirable to conduct an ethical review of products from GM animals to be imported.

Production: The production of GM animals in the Netherlands is subject to national regulations. These currently require that besides an environmental risk assessment, an ethical review is carried out. In Europe a marketing authorisation is required before a GM animal can be kept (following importation). This is a European responsibility. In such cases the GM animal must be assessed for environmental and food safety consequences and products obtained from the animal must be labelled. COGEM notes that the current European procedures give little weight to the consideration of alternatives or ethical and social aspects. The existing guidelines leave room for ethical and social considerations, but it is not clear how these can be taken into account in the decision-making. General recommendations by the EGE may be taken into consideration in the assessment, but may not carry full weight as an independent input to the decision-making process. There are no existing procedures that provide for a case-by-case review of ethical aspects that can be incorporated into the decision-making process.

3. COGEM observes that the weight given to alternatives or ethical and social aspects in the current European approval procedures may in future be considered too limited.

Field trials with insects: Field trials with animals and plants in Europe are a national responsibility. Animal biotechnology applications must be subjected not only to a safety assessment, but also to an ethical review. When the research is for a vertebrate biomedical application, an assessment by a local Animal Experiments Committee (DEC) is required. The current legislation also requires other GM applications and modifications of invertebrates, such as insects, to be subjected to an ethical review by the Committee for Animal Biotechnology (*Commissie Biotechnology bij Dieren*, CBD). When the new Animals Act (*Wet Dieren*) comes into force, however, only vertebrates and a few specific groups of invertebrates will probably be covered by the requirement for an ethical review. COGEM points out that it is not clear whether in future ethical reviews will also be required for field trials with GM insects, who should carry out these reviews, and how they should be carried out and considered within a broader evaluation framework.

4. COGEM observes that it is not clear whether in future ethical reviews will also be required for field trials with GM insects, who should carry out these reviews, and how they should be carried out and considered within a broader evaluation framework.

Trade conflicts: A situation has arisen in Europe in which cloning animals is not considered to have food safety implications, while ethical and social objections are made to the technology. In the event of a WTO conflict these arguments may, in the international context, carry insufficient weight to restrict the import of cloned animals.

5. COGEM observes that in the event of a WTO conflict ethical arguments may, in the international context, carry insufficient weight to restrict the import of cloned animals. In addition, a European ban on the use of the progeny of cloned animals in the food chain does not appear to be readily enforceable.

Consumer confidence: The use of cloned animals and their progeny in Europe is likely to increase. The possibilities for detecting cloned animals have so far been very limited. Direct clones can be distinguished from the original animal if a DNA profile of both animals is available, but the natural progeny of cloned animals cannot be identified. A European ban on the use of the progeny of cloned animals in the food chain does not therefore appear to be enforceable. There is a chance that in time products from these animals will enter the food chain, either known or unnoticed. Given the social resistance to cloned animals and their products in the food chain, the inability to enforce a labelling policy could undermine public confidence in the government and the companies involved in the food chain.

6. COGEM observes that a labelling requirement that cannot be met can undermine public confidence in the government and the companies involved in the food chain.

The existing legislation appears to allow room to include ethical and social aspects in the assessment of GM animals, but it is not clear exactly how such information can be taken into account in the decision-making. In the Netherlands, committees have been established to review the ethical aspects of animal biotechnology applications. However, several animal species seem not to be covered by this requirement for an ethical review and neither does it apply to the import of products or animals. The differences between national laws and regulations could lead to trade conflicts, while the inability to enforce detection and labelling could strain the already fragile public confidence.

Certification of product chains could be an alternative. In this regard, COGEM points to the need to make agreements with the countries where animal biotechnology is used on a commercial basis and which are involved in the international trade in GM animals and their products.

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GM ANIMALS BACK IN THE NEWS

The development of genetically modified (GM) animals began in the late 1980s. These animals are mainly used for scientific research purposes; GM mice have now become virtually indispensable in medical research. Animals are also genetically modified for purposes other than research and although the first steps in this field took place in Europe, this type of research is now conducted almost entirely outside Europe.

The process of developing a GM animal into a marketable product tends to be a long one. Owing to the expected resistance among consumers, some projects seem to have been put on the back burner and some research topics have been abandoned altogether. This is one of the reasons why developments go largely unnoticed by the general public. However, several countries outside Europe have now made concrete steps towards the use of GM animals, as is apparent from applications for permits to rear GM salmon and release GM mosquitoes. These developments have helped to put GM animals back into the public spotlight. It is expected that in future more products and uses of GM animals will appear on the market and that Europe will increasingly have to respond to these developments. This raises the question of whether Europe and the Netherlands are adequately prepared to meet these challenges.

This report addresses these recent developments and their potential significance for Europe and the Netherlands. The following section contains a non-exhaustive overview of the developments in the genetic modification and cloning of animals that have taken place around the world in recent years. Although cloning is not genetic modification, there are close links between the technologies and their applications, and most people consider them to be much the same.

1.1 DEVELOPMENT OF GM ANIMALS

The use of animal biotechnology is increasing worldwide. In the Netherlands, animal biotechnology is used primarily in biomedical research and GM animals are widely used as disease models in research into cancer, ageing diseases, metabolic diseases, congenital abnormalities, etc. Besides biomedical research, research is also being conducted outside the Netherlands into the genetic modification of animals with a view to improving animal health or reducing their environmental impact, producing valuable biological compounds, such as medicines, or for other purposes.[1] An impression of the developments in each category is given in the following sections.

1.1.1 PRODUCTION OF MEDICINES AND OTHER SUBSTANCES

Research into the production of medicines and other high-value substances in GM animals has been ongoing for some time now. This research mainly explores the possibilities for using animals as bioreactors for the production of specific proteins, which are excreted in milk (e.g. in cows, goats and rabbits) or eggs (chickens). The Dutch company Pharming was one of the pioneers in the production of medicines in the milk of transgenic ruminants, and later in rabbit milk. Other biotechnology companies focusing specifically on the production of biomedical proteins in animals (particularly glycoproteins) are GTC Biotherapeutics (goats, United States), BioProtein Technologies (rabbits, France) and Oxford BioMedica (chickens and other animals, United Kingdom). Two products are already on the market: ATryn®, a medicine for blood clotting produced in goats which was authorised for use in the US in 2009 and in Europe in 2006;[2,3] and Ruconest™ (previously Rhucin), a medicine used to treat acute angioedema attacks (swelling) which is produced in transgenic rabbits and was authorised for use in Europe in 2010.[4,5] Researchers in Brazil have developed a transgenic goat that produces the human protein 'granulocyte colony stimulating factor' to increase bone marrow production.[6] In Iran, transgenic goats have been developed for the production of a blood clotting protein to treat haemophilia patients.[7]

High-value substances other than medicines are also produced in GM animals. In 1998 American scientists at the University of Wyoming created a genetically modified goat that produces spider's web protein in her milk.[8] The goat has been cloned and subsequently more GM goats with the same trait have been bred. The researchers collaborated with other groups, including the army, which was interested in the production of web silk because it has several useful properties for both medical applications (sutures) and military uses (body armour). In recent years research into the production of web silk has shifted from production in goats to production in cell lines, bacteria and plant cells.[9,10]

1.1.2 ANIMAL MODELS AND XENOTRANSPLANTATION

Although less visible to the public, genetic modification of animals is widely used in medical research, including the use of animals as disease models and in research into xenotransplantation.

The number of animal tests carried out in the Netherlands has declined, partly because it has become easier to develop specific animal models using various techniques, including genetic modification. In 1978, the first year that animal tests were registered in the Netherlands, 1,572,534 animal tests were carried out.[11] Since then the number has fallen by more than 60%. In 2010 just over 575,000 laboratory animals were used, of which about 16% were genetically modified,[12] many of them GM mice used as dis-

ease models. To a lesser extent, rats, rabbits, amphibians and fish are also genetically modified for research purposes in the Netherlands.

Inserting human genes into animals for research into human diseases raises certain questions. In 2011 the UK Academy of Medical Sciences stated that making animal models with more complicated and multiple modifications involving human genes may in time pose ethical questions, because the boundary between human and animal will become increasingly blurred.[13]

Research into the use of animal tissue and organs in humans (xenotransplantation) has been conducted for many years. As early as 1963 a baboon kidney was transplanted into a human. Since then repeated unsuccessful attempts have been made to transplant organs (heart, liver, kidneys) into human patients. Current research focuses mainly on adapting ('humanising') donor material so that it will not be rejected by the recipient. Pigs are considered to be the most promising donor organism. Following disappointing results (rejection of donor tissue, complications in the recipient) and in the face of public resistance, the amount of research into xenotransplantation taking place in Europe has fallen off sharply, but is still being pursued in other countries. In China and Australia research is being conducted on transgenic pigs which through genetic modification have organs that closely resemble human organs.[14,15] Tentative results have already been obtained with transplanting animal cells (not complete organs) from animals into humans, such as insulin-producing cells.[16]

Transplanting organs grown in animals into humans raises several questions, including the possibility of animal diseases being transferred to humans, and so this line of research is approached with considerable caution.[17] For this reason a moratorium on xenotransplantation has been in force in the Netherlands since 2000.

1.1.3 DISEASE CONTROL

Genetic modification is also used to combat diseases. This can be done by making the animals themselves resistant to certain diseases (e.g., chickens to bird flu, cows to bovine spongiform encephalopathy (BSE)).[18] In January 2007 a group of American researchers announced that they had produced cows that do not have the prion gene (PrPc deficient). The means that the pathogenic forms of the prion proteins, such as BSE in cattle and Creutzveld-Jacobs disease (CJD) in humans, cannot be synthesised. When the GM cows are 20 months old they are clinically, physiologically and reproductively normal.[19]

A considerable research effort is being devoted to combating vector-borne infectious diseases, such as dengue fever and malaria. The British company Oxitec has developed a technology called 'Release of Insects carrying a Dominant lethal' (RIDL), in which

male insects are sterilised and released in order to reduce the size of the population and thus reduce the spread of vector-borne infectious diseases.[20] Field trials with these GM mosquitoes to control the infectious disease dengue fever have already been held in Malaysia, Brazil and the Cayman Islands.

1.1.4 FOOD PRODUCTION AND AGRICULTURE

GM insects are developed to suppress agricultural pest insects and so improve yields.[20] Oxitec, the company specialised in controlling infectious diseases, also works on the control of agricultural pest insects, such as the pink bollworm, the fruit fly and the olive fly, and also uses its RIDL technology to control some of these insects. Oxitec has carried out field trials in the US with GM pest insects such as the pink bollworm (*Pectinophora gossypiela* (Glechiidae, Lepidoptera)), a cotton pest.[21] Genetically modified pest insects are either in the pipeline or are already being tested on a small scale. In addition, farm animals, and also some fish, are being genetic modified to increase food production.

In Canada, a fast-growing salmon has been developed to boost food production, but has been awaiting marketing authorisation for some time. In addition, research is being conducted into the possibilities for raising the quality of fish meat for human consumption, for example by using salmon genes to alter the ratio between omega-3 and omega-6 fatty acids. Worldwide at least fifty fish species have been genetically modified, creating more than 400 different fish/trait combinations. A fast-growing GM river carp has been developed in China and a fast-growing GM tilapia in Cuba.[22-25] Other transgenic fish, such as trout, and shellfish are also being developed, but as far as is known there have been no applications for marketing authorisation.[26]

In 2008 China launched a 15-year programme for the development of genetically modified organisms (GMOs). Although 75% of the programme is dedicated to plants, the programme includes research into cloned and GM animals [27] and about 300 different genetically modified and cloned animals are currently being tested in large-scale production experiments. The inserted traits are for disease resistance, protein production and increased productivity. In both China and Argentina cows have been developed that produce milk containing human proteins.[28,29,30] In Canada a pig has been developed with less harmful faeces, making it more environmentally friendly than conventional pigs of the same species.[31] Researchers at the University of Missouri in the United States have successfully produced transgenic pigs containing the fat-1 gene and have multiplied them using cloning techniques.[32] The purpose of their experiments is to adjust the ratio between omega-3 and omega-6 fatty acids in pigs to increase their nutritional value for the consumer. In Australia, GM sheep have been developed with an inserted transgenic growth hormone to make them grow faster and produce more milk.[33] In New Zealand, research is also being conducted on the development of transgenic farm animals for the production of human proteins and to raise productivity.[34,35]

1.1.5 SPORT, ART AND OTHER PURPOSES

In the past genetically modified cats have been developed for sale as pets, but it is not known whether these GM cats have ever actually been sold. The company called Allerca now only offers conventionally bred (GMO free) hyperallergenic cats. GM zebra fish are available on the market in various countries (including the US and in Asia). These GM fish ('Glofish') are fluorescent and were originally developed for research purposes (to detect the presence of certain pollutants in water). Animal cloning is on the increase and is used, for example, in the breeding of race horses, cattle and pigs. In Korea, dogs have been cloned that have special abilities to sniff out drugs.[36] In addition, some artists have also expressed interest in working with living material.[37,38,39]

1.2 LEGISLATION ON GM ANIMALS

The Netherlands, the European Union and other countries have adopted legislation on the genetic modification of animals. However, the details of these regulations can vary between countries. In this section we give a brief overview of the relevant legislation in the Netherlands and Europe. The regulations in several other countries are also dealt with in the discussions of the cases in Chapters 2 to 5.

1.2.1 EU LEGISLATION ON GM ANIMALS

There is no specific centralised EU legislation on animal biotechnology. Like other GMOs, GM animals fall under the general GMO regulations. Permits are required for all research, field trials and placing on the market of GMOs (release into the environment, Directive 2001/18/EC)[40] and detailed guidance on the environmental risk assessment of various types of transgenic animals is currently being drawn up.[41] Several permits are often needed for the production and use of GM animals, for example when the animals or their products are also used in food (Novel Foods, Regulation 258/97/EC).[42] In addition, there are rules for the authorisation of pharmaceutical products obtained from GM animals or GM organisms (Directives 2001/83/EC and 2003/63/EC on medicines for human use and Directives 2001/82/EC and 2004/28/EC on veterinary use).[43-36]

Both technically and legally, cloning GM animals is not genetic modification because no changes are made to the DNA of the animals. There is no specific legislation on cloning in Europe and the technology is not covered by the GMO legislation, but food products from cloned animals fall under the Novel Foods Regulation (Regulation 258/97/EC). Besides safety aspects (human and environmental safety), ethical and social aspects may also be involved. When new technologies or products of new technologies are assessed, a general advice can be sought from the Euro-

pean Group on Ethics (EGE), which advises the European Commission on ethical and social issues. The EGE has issued advice on various topics, including synthetic biology and cloned animals.

1.2.2 DUTCH LEGISLATION ON GM ANIMALS

The Dutch legislation on GM animals is based in the first instance on the EU Directives on GMOs, which means that the production and use of GM animals fall under the GMO regulations.[47] In response to the public resistance to genetic modification in the Netherlands, additional specific legislation has been drawn up on the ethical and social aspects of the genetic modification of animals.[48,49] Authorisation is needed for research and animal testing with GM animals, which falls under the responsibility of the Ministry of Infrastructure and the Environment (IenM) (environmental safety), the Ministry of Health, Welfare and Sport (VWS) (animal welfare) and the Ministry of Economic Affairs, Agriculture and Innovation (EL&I) (ethical aspects).

Risks to human health and the environment (IenM)
The Genetically Modified Organisms Decree under the Environmentally Hazardous Substances Act states that for activities involving GMOs a permit for contained use (IG) or introduction into the environment (IM) must be obtained from the Bureau for Genetically Modified Organisms (Bureau GGO). The Commission on Genetic Modification (COGEM) advises on the determination of specific permit applications.[50]

Health and welfare aspects (VWS)
If animal testing is involved, the Experiments on Animals Act also applies.[51] Institutions and companies that want to conduct tests with vertebrate animals have to apply for a permit from the Minister of Health, Welfare and Sport. This applies to all vertebrates, whether or not they are genetically modified. Such animal tests may not be carried out when the objective of the test can be achieved without or with fewer animals or in a less harmful manner. Each proposed animal test must be reviewed by an Animal Experiments Committee (DEC), which considers whether the importance of the animal test justifies the distress caused to the animal. The Experiments on Animals Act does not apply to marketing authorisation or the import of GM animals.

Social or substantial importance (EL&I)
The Netherlands is one of the few countries in the European Union with a licensing system for the genetic modification of animals in which applications are reviewed for their ethical acceptability. Besides the Netherlands, Denmark, Switzerland, Austria and Norway have specific regulations on the ethical aspects of GM animals. In the Netherlands, the basic principle is that genetic modification of animals always involves a certain erosion of the 'species identity' of organisms, which should not be permitted unless this is clearly justified and certain conditions have been met. This principle is set

down in Article 66, paragraph 1 of the Animal Health and Welfare Act (GWWD).[52] A permit can be applied for from the Minister of Economic Affairs, Agriculture and Innovation. Permits are issued if a) the activities have no unacceptable consequences for the health and welfare of animals, and b) there are no ethical objections to the activities. Permit applications are determined by the Committee on Animal Biotechnology (CBD).

Until the end of 2010 the CBD's task was to review all research proposals involving the genetic modification of animals by weighing up the importance of the research against the consequences for the animals concerned, taking into account the possible alternatives.[53] On 1 January 2010 a regulation came into force exempting the use of animal biotechnology for biomedical research purposes in the Netherlands from this review. Because almost all applications in the Netherlands until then had been for biotechnological treatments for biomedical research purposes, this led to a considerable reduction in the CBD's workload. The Animal Experiments Committees (DECs) have now taken over most of the CBD's duties. A new law (the Animals Act) has been drafted which will eventually replace various laws and regulations pertaining to animals, including the GWWD. As long as the GWWD is in force and a category of biotechnological treatments on animals continues to exist for which a permit is required, there is a legal requirement for the CBD to be consulted when determining permit applications,[54] for example for the creation of GM animals for production purposes in the Netherlands. Reviews by the CBD are not required for marketing authorisation in other EU countries or for the import of GM animals into Europe.

1.3 INTRODUCTION OF CLONED AND GM ANIMALS INTO EUROPE

Cloned and GM animals are already being developed outside Europe for food production, disease control and solving environmental problems. Several of these applications have entered the marketing authorisation process and it is just a matter of time before the first GM animals or products become available on the market. The globalisation of the world market means it is probable that these will also make their appearance in Europe, for example via imports. In that case, permits from the European Commission will be needed.

1.3.1 EFSA DEVELOPING GUIDELINES FOR THE ENVIRONMENTAL RISK ASSESSMENT OF GM ANIMALS

The European Commission has asked the European Food and Safety Authority (EFSA) to draw up guidelines for the environmental risk assessment to be carried out for the approval or placing on the market of transgenic animals.[41] This request was prompted

by recent developments outside Europe in which GM animals are being developed for the commercial market to support food supply, the production of medicines and sustainability improvements. In addition a (confidential) legal advice was recently submitted to the European Commission on possibilities for curbing the import and production of cloned animals in Europe.

Initial inventories of the environmental risks of a number of animals have been drawn up for the EFSA by consultants and reports have been published on environmental risk assessment criteria for GM fish, GM insects and GM mammals and birds.[55-57] These reports contain initial inventories of the risk aspects and form the basis for the future risk assessment guidelines. The preparation of formal Environmental Risk Analysis Guidance Documents for these animals is planned during the next two years. These documents are expected to be completed in 2012.[41]

1.3.2 CROSS-BORDER SPREAD OF GM ANIMALS CANNOT BE RULED OUT

Recent developments in GM animals concern animals that are not always held in contained facilities and animals that are deliberately released into the environment, including GM birds, GM fish and GM mosquitoes. The escape and dispersal of GM animals in the environment is therefore a realistic scenario. The authorisation of these GM animals for placing on the market in another country or region means that their spread across borders cannot simply be ruled out or minimised.

1.3.3 MAJORITY OF EUROPEAN POPULATION CRITICAL OF GM ANIMALS

A majority of the Dutch and European populations is opposed to the use of cloned and GM animals for food production. This is reflected in various opinion polls conducted over the years in the Netherlands and Europe (*see Table 1*).

TABLE 1: SUMMARY OF DUTCH AND EUROPEAN OPINION POLLS

1991	**Europe – Eurobarometer on biotechnology [58]**
	• Genetic modification of animals for research is acceptable
	• Genetic modification of animals for the food chain is risky
2005	**Europe – Eurobarometer on biotechnology [59]**
	• No questions on GM animals – nothing on the market
2008	**Europe – Flash Eurobarometer on cloning [60]**
	• 60%: Cloning for food production unacceptable
	• 85%: Food from cloned animals must be labelled
	• 56%: Cloning for animal disease resistance is acceptable
	• 67%: Cloning to preserve rare breeds is acceptable
2008	**Netherlands – stakeholder survey on cloning (Ministry of Agriculture, Nature Management and Fisheries) [61]**
	• Developments are still a long way off
	• Labelling and traceability is important
	• Innovative capacity of the Netherlands in international breeding sector mentioned
2010	**Europe – Eurobarometer on biotechnology and cloning for food production [62]**
	• 82%: Animal cloning for food is unacceptable
	• 62%: Opposed to GM food
2011	**Netherlands – LNV Consumentenplatform on cloning [63]**
	• 70%: Opposed to cloning for food production
	• 43%: Opposed to medicines from cloned animals
	• 43%: Support medicines from cloned animals

Opinions about the genetic modification of animals are often different outside Europe. For example, in North and South America and in Asia there appears so far to be less resistance to research in which animals are used for more instrumental purposes, such as food production. Although NGOs are campaigning to reduce animal testing and the use of animal biotechnology in many countries around the world, few countries have included the ethical and social aspects of these activities in laws and regulations. The Netherlands and a few other countries in Europe are the exceptions to this general rule. In almost all countries outside Europe the emphasis is on assessing environmental and food safety.

1.3.4 CURRENT DEVELOPMENTS CALL FOR A POSITION STATEMENT

The EFSA is preparing to develop an environmental risk assessment method for transgenic mammals, fish and birds with a view to future applications for marketing authorisation in Europe. Although formally only environmental risks have to be taken into account, public resistance to GM animals means that ethical and social issues will also be raised should any requests be made to authorise the placing of such animals on the market in Europe. But even if these animals or products obtained from them are not formally authorised for placing on the European market, they may still pose an unwanted problem in Europe because it will not always be possible to detect and label them when imported, and their spread across borders cannot be ruled out. This situation has already arisen in the case of cloned animals or their progeny. Over the coming years the European and Dutch authorities will have to consider their position on the development of cloned and GM animals and how they should respond if they want to avoid being caught off guard when such animals cross their borders. They should consider whether they want to permit these developments in their own countries and whether they want to prevent products obtained from them entering the country. Another issue to be addressed is what to do if cloned or GM animals inadvertently cross the national border after they have been intentionally or unintentionally released into the environment. Opponents of such developments in particular could declare the government to be in default and demand more effective government action.

1.3.5 STRUCTURE OF THE REPORT

An initial inventory of worldwide developments in the field of GM animals has revealed that they are used for a wide range of purposes. This also means that the debate about GM animals has broadened and is no longer simply a yes or no discussion. Assessment of the various applications involves not only safety issues, but also ethical, social and economic considerations. In the years to come these will have to be addressed in one way or another in discussions about the assessment and approval of GM animals, both in the Netherlands and in Europe.

This report contains four cases studies of GM and cloned animals that are in an advanced stage of development. The case studies are about food production (GM salmon), controlling environmental problems (GM pig), controlling infectious diseases (GM mosquitoes) and breeding and selection (cloned animals). For each case, the development and the context within which it is taking place are discussed, and the various arguments and considerations that may be relevant to the discussion are reviewed. These considerations concern technoscientific, ethical, social and economic aspects. Moreover, both specific and context-related aspects are considered. In the last two chapters several

potential problem areas are identified that are relevant to all cloned or GM animals and a number of important issues are highlighted.

This report was compiled from discussions between the members of COGEM and its subcommittees, which in turn were based on an extensive literature study. In addition, in autumn 2011 COGEM organised a symposium on 'GM Animals: Perspectives and Perceptions' at which a number of case studies discussed in this report were presented. During the symposium the various visions and perspectives on each case were discussed and an inventory of the identified arguments and considerations drawn up. COGEM hopes that this report will help to clarify the great diversity of arguments and developments. In particular, it attempts to address in an even-handed way the ambiguity of the various arguments and aspects that play a role in the discussion about genetic modification and animal cloning. In addition, COGEM points to several problem areas in the European and Dutch legislation and regulations.

2

GENETICALLY MODIFIED SALMON

2.1 INTRODUCTION

The development of transgenic fish for food production began in the mid 1980s. A few examples of transgenic fish have already been mentioned in the Introduction of this report. One of the best known and certainly the most talked about in recent years is a fast-growing salmon produced by the Canadian company Aquabounty.[64] The AquAdvantage® salmon is a genetically modified Atlantic salmon developed for food production purposes. This GM salmon grows faster than conventional salmon of the same species and achieves its adult weight sooner, which reduces the amount of fish feed needed per salmon compared with the usual production cycle. According to Aquabounty, the GM salmon is intended for use in closed aquaculture facilities (i.e., the fish farm is a closed system).

2.2 CONTEXT: AQUACULTURE

Aquaculture has been around for centuries, but has grown rapidly over the past fifty years and has become more industrialised. In general, 'aquaculture' refers to the culture of fish, plants, crustaceans and shellfish, either in salt water (marine aquaculture) or fresh water (freshwater aquaculture). Various methods are used which are to varying degrees either closed or open systems. These may be intensive closed systems in which the input of food, discharge of waste materials and the temperature and composition of the water are all regulated, or open cages in the sea or a lake, or, for shellfish, a system of bottom culture or hanging culture. The discussion in this report is limited to fish culture and the farming of Atlantic salmon in particular.

2.2.1 FISH CONSUMPTION AND AQUACULTURE ARE GROWING RAPIDLY

The global population is growing and in developed countries consumption of animal protein is increasing. Fish is therefore also becoming a larger component in the diet of the average consumer. The worldwide consumption of fish and shellfish has risen from about 0.7 kg per person per year in 1970 to more than 7.8 kg in 2008.[65] In the Netherlands on average 3.6 kg fish was consumed per head of the population in 2010.[66]

The rising global population and the decline of fish stocks in the world's oceans and lakes means that an increasing proportion of the fish consumed is produced by aquaculture. In 2009 more than a third of all the fish produced for sale came from fish farms. The amount of fish and shellfish produced by aquaculture worldwide has risen from less than 1 million tonnes in 1950 to 52 million tonnes in 2008. Most of these cultured fish are freshwater fish (54.7%) and of all the freshwater fish produced for consumption, three-quarters (76.4%) are produced by aquaculture (*see Table 2*).

TABLE 2: PROPORTION OF GLOBAL PRODUCTION ATTRIBUTABLE TO AQUACULTURE BY SPECIES

(Source: FAO State of World Fisheries & Aquaculture 2010)

Species	% aquaculture	% global production
Freshwater fish (e.g., carp, tilapia, pangasius)	54.7	76.4
Shellfish (e.g., oysters, mussels)	24.9	64.1
Crustaceans (e.g., lobster, shrimp, crab)	9.5	46.4
Freshwater/marine fish (e.g., salmon, trout)	6.3	68.2
Marine fish (e.g., turbot, halibut, cod)	3.4	<5
Other (e.g., turtle, frog)	1.2	~58%

Almost 89% of the global production of cultured fish comes from Asia, the biggest producer being China, which accounts for 62% (*see Table 3*). The majority of cultured fish belong to the Cypriniformes order and are produced in Asian fish farms. In European countries the main types of cultured fish are salmon, trout, eels and catfish. In the Netherlands, mainly eel and catfish are farmed on a commercial scale.[67]

TABLE 3: TOP 10 AQUACULTURE PRODUCERS

(Source: FAO State of World Fisheries & Aquaculture 2010)

Country / year (production in tonnes x 1000)	1990	2000	2008
1. China	6,482	21,522	32,736
2. India	1,017	1,943	3,479
3. Vietnam	160	499	2,462
4. Indonesia	500	789	1,690
5. Thailand	292	738	1,374
6. Bangladesh	193	657	1,006
7. Norway	151	491	844
8. Chile	32	392	843
9. Philippines	380	394	741
10. Japan	804	763	732

2.2.2 IMPORTS AND EXPORTS OF FISH

China, Norway and Thailand are the biggest exporters of fish from fisheries and aquaculture combined. The biggest importers are Japan, the US and Europe. The EU accounts for 28% of the global fish imports. If imports and exports between EU countries are also included, the EU accounts for as much as 42% of the global trade in fish. The majority of the fish consumed in the Netherlands is also imported, a considerable proportion being white fish such as pangasius, tilapia and Nile perch from countries outside the EU. The Netherlands also imports and exports fish from and to other European countries. For example, shrimp and plaice are exported and salmon is imported.[67,68]

2.2.3 ATLANTIC SALMON AQUACULTURE

Salmon is one of the most popular fish species for consumption, particularly in Western countries. Various sorts of salmon are eaten (including salmon trout, Pacific Chinook salmon, Coho salmon and Red salmon), but the Atlantic salmon is the most popular. Like many other fish, most salmon for consumption is produced by aquaculture; aquaculture accounted for more than 99% of Atlantic salmon production in 2009 (*see Table 4*).

TABLE 4: WILD VERSUS CULTURED ATLANTIC SALMON

(Source: FAO Fisheries and Aquaculture Department, Species Fact Sheets 2010)[69]

	Tonnes	%
Wild salmon (e.g., Scotland, Ireland, Alaska)	2,369	0.16%
Aquaculture	1,440,725	99.8%
Total	1,443,094	100 %

Norway (36.4%) and Chile (28%) are the biggest producers of farmed salmon. The Atlantic salmon is not native to Chile, but is cultivated there on a large scale. Salmon is cultivated in various European countries (18.9%) and in Asia (7.9%) and the US (7.4%).[65] Most of the salmon imported into the Netherlands and many other European countries comes from Norway.

2.2.4 PROBLEMS IN AQUACULTURE

The aquaculture industry has grown rapidly during the past fifty years, almost three times as fast as the increase in the production of meat during the same period.[65] This reflects the fact that aquaculture is quite a young industry, which also brings its own problems. The main problems are discussed in this section, which focuses on the problems in the culture of salmon, and the Atlantic salmon in particular.

Fish feed

Many popular farmed fish species produced in aquaculture are carnivores, which makes it necessary to include fish in the feed. About a third of the global fish catch is used in the production of fishmeal. To produce 1 tonne of salmon, 3.3 tonnes of sand eels and sprat have to be processed into fishmeal. For other fish species, such as pangasius, the ratio of fish to fishmeal is one to one. Some fish, like tilapia, eat only vegetable food,

while others, like barramundi, have a mixed diet. The fish feed sector is developing alternative feed for carnivorous fish that consists partly or even entirely of vegetable matter.[70] A mixed diet can also be fed to cultured salmon.

Nutrient surplus

In open and semi-closed culture systems (such as fjords that are separated from the open waters by nets) wastes such as nitrogen and phosphate from the fish excrement and feed remains are a growing environmental problem.[71] In closed culture systems it is possible to filter and purify the water for reuse. In Norway, the open aquaculture systems (mainly for salmon and cod farming) are the largest source of phosphate emissions and the second largest source of nitrate emissions.[72] A widely used open culture system in Norway involves the use of sea cages, which are either square or round (10 to 30 metres across) and can contain up to 90,000 salmon.[73] Some of the waste from these culture systems is flushed out into the open sea, but the remainder pollutes the production area.

Diseases

Cultured fish are vulnerable to fish diseases such as viruses (e.g., infectious salmon anemia virus, ISA) and parasites (e.g., *Caligus rogercresseyi* and *Gyrodactylus salaries*). Because fish farms contain large numbers of fish in a small volume of water, these diseases can easily spread and cause considerable damage to the fish population. Between 2005 and 2010 an outbreak of ISA caused the loss of three-quarters of the salmon production in Chile (from 400,000 tonnes to 100,000 tonnes). To control these diseases various antibiotics, organophosphates and insecticides are added to the fish feed or to the water in the culture system. The use of pesticides in particular can have a negative impact on other organisms in the ecosystem.[74,75] Fish farms can also be a source of infection and present a threat to wild fish populations.

Escape

A 2007 study in Norway revealed that between 9% and 34% of the salmon caught in the wild had escaped from fish farms. It is estimated on the basis of voluntary reports that hundreds of thousands of cultured salmon escape each year (*see Table 5*).[76]

TABLE 5: NUMBER OF REPORTED ESCAPED CULTURED SALMON IN NORWAY

(Source: The Directorate of Fisheries, Norway)[77]

Year	2000	2001	2002	2003	2004	2005	2006	2007
Number	351,000	368,000	730,000	550,000	563,000	722,000	911,000	618,000

The escape of salmon from fish farms can have various ecological consequences, including the transmission of diseases to wild salmon and deterioration in the fitness of the wild population. Research indicates that cultured fish have fewer biological abilities (e.g., the ability to return from the sea to the river) and has shown that wild salmon and cultured salmon interbreed, which in time can reduce the viability of the wild species.[78,79] A third of all salmon production takes place in regions where salmon do not naturally occur (such as Chile). Escaped salmon have been found in these areas, but no cases are known of escaped salmon that have become established and reproduced there.

2.3 CASE 1: THE AQUADVANTAGE® SALMON

Aquabounty started to develop a fast-growing transgenic salmon in the early 1990s and was successful in 1995. The authorisation procedure for placing this salmon on the American market has been running for more than fifteen years and there is still no end date in sight.

2.3.1 TECHNICAL DETAILS

The AquAdvantage® salmon contains a growth hormone from the Pacific Chinook salmon (*Oncorhynchus tshawytscha*) and a promoter gene from the ocean pout (*Zoarces americanus*). The Pacific Chinook salmon belongs to the genus *Oncorhynchus*, whereas the Atlantic salmon belongs to the genus *Salmo*. These species cannot naturally interbreed. The addition of these genes makes the GM salmon achieve its final weight in 18 months, as opposed to 3 years, which means that 10% to 30% less feed is needed than for conventional cultured salmon. Aquabounty claims that the salmon is biologically contained because only triploid female fish will be put on the market.

Production of reproductively sterile fish (triploids)

Triploid fish have three sets of chromosomes (3n) in their cells instead of two. Triploidy can be induced in fish by thermal shocks, hydrostatic pressure or chemical shocks. The technique is based on the prevention of the second meiotic division in fish eggs shortly after fertilisation. Triploid fish have two sets of chromosomes from the mother (2n) and one set of chromosomes from the father (1n). The extra copy of genetic material disrupts the gametogenesis and the formation of sex organs to an extent that makes the fish almost completely sterile.

Producing triploid fish has two important consequences. First, the fish are sterile and cannot reproduce with wild salmon of the same species if they escape. Second, triploid

fish are sterile because they do not become fully mature. This means that triploid fish can continue to grow for longer because they expend less energy in becoming sexually mature, whereas the weight and quality of the flesh of normal fish decline as they become sexually mature.[80] The pressure shock method of inducing triploidy is more than 99% effective, which means that a small proportion of the salmon arising from the treated fish eggs are heterozygous diploids and thus fertile. The production cycle of Aquabounty's GM salmon is illustrated in Figure 1. A review of the literature shows that triploid fish are not always 100% sterile and there are reported cases of triploid fish that very irregularly produce eggs or sperm.[81] The chance of this occurring is higher among male fish than female fish.

2.3.2 STATUS OF MARKETING AUTHORISATION

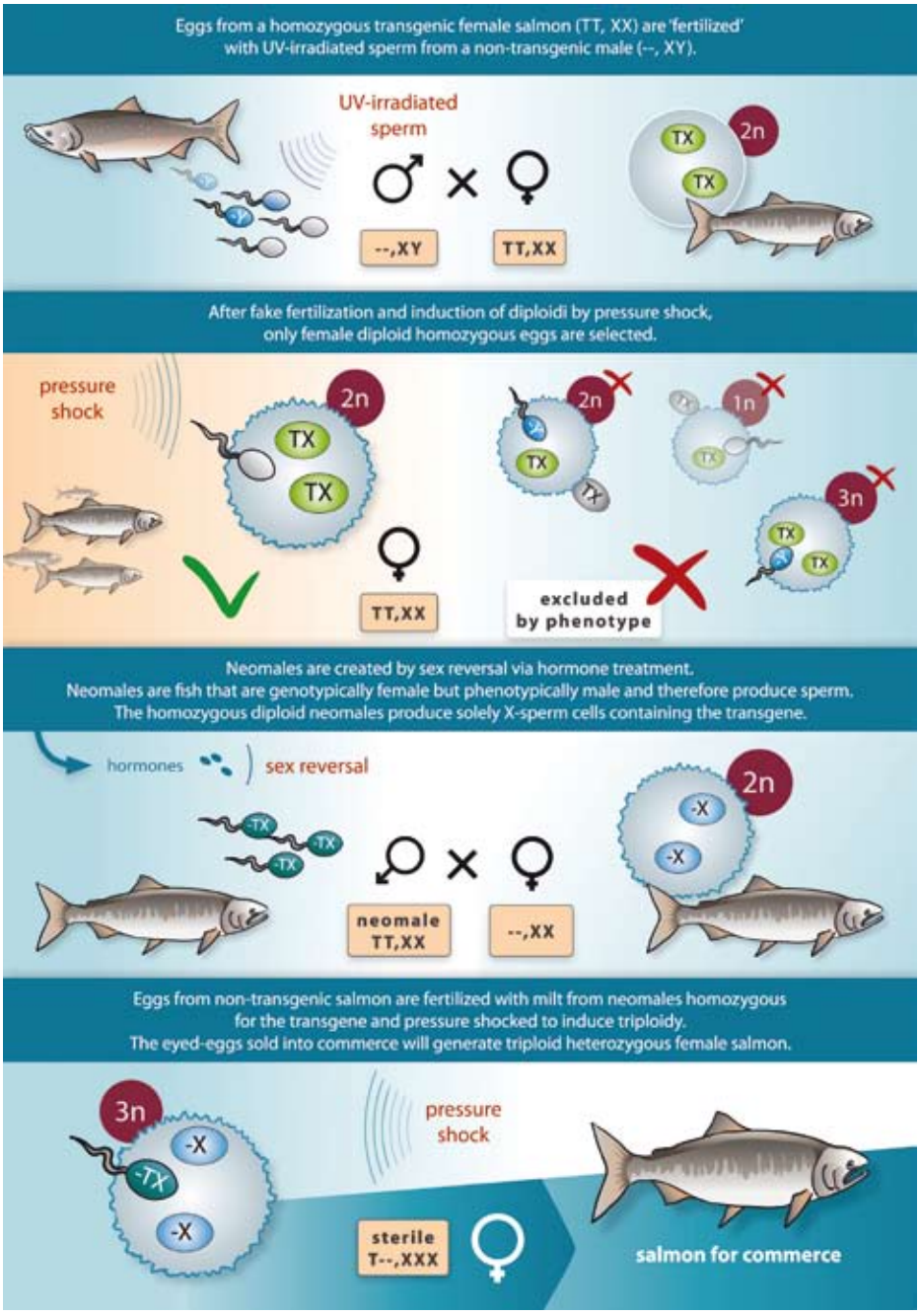
The marketing authorisation procedure for the fast-growing salmon in the US started in 2009, although the application was submitted fifteen years earlier. The fish production company Aquabounty submitted an application for the commercial cultivation of transgenic salmon with an increased growth rate in November 1996. The application is being assessed in the US by the Centre for Veterinary Medicine of the Food and Drug Administration (FDA) under the Food, Drugs and Cosmetics Act. The reasoning for including transgenic fish and animals in this law is that a transgene or newly produced protein can influence the structure and function of the recipient animal in the same way as pharmaceutical products.

Under the FDA's assessment regime, the GM salmon is being assessed for 1) the safety of the recombinant DNA construct for the animal, 2) the food safety of products obtained from the animal, 3) its environmental impact, and 4) its effectiveness and the evaluation claim by the applicant. During the assessment process various documents were made public and citizens and stakeholders have had several opportunities to make representations.[82,83] A separate hearing was organised on the possibilities for labelling products from the GM salmon. In 2010 the FDA found the salmon to be safe for consumption, but a decision on marketing authorisation has yet to be made. After the hearing the FDA stated that it had insufficient information on which to base a decision. One of the options is to carry out a full impact assessment of the salmon, which would cover not only the environmental and food safety aspects but also the social and economic impacts.[84,85]

Aquabounty intends to produce the salmon eggs in a facility on Prince Edward Island in Canada. The eggs would then be transported to closed culture systems in Panama to grow into mature GM salmon. They would then be imported as food into the US, after a permit had been granted. For the production of the salmon eggs a permit is needed from the Canadian authorities. The current position regarding this authorisation is not known.[86,87]

FIGURE 1: PRODUCTION MODEL FOR AQUADVANTAGE® SALMON

Illustration based on: FDA (2010) Environmental Assessment of the AquAdvantage® salmon)



Should the salmon be authorised for market introduction under the current procedure, its production will be subject to certain restrictions. The salmon will only be allowed to be produced according to the proposed production plan, which means producing the salmon eggs in Canada and transporting them to Panama to be cultured in FDA controlled facilities. It is unlikely that the salmon will be labelled as GM products in the US. In response to public objections, the FDA has stated that this would be difficult to do under the current legislation, because the salmon does not actually possess new traits and only grows at a faster rate.

The chance that the salmon will also be put on the European market following introduction in the US is small, because Europe and the Netherlands import salmon almost exclusively from Norway and Scotland. As far as is known, most salmon fish farms in these countries are semi-closed aquaculture systems, and so it is unlikely that they will switch to closed culture systems to farm the GM salmon. Nevertheless, an application for an import licence cannot be ruled out. If such an application were made, an authorisation procedure for the import of GMOs under EU Regulation 1829/2003/EC would have to be followed in which the environmental and food safety risks would be assessed. Moreover, the Novel Food Regulation would also apply to the GM salmon and its products.

2.3.3 ENVIRONMENTAL RISKS

In response to the development of this GM fish, COGEM published an advisory report in 2003 titled 'Transgenic Salmon, a Safe Product?'[88] One of the conclusions of this report was that no generic risk assessment was possible for GM fish and that assessments can only be made on a case-by-case basis. The European Food Safety Authority (EFSA) recently had a specific study carried out into the risk analysis of GM fish.[55] This section describes a number of potential environmental risks associated with GM salmon.

The environmental risks of GM salmon arise mainly from the potential consequences of the fish entering the environment. In general, the risks are associated with the possible consequences for the natural salmon population, the ecosystem and other animals/predators in the ecosystem. If the GM salmon should escape, the immediate question is whether it could survive in the wild. For the longer term the question is whether the GM salmon could reproduce and establish a population in the wild.

An important point in the risk assessment is the fact that the triploid strategy to make the salmon sterile is not 100% effective and the possibility of a few diploid fertile (heterozygous) female salmon being produced cannot be ruled out. The applicant states that triploidy makes it extremely unlikely that the salmon are fertile, but does not give a full guarantee that the fish have no reproductive capabilities. If a GM salmon that is not completely sterile (the GM salmon intended for production are heterozygous

female triploid salmon) should escape and is able to reproduce with wild specimens or other escaped cultured salmon, there is a 50% chance that the transgene will be passed on to the progeny. The question is whether this transgene would persist in the population through further reproduction and what consequences this could have for the fitness of the population as a whole.

The last issue is what options are available for managing and containing these identified risks. The company has already included measures in the production process to limit the identified risks: the triploid strategy and creating a physical containment via the closed culture system on land in a region that does not provide a favourable environment for the salmon (unfavourable temperature and salt content of the water). These minimise the chance of the salmon escaping and any damaging consequences for the wild population.

2.4 ARGUMENTS AND CONSIDERATIONS

The discussion about the fast-growing GM salmon involves a wide assortment of arguments and considerations, from safety considerations to questions of principle and social and economic considerations. This section reviews these issues as they have been presented in the available literature and news reports. The arguments are not listed by order of importance but by specificity, without drawing any hard and fast divisions. This means that the considerations at the top of the list relate more specifically to the GM salmon, while those further down also relate to aquaculture and fish consumption in general.

Need and purpose

The global human population is growing and with it the demand for fish for consumption. The producer claims that the GM salmon grows faster than conventional fish of the same species and so more fish can be produced per unit time. The closed aquaculture system makes regional production possible, thus reducing the ecological footprint, and also reduces the pollution of coastal waters, which is a problem with sea cage aquaculture. The GM salmon therefore makes a contribution to more sustainable fish production, argues the producer.

Environmental risks

The main environmental risk associated with the GM salmon is the chance of fish escaping into the surrounding environment and the resulting consequences. The legislation currently in force in the US allows conditions to be attached to the approval of the GM salmon. These state that the GM salmon is intended only for use in land-based closed culture fish farms and not for introduction into the environment. Moreover, the salmon is to be cultured at an FDA approved facility and a new permit is required for culture of the fish at any other location. A possible complicating factor in the environmental risk

assessment in this case is that the production of the salmon involves activities in three countries: Canada (egg production), Panama (culture of the fish) and the US (import and consumption). The question is whether the national regulations in these countries are sufficiently compatible to ensure the enforcement of the FDA's conditions.

The physical and biological containment in the closed systems should minimise the likelihood of fish escaping into the wild. The chance of GM salmon escaping and reproducing in the wild is therefore many times smaller than if they were farmed in a conventional facility. The marketing authorisation for the GM salmon concerns only the triploid sterile female fish. As the triploid strategy is about 99% effective, there is still a chance that a GM salmon will be produced that can reproduce.

Food safety

The FDA has assessed whether consumption of the GM salmon or products of the salmon will have any direct or indirect human health effects. They examined a range of aspects, including the biological characteristics, composition, structure, allergenicity and toxicity of the GM salmon compared with conventional salmon of the same species. The composition of the GM salmon is different from conventional fish of the same species in that the cells of the salmon are triploid and contain an extra gene. On the basis of the information provided, the FDA determined that this has no consequences for food safety and stated that the salmon is as safe for consumption as the conventional variety. This also means that people who are allergic to conventional salmon will in all probability also be allergic to products of the GM salmon. About 3% of the American population is allergic to fish or shellfish.[89]

Freedom of choice

Producer and consumer choice are generally considered to be important. The ability to choose whether to accept or reject GMOs is particularly important in Europe.[90] In Europe the GM salmon would be subject to compulsory labelling. Some consumers in the US have also indicated that they want fish products labelled so that they can see whether the fish they buy is genetically modified or not. Under the international Cartagena Protocol, living GM animals must be identifiable during cross-border transportation, for example by means of labelling.

Cartagena Protocol

The Cartagena Protocol on Biosafety (or the Biosafety Protocol, BSP) is a legally binding protocol under the UN Convention of Biological Diversity. The Protocol aims to ensure human and environmental safety during the handling, transport and use of GMOs that may have adverse effects on the protection and sustainable use of biodiversity. The Protocol provides Parties that do not have biosafety legislation in place with a legal framework for biosafety.

The Protocol prescribes that before living GMOs intended for introduction into the environment (e.g. for field trials or commercial production) can be transported across international borders the exporter must inform the importing country about the proposed cross-border transport and must wait for consent from the importing country (this is called the 'advance informed agreement' procedure, or AIA procedure). The importing country may refuse the GMO transport on the basis of a risk assessment. The Cartagena Protocol contains a description of the risk assessment methodology and the procedures and time frames for the advance informed agreement. The Protocol established a Biosafety Clearing House. This holds the currently valid biosafety legislation and information about the competent authorities in the various countries that are responsible for drawing up and implementing these regulations. The risk assessments carried out in the various countries to inform decisions made under the Protocol must also be made available.

The Protocol also addresses several other issues, such as social and economic considerations and regulations governing cases in which the Protocol is not observed. The Protocol contains an article on liability and redress and a supplementary protocol on rules and procedures has since been drawn up, the Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety.

The Protocol came into force on 11 September 2003. Currently (per 13 December 2011) 162 countries are Parties to the Protocol. COGEM notes that a number of the major GMO producing countries have not signed the Protocol (such as the US) or have signed it but not yet ratified it (including Argentina and Canada).

Food production within national borders, however, is subject to different national regulations. According to the American law, the FDA can only impose a labelling obligation in cases involving the introduction of a demonstrably new trait compared with the conventional organism. According to the FDA, this is not the case with the GM salmon. The producer may voluntarily label products. If the GM salmon is not labelled in the US, this could lead to dissatisfaction among some consumers.

Confidence

A key aspect of the authorisation process for GMOs is trust and confidence in the assessment process: not only citizens, but also NGOs and other stakeholders, like the aquac-

ulture sector, must trust and have confidence in the government and the agencies that carry out the assessment. Lack of confidence is a recurring argument in the discussion about GMOs in both Europe and the US. During the procedure for the AquAdvantage® salmon the expertise of the FDA in carrying out risk assessments of GM fish was criticised from various quarters.[91] The fishery sector questioned the expertise within the FDA on the biology and function of the salmon in the ecosystem. The FDA's conclusion on the food safety aspects was also called into doubt by some stakeholders. A discussion arose about the interpretation of the data on the allergenicity of the salmon, specifically whether the GM salmon has higher concentrations of endogenous fish allergens than the wild Atlantic salmon. There is no agreement in the scientific and medical world on when an increase in endogenous allergens in food actually poses a public health risk.[92] In addition, there is widespread mistrust about the long-term effects of the GM salmon. Some consumers fear that unforeseen risks (e.g. in the area of food and environmental safety) will become manifest much later on when it will be almost impossible to reverse the consequences.

Social and economic aspects

The aquaculture and fishery sectors have expressed concern about the possible economic consequences of approving the GM salmon.[93] Introducing the GM salmon could affect both the production (supply side) and consumption (demand side) of salmon. Higher production levels and a lower cost price could depress the price of salmon, making it more difficult for conventional farmed fish to compete on price. In fact, for the last twenty years the state of Alaska has prohibited salmon farming on economic grounds to protect the fishing industry. A specific consideration in the case of the GM salmon, given the public sensitivity to genetic modification, are the possible consequences for the sector if some of the salmon escaped and succeeded in breeding in the wild. Should the transgene become established in the wild population, this could negatively affect demand for wild salmon. Stakeholders from the fishery and aquaculture industries have argued for the socio-economic effects to be taken into consideration in the assessment.[94]

Animal welfare and integrity

The fast-growing salmon itself does not benefit from its accelerated growth rate; this trait is designed purely to provide more fish for human consumption. From this it follows that the animal is being instrumentalised and it can be said that the integrity or intrinsic value of the salmon is being violated.[a] According to the submitted information, the salmon is the same as conventional fish of the same species in its behaviour, eating habits and susceptibility to disease. It has not been demonstrated that the salmon experiences physical

a The intrinsic value of animals refers to their 'inherent worth', in other words, that they are not only valuable as a means to achieving an objective, but also in themselves or for their own sake. From this it follows that animals do not just have instrumental value and so they may not be used or treated as a resource or thing without good reason.

harm as a result of its rapid growth. The fast-growing GM salmon has a shorter life than the conventional variety in aquaculture because it reaches its final weight sooner and is then harvested for consumption. From an animal rights perspective, this aspect can be seen as either a positive point (if the life of farmed salmon is considered to be one of suffering) or a negative point (if each reduction in the lifespan is seen as a deprivation).

An argument that applies to aquaculture in general is that the salmon cannot swim freely in their natural habitat or follow their natural instincts (such as the salmon's migration from river to sea and back). The GM salmon is intended for cultivation in land-based closed system fish farms and will grow up in an entirely artificial environment. In addition, several further animal welfare arguments can be made that are similar to those concerning intensive livestock farming: the fish in fish farms are packed together in large numbers and the high densities of the salmon in pond or cages can lead to damage to the fish (fins, mouth, tail) and more frequent and rapid spread of disease.

Human health

Eating oily fish with a high omega-3 fatty acid content, such as salmon, is generally considered to be healthy. These fish are mainly carnivorous. A fall in the price of the fish due to increased fish production, besides the financial benefit, can make it more attractive to consumers to buy this type of fish, which can indirectly deliver health benefits. Recommending the consumption of more fish can indirectly have an adverse effect on the ecosystem, because most fish with a high content of omega-3 fatty acids are carnivores and require fishmeal in their diet.[95]

Food security

The amount of fish available in the world's oceans and lakes is declining, while the global population, and therefore also fish consumption, is increasing. This is why increasing volumes of fish are being produced by aquaculture. As Atlantic salmon for consumption are now almost entirely produced in fish farms, the fast-growing GM salmon can help to boost fish production. However, it is questionable whether the development of GM salmon will help to improve food security. The GM salmon was developed fifteen years ago, and it is possible that in the meantime the production of cultured conventional salmon has been further optimised, eroding the potential growth advantage of the GM salmon.

Desirability

Various stakeholders, including NGOs and consumers, have reservations about authorising GM salmon for the market. Besides the issues mentioned above, these reservations are based to a large extent on the feeling that developing GM salmon is undesirable in principle. These objections may be based on religious grounds (playing God) or issues of principle (against the misuse of animals), or simply on a general feeling of unease.

An important consideration regarding the desirability of GM salmon is their role in stimulating or facilitating intensive fish farming. The debate about the AquAdvantage® salmon has prompted a wider discussion about fish farming and the mass production of fish.[96] While the majority of consumers think that intensive livestock farming is objectionable, price is one of the most important considerations in the choices consumers make about which product to buy. Although the number of vegetarians and flexitarians is steadily rising, many consumers are not prepared to reduce their consumption of meat or fish. There is therefore a discrepancy between the different desires of the consumer.

Alternatives

Another issue in the debate about GM and conventional salmon is the existence of other, possibly better alternatives, such as eating less fish, eating herbivorous fish species or eating fish substitutes (vegetarian or non-vegetarian). In addition, research is taking place into developing vegetable-based substitutes for fishmeal in the feed for carnivorous fish. This could have a positive effect on wild fish populations that are caught to produce fishmeal, because about a third of the total fish catch is not intended for human consumption, but is used to produce fishmeal. However, it would not help to reduce the overfishing of fish for consumption, because different species are used to produce animal feed. Moreover, the development of vegetarian fishmeal for carnivorous cultured fish itself raises the question of whether forcing carnivorous fish to eat a vegetarian diet to allow consumers to continue to eat fish can be justified.

3

GENETICALLY MODIFIED PIG

3.1 INTRODUCTION

Creating organisms to solve environmental problems caused by human activities, such as those resulting from industrial production, environmental accidents or disasters, is attracting increasing interest. An example is the use of GM microorganisms to remove certain pollutants from soils or drinking water. Organisms are also being developed to tackle environmental problems related to food production, such as eutrophication, depletion of natural resources and pollution of soil and water caused by the intensive livestock farming sector. An example of a GM animal developed to solve these problems is the Enviropig™.

The GM Enviropig™ has been under development since the 1990s. It is genetically modified to reduce the amount of phosphate in its faeces, thus making the pig less of a burden on the environment. In recent years this pig has regularly been in the news following submission of the first applications for commercialisation of the animal for use in the pig farming sector to the American Food and Drug Administration (FDA).[97]

3.2 CONTEXT: PIG FARMING

Pigs are farmed to produce meat for consumption. Pork is the most consumed meat in the world. The highest pork consumption per head of the population is in Hong Kong (67.5 kg per person per year), followed by Belarus (47.7 kg) and Europe (43 kg). The least amount of pork is eaten in African countries (on average 3 kg per person per year) and countries with largely Muslim populations.[98] The largest producer of pork is China, which had more than 477 million pigs in 2011, or more than 65% of the global pig population. Some way behind are the EU, with 150 million, and the US, with 64 million pigs. Table 6 lists the worldwide production of pork by country.

TABLE 6: WORLDWIDE PRODUCTION OF PORK (X 1000 TONNES) IN 2010

(Source: Product Board for Livestock and Meat)[99]

China	50,235
EU	20,650
USA	8,635
Brazil	2,644
Russia	2,921
Japan	2,547
Other	9,410
Total	**97,042**

3.2.1 PIG FARMING IS HIGHLY CONCENTRATED

The production of pork is highly concentrated in several countries and regions. Pork is traded internationally in considerable quantities. China is not only the biggest producer, but also the biggest consumer of pork, and so Chinese pork exports are not large and account for only about 4% of the global trade in pork. This meat is exported mainly to Hong Kong (55%) and Japan (20%). China imports pork mainly from the US (75%) and Canada (20%). The biggest importer of pork is Japan, followed by Russia and the US (*see Table 7*). For a long time the EU was the biggest exporter of pork, but has recently been overtaken by the US and Canada.

TABLE 7: GLOBAL IMPORTS AND EXPORTS OF PORK (2010)

(Source: Product Board for Livestock and Meat)

Global exports of pork (x 1000 tonnes)	2010	Global imports of pork (x 1000 tonnes)	2010
USA	1,866	Japan	1,179
Canada	1,447	Russia	852
EU	1,264	USA	713
Brazil	641	Mexico	487
Other	590	China	400
		South Korea	323
Total	**5,808**	**Total**	**3,954**

Pig farming in Europe and the Netherlands

The biggest producers of pork in Europe are Denmark, Germany, Spain, France, the Netherlands and Poland. Pig farming in Europe is concentrated in a number of regions with clusters of large intensive pig farms. About three-quarters of all pigs in Europe are reared by 1.5% of the pig farmers. Most of the smaller pig farms are found in the new EU member states.[100]

The Netherlands has about 9,000 pig farms and more than 12 million pigs.[101] Pig farms in the Netherlands qualify for the epithet 'mega farm' when they contain at least 2,500 pigs. In 2010 there were 133 pig farms in the Netherlands containing more than 5,000 pigs. Two-thirds of the pork produced in the Netherlands is exported to other EU countries.[102] Other exports go to Russia and Hong Kong.

3.2.2 CHARACTERISTICS OF PIG PRODUCTION

There are more than 100 breeds of domesticated pig (*Sus scrofa domesticus* or *Sus domesticus*), which are farmed primarily for meat production. These breeds are all descended from the wild boar (*Sus scrofa*) and can interbreed. Each country or region often has its own landrace (e.g., Norwegian, Finnish, French, German and American

landraces) which are cross-bred and reared in the country or region. Fattening pigs are therefore usually hybrids, the sows being selected for fertility and the number of piglets per litter, and the boars for growth, meatiness and feed conversion efficiency. Pig breeding occurs mainly higher up the production column, in the (top) pig breeding farms that work together on the breeding programme (as a breeding society or herdbook association). The multiplying farms buy animals from these (top) breeders in the form of sperm or boars and sows or hybrid sows. Almost all pig reproduction on farms is by artificial insemination and there is an international exchange of genetic material.

With the exception of China, the largest producers often keep their pigs in specialised production units. Pig farms for fattening pigs in China are still relatively small and dispersed throughout the country, but the number of this type of farm has declined rapidly in recent years (2008: 52%) in response to the rising demand for pork and the increasing industrialisation of production. In Western countries large pig production businesses are divided into separate multiplying farms and fattening pig farms or combined within a single farm divided up into specialised production units. In Europe, Denmark focuses mainly on multiplication, Spain mainly on meat production and the Netherlands on both.[100] Within the various production units the pigs are born, reared and fattened in the most efficient way possible, aided by well balanced feed and climate-controlled environments. Synchronisation of the production cycle by synchronising the estrus cycles of the sows and inducing parturition (*see Chapter 5*) is routinely practised. Pig farming in Europe has been under pressure in recent years from rising feed prices and because production in other countries is cheaper and subject to less exacting animal welfare regulations.[103]

3.2.3 PROBLEM AREAS IN THE PIG FARMING SECTOR

Besides the question of whether intensive pig farming is necessary or desirable, this production method involves animal welfare issues and environmental problems. Keeping large numbers of animals on a small area of land leads to manure surpluses and can cause odour nuisance. In addition, pig production makes an indirect contribution to the global phosphate problem and in some regions escaped pigs can cause considerable environmental damage.

Eutrophication

Keeping large number of animals on a relatively small area of land causes environmental problems. The animals produce more manure than the farms can spread on their land (or are permitted to by law) because the accumulation of large amounts of phosphate and nitrate from manure in the soil causes environmental impacts. In this report the focus is on the part played by phosphate in causing eutrophication.

In areas of intensive pig farming, the application of manure (or excessive quantities of manure) on agricultural land can lead to phosphate surpluses in the soil. The phosphate accumulates until the soil becomes saturated and then leaches with rainwater or irrigation water into rivers and surface waters. A high water phosphate concentration is an important condition for algal growth, which reduces the oxygen content of the water. This in turn can cause fish die-off and the water may become unsuitable for the abstraction of drinking water.

Phosphate from manure and fertilisers is responsible for almost two-thirds of the phosphate pollution in the world, with phosphate from chemical fertilisers making the greatest contribution. Other sources of phosphate pollution are sewerage, industry and waste processing companies. In the US only 20% to 50% of the pig farms have sufficient land on which to dispose of their manure. In China, livestock farming is responsible for 40% of the phosphate pollution.[104,105] Eutrophication is also a problem in the Netherlands, where the current manure and fertiliser policies cannot cope with the relatively large national herd on a small area of land because there is not enough land to accommodate the nutrients. Instead of being a valuable source of nutrients, manure has become a waste product that is very expensive to dispose of. In 2008 the Agricultural Economics Research Institute (LEI) predicted that the Netherlands would have a structural manure surplus from 2009.[106] From 2015 it is likely that there will only be enough capacity in the nation's agricultural land to accommodate 92% of the manure produced in the Netherlands, which means that it will not be possible to legally dispose of the remaining 8%.[107] Attempts are being made to find solutions to the manure surplus by changing the composition of animal feeds to reduce the phosphate content of manure and through different ways of disposing of or using the manure.

About 50% to 75% of the phosphate in maize and wheat grains and soybeans contained in animal feed exists in a form (phytate) that the animals cannot digest. Phytate, or phytic acid, is a carbohydrate in which phosphate groups are attached by covalent bonds, which makes them unavailable for digestion. This component of the feed is therefore discharged to the environment in the faeces in a concentrated form (about four times as concentrated because the proteins and other carbohydrates in the feed are taken up and digested). To counter this effect, phytase has been added to pig feed since the 1990s to break down the phytate and make it available for digestion. Most of this phytase is now produced in GM bacteria. Mineral phosphate is also added to the feed to stimulate faster and more efficient growth. Adding phytase, replacing proteins with synthetic amino acids and matching the diet better to the nutrient requirements of the pigs can reduce the nitrogen and phosphate content of the manure by up to 50%.[108] Reducing the phytase content of the feed, however, can cause diarrhoea or constipation in the pigs and can also affect their growth and disease susceptibility. This in turn means that higher doses of antibiotics are required, which is undesirable. Adding meat and bone meal as a protein component in animal feed can increase the amount of digestible phosphorus in the feed. However, since 2000 the use of meat and

bone meal in animal feed has been prohibited in the interests of food safety and to prevent the spread of diseases like BSE. There is also an anti-cannibalism ban: a prohibition on species-to-species feeding of meat and bone meal. Pig farmers are reluctant to adjust the composition of pig feed because this leads to problems with optimising the diet.

The introduction of the EU Nitrate Directive has limited the amount of manure that can be applied to the land, while transporting manure over long distances is not cost-effective because the costs outweigh the revenues. Moreover, farmers tend not to use manure from other farms and this practice is undesirable because it increases the risk of spreading diseases. Farmers also prefer to use chemical fertiliser instead of manure because it is easier to apply the right dosages of nutrients and the fertilisers are easier to handle. As chemical fertiliser also contains considerable quantities of phosphate (in mineral form) it makes a major contribution to the problem of eutrophication. Organic farming systems use mainly manure as a fertiliser. The possibilities for using manure as biomass are being studied, but so far this causes other environmental problems because it cannot be burnt efficiently or in an environmentally acceptable manner.

Animal welfare

Intensive pig farming is a typical example of a highly industrialised form of food production. In mega pig farms large number of pigs are kept in small areas efficiently divided up into production units. This production method can be detrimental to animal welfare. A common problem, for example, is the pigs biting each other's tails through boredom. To prevent sows smothering their piglets they are kept in farrowing pens, which are very small pens with crates that prevent the sow from moving, but allow the piglets to move about. This also has animal welfare issues. In the pig breeding sector increased piglet death has been observed in some breeding lines as a result of continued selection for certain traits.

Changes are being implemented in Europe and regulations have been drawn up to improve animal welfare in the pig farming sector. Over the years additional and more stringent rules have been drawn up in both the EU and elsewhere on the conditions under which pigs are held, including the room they have to move about. For example, in the UK and in various EU member states and in the US, the use of very small farrowing pens is now prohibited or is being phased out.[109,110] In addition, a new European treaty prohibiting unanaesthatised castration came into force in 2012.[111] This practice was banned in the Netherlands some time ago.

Escape of domesticated pigs

All domesticated pigs (*Sus scrofa. domesticus* or *Sus domesticus*) are descended from the wild boar (*Sus scrofa*) and can still breed with these wild pigs. Wild boar were originally native to North and Central Europe, North Africa and Asia. Pigs were introduced into other parts of Asia, Australia, the US, Canada and South America for hunting and food

production. Domesticated pigs regularly escape in both Europe and America and can establish themselves in the wild and breed with wild pigs. The feral populations damage trees and other vegetation, eat crops and are a danger to ground birds and their nests. When foraging they sometimes churn up large areas of land. They can also spread diseases to wild boar. Populations of feral pigs cause financial and other damage and in some parts of the world (US, New Zealand) are considered to be an invasive species.[112]

Phosphate shortage

The agricultural sector is indirectly affected by another problem: the impending of a global phosphate shortage. Phosphate is key to the growth of plants and animals because it is essential for the energy metabolism in cells and the construction of bones, membranes and genetic material (DNA and RNA). Mineral phosphate is therefore added to animal feed and chemical fertilisers. China accounts for 30% of phosphate consumption via chemical fertiliser, followed by India (15%), the US (11%) and the EU-15[b] (7%).

Soils naturally contain little phosphate, which limits plant growth. Since the industrial revolution the greater ease with which phosphate-containing fertilisers can be added to soils in accurate doses has led to an enormous increase in food production. During this period chemical fertilisers have become an increasingly important source of phosphate as a substitute for animal manure. In Western countries chemical fertilisers are applied in large quantities (about 25 kg/ha per year compared with 2 kg/ha per year in Africa) and their use is also growing in non-Western countries, where incomes are rising and food consumption patterns are changing. Phosphate is also added to animal feed and is used in industrial processes (11–12%). However, global reserves of phosphate are limited and concentrated in just a few countries or areas.[113] Most of the world's phosphate reserves are in Mexico, the Western Sahara and China. Small amounts are found in the US, South Africa and Jordan.

Once phosphate is mined and processed into chemical fertiliser or animal feed it is very hard to recover. More than 80% of mined phosphate is eventually lost to the environment (largely via food production) in the form of fertiliser and other waste streams. Fertiliser phosphate becomes fixed in the soil where it is no longer directly available to plants. Overfertilisation is common in agricultural practice and six times as much phosphate is used in agriculture than is taken up by the plant and eventually consumed by people via the food that is produced. Much of this phosphate is lost through erosion (by wind and water) and is eventually deposited in the sediments of rivers and lakes. The natural recycling of phosphate is a geochemical process that can take millions of years and takes place via volcanic activity, sea level rise and tectonic shift. No efficient method for recovering phosphate has yet been discovered.

b EU15: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, United Kingdom.

The EU is completely dependent on phosphate imports because it does not have any reserves of its own. These imports are in the form of animal feed and chemical fertiliser. The EU imports 10% of the global production of chemical fertiliser. Global demand for phosphate is rising and the easily mined reserves are expected to be exhausted within fifty to ninety years. The price of mineral phosphate has risen sharply in recent years. Work is underway to develop methods for closing the phosphate cycle, such as reducing industrial use (replacing phosphate in detergents) and domestic use (reducing meat consumption and food wastage), and through waste processing (reuse of animal manure, use of abattoir waste as a phosphate source and better wastewater treatment).

3.3 CASE 2: THE ENVIROPIG™

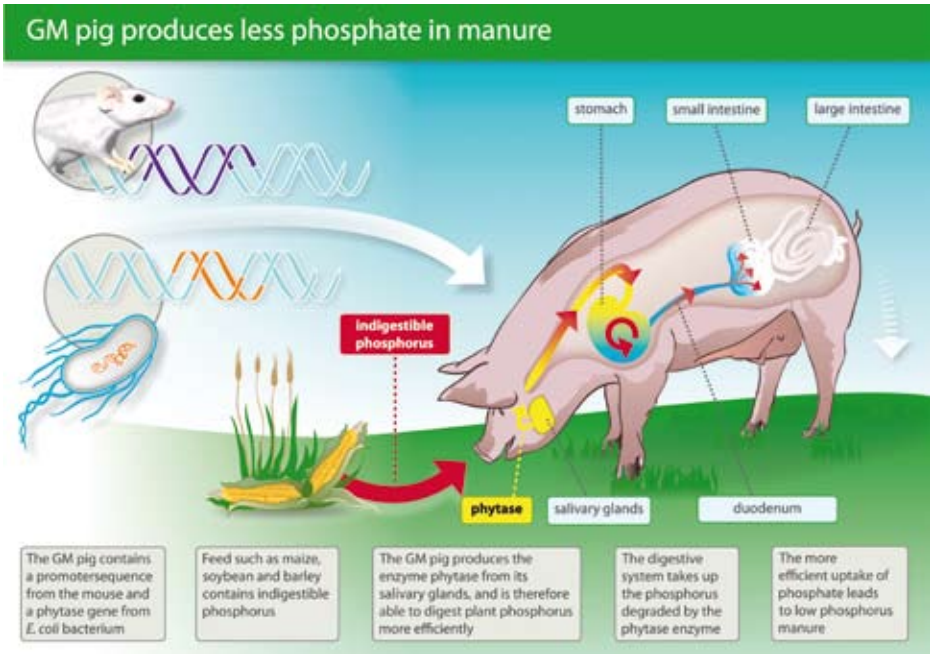
The Enviropig™ is a GM Yorkshire pig developed at the University of Guelph in Canada.[114] The pig contains a phytase gene which makes it better able to utilise the phosphate in feed. This means that less phosphate is needed in the feed and that the pigs excrete less phosphate in their faeces, which reduces the environmental impact of pig production. This is illustrated in Figure 2.

3.3.1 TECHNICAL DETAILS

The Enviropig™ contains a promoter gene sequence from the mouse and a phytase gene from the bacterium *Escherichia coli* inserted into the pig genome by pronuclear microinjection.[115] This gene makes the Enviropig™ produce phytase, an enzyme secreted in the salivary gland that can break down phytic acid, while the promoter ensures that phytase is continually produced in the salivary gland of the GM pig. The enzyme in the saliva is mixed with the feed in the pig's mouth, but is most active in the acidic environment of the stomach (pH 2.0 to 5.5 during food consumption) where it breaks down the phytate molecules in the grain component of the feed. The released phosphate molecules are then absorbed in the small intestine, where the phytase enzyme is broken down and not excreted (*see Figure 2*).

FIGURE 2: THE ENVIROPIG™

(Illustration based on: University of Guelph)



Because the pig can absorb more phosphate, less is excreted in the faeces, which in turn reduces the environmental impacts of pig production, especially the water pollution component. The Enviropig™ excretes about 30% to 70% less phosphate in its faeces than non-genetically modified pigs (depending on age and diet). According to the researchers, the insertion of the gene does not alter any of the other characteristics of the pig, including its reproduction, and the gene is inherited in a stable manner by successive generations.

The Enviropig™ can also reduce the costs of pig feed because fewer additives (phytase, phosphate) are required. Phytase is a relatively cheap component of animal feed and is usually added in excess quantities, but phosphate is becoming increasingly expensive.

3.3.2 STATUS OF RESEARCH AND MARKETING AUTHORISATION

The Enviropig™ has been under development since the 1990s and has so far only been kept in research facilities. The table below summarises the history of the Enviropig™ (*see Table 8*).[116]

TABLE 8: DEVELOPMENT OF THE ENVIROPIG™
(Source: University of Guelph)

Year	Development of the Enviropig™
1995	Scientists at the University of Guelph devise the concept behind the pig
1996	A gene from Escherichia coli that codes for acid phosphatase, or phytase, was identified as a candidate for the production of endogenous phytase
1997–1998	Construction of the phytase transgene using the right promoter; funding obtained for the project
1999	Creation of the first phytase producing pig (Wayne), followed by Jacques, Gordy and Cassie and 30 more transgenic pigs with the same construct
2000	Patents applied for in China, the US and Canada
2001	Scientific publications on the expression of phytase in the salivary glands of mice and pigs
2003	Start of data collection for regulatory studies on the Cassie line
2006–2007	Patents awarded in China and the US
2007	Submission of data on food and environmental safety to FDA for authorisation of the Cassie line of Enviropig™ for human consumption and commercialisation in the US
2009	Start made with the application for authorisation of the Cassie line of Enviropig™ for human consumption and commercialisation in Canada and the US
2010	Environment Canada permits production permitted outside the contained research facility (but still separate from other animals)
2011	FDA audit of the facility, documentation and pigs at the University of Guelph Ninth generation pigs and cooperation with FDA, HC and CFIA on the procedure for authorisation for consumption

So far the Enviropig™ is being produced and kept in Canada, where the national regulations apply. Marketing authorisation has been applied for in the US.

In Canada various permits have been issued for the production and rearing of Enviropigs. Four sets of regulations and three government agencies are involved. The food safety aspects of the pig are assessed by Health Canada under the Novel Food Guidelines, environmental safety is assessed under the Canadian Environmental Protection Act by Environment Canada, the use of various parts of the pig in animal feed is assessed under the Feeds Act by the Canadian Food Inspection Agency (CFIA), and disposal of the manure from the pig is controlled under the Fertilizer Safety Act by the CFIA. In February 2010 the Canadian Ministry of the Environment stated that the Enviropig™ can be produced and reared outside the completely contained research facility, but separate from other pigs. Manure from the Enviropig™ has been determined to be non-toxic and may be applied to the land held by the University of Guelph, but it may not be categorised as a fertiliser. During the initial phase of the research an incident occurred in which several GM pigs were inadvertently processed into animal feed.

GM pigs accidentally enter food chain

In 2002 eleven Enviropig™ piglets that had died shortly after birth were inadvertently rendered and turned into animal feed. The piglets were part of the research programme being conducted at the University of Guelph into the development of a GM pig that is better able to digest phosphorus in grain, reducing the amount of phosphorus excreted in the faeces. The carcasses of the GM piglets were sent for rendering by mistake and added to 675 tonnes of poultry feed, which was sold to egg farms, turkey farms and chicken broiler farms. Products of the GM pig have not been approved for consumption. The Canadian food safety organisation initiated a recall action for the feed, but the animals that had been given the feed were not destroyed. The food inspectorate concluded that consumption of the chickens and turkeys posed no threat to human health.[117,118]

In 2007 the university submitted the first applications for commercial authorisation of the pig to the US FDA. Like the GM salmon, the application falls under the responsibility of the Centre for Veterinary Medicine of the FDA. The application documents are not publicly available. The assessment of the Enviropig™ includes consideration of the researchers' claims about the unique properties of the pig. Other aspects being investigated are the molecular characterisation of the genetic construct and the recipient animal, the phenotypic characteristics, the stability of the gene over generations, food, feed and environmental safety, and whether post-monitoring agreements are necessary.[119] No indications have been given about when or whether this authorisation will be given.[120]

Meanwhile, nine generations of the Enviropig™ have been produced, including both homozygote and heterozygote animals and both sows and boars. The pigs can be identified and traced by the presence of the phytase gene. In addition, they have a unique tattoo (UGEP of the University of Guelph) and are registered with CDN Livestock Records Corporation in Canada. Finally, the piglets have ear-marks with information that shows which litter the animal is from. As labelling of GM food from GM plants or animals is not compulsory in the US and Canada, authorisation of the GM pig for food production purposes would mean that the products would be traceable, but would not have to be labelled in the US and Canada. The University of Guelph and its sponsor Ontario Pork are reported to have been holding negotiations with China for some time on agreements about the sale and export of the Enviropig™.[121]

Various countries in Europe, including the Netherlands, are major players in the global production of pork, which is one of the reasons why eutrophication caused by the production of manure is a problem in Europe. If the Enviropig™ receives marketing authorisation in the US, it cannot be ruled out that European livestock farmers will also express interest in the pig. If this is the case, the GM pig will also have to go through the marketing authorisation procedures in Europe. Directive 2001/18/EC (release into the environment) and the Novel Food Regulation 258/97/EC will in any case apply. Any products from the GM pig would have to be labelled.

3.3.3 ENVIRONMENTAL RISKS

The main potential environmental risks of the Enviropig™ are the possible consequences of the animal escaping into the wild,[57] and specifically what the impact and consequences of the inserted gene would be. The GM pig is in principle better able to take up phosphate from grain feed and will therefore have a selective advantage. However, the diet of an escaped pig will probably be different and less balanced than the diet it receives on the farm. The composition of pig feed is designed for the production of a certain quality of meat, whereas pigs are naturally omnivorous. It is not known whether escaped domesticated pigs are adversely affected by a lack of phosphate, but it is known that that they are well able to survive and become established in the wild.

Many countries where domesticated pigs are reared have populations of wild boar and/or feral populations of domesticated pigs. Both can breed with domesticated pigs and hybrids are known.[122-124] The stable inheritance of the phytase gene makes it likely that an escaped Enviropig™ will in theory be able to transfer the introduced gene to other pig species. Depending on whether the escaped pig is homozygous or heterozygous for the phytase gene, either 50% or 100% of the progeny will have the gene. The key question, though, is whether the presence and spread of the phytase gene among pigs in the wild is possible and whether this is damaging and therefore poses an environmental risk.

3.4 ARGUMENTS AND CONSIDERATIONS

The discussion about the authorisation of the Enviropig™ involves a wide range of arguments and considerations, from questions of principle to social and economic considerations, relating both to the GM pig in particular and to intensive livestock farming and breeding in general. This section reviews these considerations. They are not listed in order of importance, but by specificity. The considerations at the top of the list relate more specifically to the Enviropig™, while those further down also relate to pig farming in general.

Need and purpose
The Enviropig™ can digest phytate in grain more effectively, which means that less phytase and less phosphate has to be added to the feed. As the pig can digest more phosphate, it excretes less of it in its faeces. This reduction in the environmental burden of the pig therefore helps to reduce the problem of eutrophication, while its more effective digestion of feed delivers a financial benefit to the farmer and helps to ease demand for mineral phosphate supplies.

Environmental risks
Domesticated pigs sometimes escape from pig farms. It is known that in some countries these pigs can survive and establish themselves in the wild and can breed with wild pigs. The environmental risks of such escapes generally involve the possible transmission of diseases and specifically in the case of the Enviropig™ the possible spread of the transgene. The question is what the consequences could be of the spread of the gene in the environment.

Social and economic aspects
Social and economic considerations include the efficiency of production: the Enviropig™ digests phosphate in feed more efficiently and needs fewer additives (phytase, phosphate) in its feed, which lowers costs. Farmers would save about 1.50 to 1.75 dollars per pig per year if they no longer had to add phytase to the feed. This represents a financial benefit for large farms with thousands of pigs.

Given the public resistance to GM animals, approval of the GM pig in the US could lead to loss of sales in other countries. In fact, Europe imports hardly any pork from Canada, which is the world's third largest pork exporter, primarily to the US and Japan.[125] The Japanese public in general is critical of GM food.[126]

Sustainability
With regard to sustainability, the Enviropig™ can help to reduce the eutrophication problem. In addition, the reduced need for phosphate in the feed contributes to more efficient use of the limited global phosphate reserves.

Freedom of choice

Producer and consumer choice are generally considered to be important. Opinion polls indicate that a majority of European consumers want products of GM animals and plants to be labelled. Several consumer organisations are actively lobbying for labelling of GMOs in food in the US and Canada, where, in contrast to Europe, the labelling of GM food is not compulsory. An inadvertent spread of the transgene in a population of domesticated pigs as a result of GM and conventional animals being kept together would compromise consumer choice, both in the US and Canada and in Europe.

Little is known about the preferences of producers for or against the Enviropig™. From the financial support given by Ontario Pork, Canada's biggest pork producer, it can be concluded that they take a favourable view of the development. Chinese producers are also reported to be interested.

Animal welfare

Given the nature of the genetic modification (addition of a phytase gene) it is not expected that the Enviropig™ itself will experience any negative consequences with regard to welfare and behaviour. According to the researchers, the addition of the gene has no influence on the reproduction of the GM pig. However, the Enviropig™ does appear to be the ultimate example of the instrumentalisation of animals as it is designed to be a solution to the problem of eutrophication which has arisen as a result of the increasing human consumption of meat. The demand for meat has led to large-scale production, which for economic reasons occurs increasingly in intensive livestock production systems. Introduction of the Enviropig™ could further encourage this trend or alleviate the need to look for alternative solutions.

Confidence

Little is known about the approval process for the Enviropig™. The application documentation is not public and it is not clear what the planned timetable is for marketing authorisation. A few organisations have stated that this lack of transparency does not instil much confidence in the procedure.[127] Several environmental and consumer organisations have commented that the FDA has not developed a specific risk assessment procedure for GM mammals and for this reason have little confidence in the assessment procedure.

Desirability

A consideration regarding the desirability in principle of GM pigs is the part they play in stimulating or facilitating intensive livestock farming. Protests have been made from various quarters against the commercialisation of the Enviropig™, which opponents have dubbed the 'Frankenstein pig'.[128,129] Besides the use of animals to help solve the problems caused by human actions, the objections are also based on the fear that introduction of the pig will facilitate development of the intensive livestock sector.

An indirect link is made with the consumption of (non-sustainable) soy in the animal feed.[130,131] Opponents point out that the pig itself is not the problem, but the intensive livestock farming system devised by humans. However, consumers also want sufficient quantities of cheap meat, including pork. The objections to intensive pig farming (which helps to keep the price of pork down) are therefore at odds with people's consumption patterns.

Alternatives

The reason for developing the GM pig is to cut back on additives in the feed and reduce the amount of phosphate in pig manure. Besides curbing the environmental burdens associated with pig farming, the GM pig will allow the sector to operate more efficiently. The debate about the Enviropig™ revolves largely around the possible alternatives, which can be divided into alternatives for specific uses of the Enviropig™ and alternatives for the wider problems associated with the pig farming sector in general.

With regard to the poor digestion of phytate by pigs, various other options are currently being investigated. The question is the extent to which genetic modification is more effective and efficient or more economic than adding phytase to animal feed. While the use of microbial phytase is not yet as highly efficient as the Enviropig™,[132] more powerful phytases are expected to come onto the market, which will allow reductions in the amount of phosphate added to the feed. Research has also shown that matching the composition of the feed more accurately to the needs of the pigs at various stages in their growth can raise the efficiency of food conversion.[132] An example is the use of grains with lower phytate contents. A disadvantage of these grains, though, is that they have a lower viability and lower seed weight.[133,134] Moreover, feed with a different composition, such as ingredients that contain more easily digestible phosphate, is often more expensive. Meat and bone meal can also be a source of more easily digestible phosphate, but this is banned in Europe because of the risk of spreading diseases, among other reasons. It is not clear exactly how many phosphate supplements are used and how much they cost.

Some of the alternatives under discussion are not specific alternatives to the GM pig, but to intensive pig farming in general. Many people consider intensive pig farming to be unacceptable in terms of animal welfare and the instrumentalisation of animals. An alternative is to reduce meat consumption and therefore the size of the pig population. Keeping fewer pigs per farm and a better distribution of pig farms within countries and regions can also deliver partial solutions to these problems. However, research has shown that animal welfare and health will in principle be no better or worse in large-scale farms than in smaller farms.[135] Moreover, in small countries like the Netherlands a wider distribution of pig farms would run up against space restrictions. It should be noted here that current intensive pig farming methods are a response to social and economic pressures and the question is which alternatives are realistic from this perspective. Consumers themselves are also a major factor in this regard.

4

GENETICALLY MODIFIED MOSQUITOES

4.1 INTRODUCTION

The introduction of GM insects offers new prospects for controlling pests and diseases. An important development in this respect is the research into transgenic mosquitoes. Research into the development of GM mosquitoes to combat vector-borne diseases like malaria and dengue fever has been ongoing since the 1990s. A genetic alteration to the mosquitoes ensures that they are unable to transmit diseases like malaria and dengue fever to humans. In 2005 COGEM produced a report on current progress with the development of transgenic mosquitoes,[136] concluding that further research into the safety and effectiveness of these methods was needed. Now, more than five years later, research into GM insects has moved on and field trials are underway in various countries to test the use of GM insects, including tests with GM mosquitoes to control the transmission of dengue fever.

4.2 CONTEXT: CONTROL OF DENGUE FEVER

Dengue fever, or breakbone fever, is a potentially lethal tropical viral infection trans*mitted by female mosquitoes (Aedes aegypti), which live in and around stagnant water (see Table 9*). Dengue fever is found in tropical and subtropical climates and is concentrated in urban and semi-urban areas. Favoured breeding grounds of the mosquito are urban areas where water is stored (households) or where waste water is not properly discharged and removed. Humans are the main dengue virus host, but the virus is also found in a few non-human primates.

TABLE 9: DENGUE FEVER VIRUS (DENV)

(Source: WHO fact sheet)

Virus	Genus: *Flavivirus* Family: *Flaviviridae* Positive single-stranded RNA genome Serotypes: DEN-1 to DEN-4
Vector	Aedes mosquitoes, primarily Aedes aegypti
Endemic	Africa, North and South America, Middle East, Southeast Asia and the Western Pacific
Emerging	United States, various Latin American countries, the Caribbean and parts of Europe
Annual infections	50 million infected 500,000 hospitalised 25,000 fatal
Mortality	Average 2.5% (up to 20% without treatment)
Symptoms	Flu-like symptoms (Dengue Fever, DF) Dengue Haemorrhagic Fever (DHF) Dengue Shock Syndrome (DSS)
Treatment	Antiviral drugs / rehydration
Vaccine	No

There are four serotypes that cause dengue fever (DEN-1 to DEN-4).[137] Although only 65% of the genomes of these serotypes are identical, they all cause similar symptoms.[138,139] Patients who recover from infection by one of the four serotypes are immune to this variant for a long time, but not to the other variants. Infections often become more severe after multiple infections with different serotypes. The symptoms of most dengue virus infections (80%) resemble flu and are therefore often not identified. In serious cases (5%) or when not treated in time, Dengue Haemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS) (<5%) may develop, from which the patient may die. As yet there is no vaccine for dengue fever.[140] The mortality rate is around 2.5%, but in areas where medical care is inadequate, this can rise to about 20%. The World Health Organization estimates that early detection and treatment can lower the fatality rate to below 1%.

4.2.1 DENGUE IS A GROWING GLOBAL HEALTH PROBLEM

The WHO has identified dengue as a growing international health problem. The number of cases of dengue increased thirty-fold from 1960 to 2010. Not only is the number of epidemics increasing, but the areas where the disease occurs are also expanding. In recent years the incidence of dengue in subtropical and temperate areas has risen, possibly as a result of the disease being spread by the international transport of goods and via passengers.[141]

About two-fifths of the global population (2.5 billion people) are at risk, most of them in developing countries. It is estimated that 50 million people are infected each year and that more than 22,000 of them die as a result. Many of these are children.[142] The social costs of infectious diseases such as dengue are usually expressed in monetary terms (US$) or years of life lost (disability-adjusted life years, DALYs). In endemic areas the social costs of dengue fever are around 1,300 DALYs per million inhabitants.[143] The worldwide economic costs of dengue fever are estimated to be about 5 billion dollars. These costs vary considerable from country to country because of the distribution and incidence of dengue epidemics and the size of the national economy.[144]

4.2.2 CONTROL OF DENGUE FEVER

As yet there is no vaccine to protect against dengue fever. Preventing mosquito bites is therefore the only effective prophylaxis, for example by wearing clothing that covers arms and legs and the use of insect repellents such as DEET.

Dengue vaccine

Work on developing a dengue vaccine has been ongoing for many years. Progress has been made in recent years, but no vaccine is yet available on the market. One of the obstacles is the existence of the four different serotypes, which share only 65% of their genomes. An optimal vaccine should provide immunity against all four types. Moreover, little is known about the interaction between the virus and the host immune system and there is no suitable animal model. Apart for a few non-human primates, dengue is only found in humans.[145] The most promising options appear to be living attenuated vaccines or the development of a vaccine via recombinant DNA technology. Two vaccines are now being tested in clinical trials, including a vaccine developed by Sanofi Pasteur. This company has developed a living tetravalent (against all four serotypes) attenuated recombinant chimeric vaccine based on the yellow fever vaccine. Phase III clinical trials with this vaccine began in October 2010.

The prevention and control of the dengue virus is geared primarily to controlling breeding habitats and identifying virus infections at an early stage. In contrast to malaria mosquitoes, *A. aegypti* is active mainly during the day, which means that the use of mosquito netting or insect repellents is not very effective. Various methods are used to control the mosquitoes, such as chemical and biological control and environmental management.

Chemical control

A widely used method for destroying mosquitoes infected with the dengue virus is to apply chemical insecticides. During the first half of the last century DDT and similar compounds were used, but the *A. aegypti* populations developed resistance to them. Other methods were then developed, two of which are still used. The first is applying larvicides to water storage containers.[146] These low toxicity insecticides are applied in tablet form to household water storage containers, preventing the mosquito larvae from developing. The other method is to kill the adult mosquitoes with chemical insecticides, which are applied in the form of thermal mists or ultra low volume (ULV) aerosols.

Environmental management

Environmental management is less costly and the most widely used method of controlling dengue, particularly in poorer areas. These methods attempt to prevent reproduction of the vector and reduce contacts between mosquitoes and people by changing the mosquito's behaviour and modifying the environment. Examples include covering emptying and cleaning domestic water storage containers, correct storage of materials to prevent standing water (e.g., used car tyres), the use of insect repellents such as DEET, and wearing long-sleeved clothes.

Biological control

Besides the use of chemicals, biological methods are also used to control the mosquitoes and larvae. The bacterium *Bacillus thuringiensis israelensis* (BTI) is used worldwide as a larvicide and organisms that eat the mosquitoes and larvae, such as larvae-eating fish and small crustaceans (copepods), are kept in water storage containers. The advantage of these methods is that they have no environmental impact and do not affect the rest of the ecosystem.

Sterile insect technique (SIT)

Another biological control technique is the sterile insect technique (SIT). This is a technique in which male insects are sterilised by irradiation and then released into the environment.[147] Because fertilisation by the sterile males does not lead to the production of progeny, the population size is reduced and thus also the occurrence of the disease. The advantage of SIT is that no harmful or toxic materials are released into the environment.

Sterile Insect Technique (SIT)

SIT was developed in 1950 by the American entomologists Bushland and Knipling. The technique was successfully used to exterminate the screw-worm fly (*Cochliomyia hominivorax*) from parts of North America. In the 1950s the larvae of this fly caused extensive damage (US$ 200 million per year) to the American meat and dairy industry. The first successful trials with SIT were carried out on Curaçao in 1954, followed by the US, Mexico and other regions in Central America. Between 1944 and 1994 more than 30 SIT releases of organisms have been made worldwide to combat pests and diseases.[148] The technique has been used in Mexico to control the fruit fly, in Japan to control the melon fly and in Africa to control the tsetse fly (which causes sleeping sickness). In 1992 Bushland and Knipling received the World Food Prize for their research. It is estimated that using SIT in large areas is cost competitive with conventional control techniques. The technique is still used in various countries, including the Netherlands where it is used to control the onion fly (*Delia antique*).[149] Besides these success stories, mistakes have also been made with SIT. The mass irradiation of insects has sometimes not been properly carried out and as a result large numbers of non-sterilised laboratory-reared insects have been released into the environment.[150]

Wolbachia bacterium

Various studies have recently been published on controlling dengue by infecting the vector with a bacterium that prevents transmission of the virus. Researchers have infected a mosquito population with the bacterium *Wolbachia pipientis*, a parasitic or symbiotic bacterium that occurs in insects and nematodes (60% of the insects can become infected). After infection with the bacterium, *Aedes* mosquitoes are no longer able to transmit the dengue virus.[151] When an infected male mates with an uninfected female the eggs are not able to develop (because of an abnormality called cytoplasmic incompatibility (CI)). When two infected mosquitoes mate, viable progeny do develop, but they are also infected with the bacterium and therefore pass it on, which means the *Wolbachia* bacterium quickly spreads through the mosquito population. Field trials with these infected mosquitoes have been held in Australia.[152] Little is yet known about the possible consequences for the ecosystem of actively introducing *Wolbachia* into the mosquito population. In Europe and the Netherlands, this application does not fall under any legislation and so an environmental risk assessment is not compulsory.

Biotechnological control

Besides chemical and biological control and environmental management, it is also possible to control dengue with GM insects. The insect is genetically modified either to make it unable to transmit the pathogen or to make it sterile. Work on developing GM insects to combat infectious diseases such as dengue fever and malaria, as well as using GM insects against agricultural pests such as the pink bollworm (a cotton pest), has been ongoing for some time.

4.2.3 PROBLEMS WITH CONTROLLING DENGUE

The disadvantages of chemical control are the development of resistance to the compounds used, possible environmental and health risks and the need for repeated applications. Insecticides are generally not species specific and can therefore disrupt ecosystem functioning because other organisms are also killed. The use of insecticides inside the home can be harmful to human health. Spraying with chemicals also has limited effect because the breeding places are sometimes difficult to target. Moreover, the costs of these chemicals for individual households can be considerable.[153] Diseases like dengue fever generally affect the poorer regions of the world where these compounds are not easy to obtain or are prohibitively expensive. The development of resistance has been observed in response to the use of insecticides and medicines.

Problems with the biological control of larvae and mosquitoes using predator species are mainly operational in nature. The organisms used are native to specific areas and their production and distribution involves high costs and logistical problems.

A disadvantage of SIT is that its effectiveness is temporary and limited to certain areas. In addition, it can be difficult to determine the correct dose of radiation. A high dose of irradiation can weaken the insects, making them less able to compete with the normal male insects and therefore less effective in suppressing the insect population, but if the radiation dose is too weak it will not sterilise the males.

4.3 CASE STUDY 3: TRANSGENIC INSECTS

The British biotechnology company Oxitec has developed GM mosquitoes to control the spread of the tropical viral infection dengue fever.[20]

4.3.1 TECHNICAL DETAILS

The company produces male mosquitoes with a genetic modification that prevents the larvae produced when they mate with 'wild' female mosquitoes (the carriers of the dengue virus) from developing into adult mosquitoes. The patented technology RIDL (Release of Insects carrying a Dominant Lethal genetic system) is based on the principle of biological containment and aims to reduce the natural population of a specific target insect. As described in the previous section, there are various strategies for controlling pest insects that involve reducing the size of the natural population or replacing the natural population. The effect of the strategy can be self-limiting and temporary, or can be self-sustaining.

Classification of pest control techniques

A number of different strategies for controlling certain infectious diseases have been discussed (SIT, RIDL and *Wolbachia*). These can be classified according to their effect on the population:

- **Population suppression: reducing the size of a mosquito population to suppress the transmission of a pathogen. The methods are inducing sterility, shortening the lifespan and reducing the size of the larval population. Example: RIDL.**
- **Population replacement: replacing the wild population with a less harmful type. Example: *Wolbachia.***

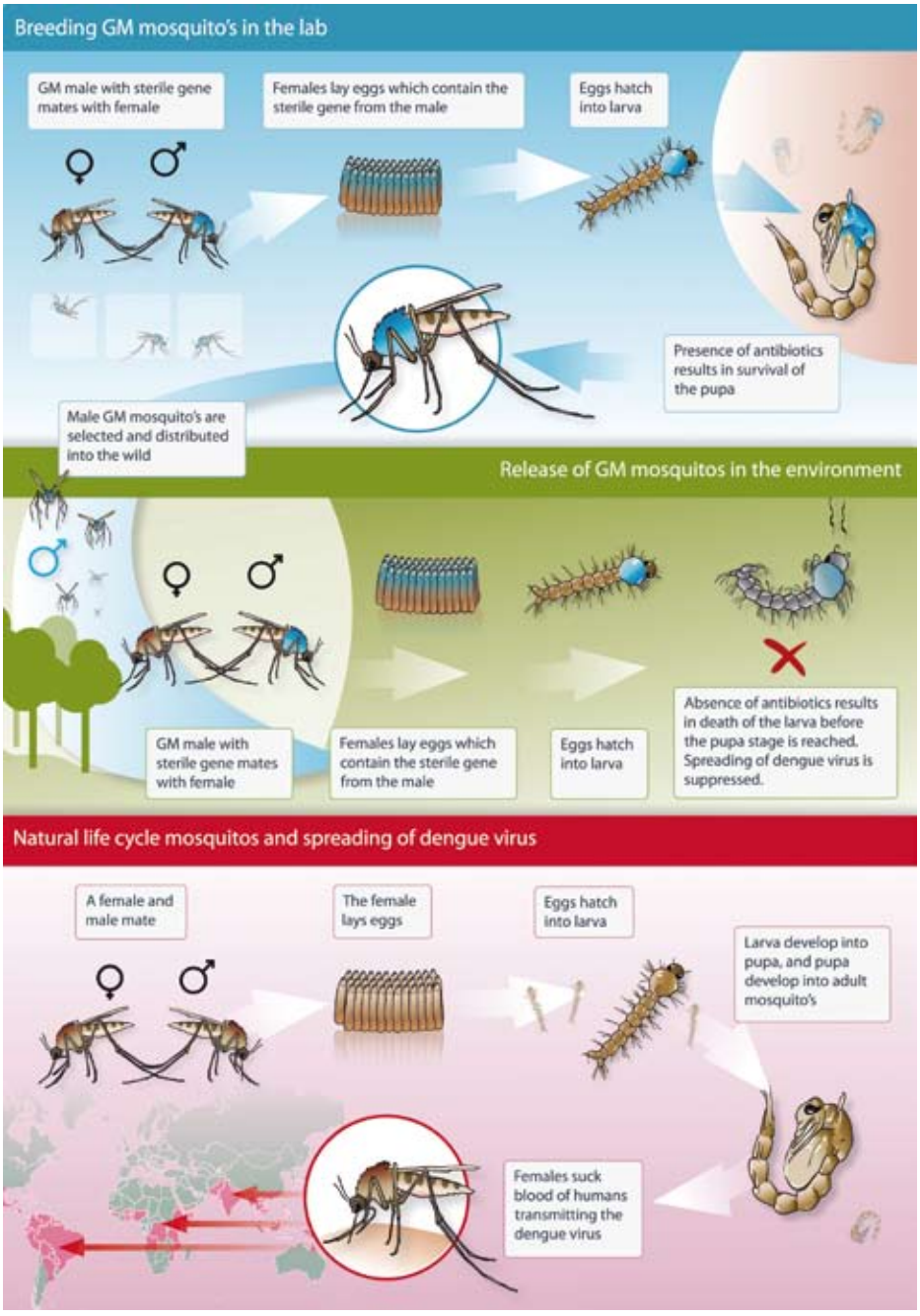
The methods can be self-limiting or self-sustaining:

- **Self-limiting: the method is temporary and comes to an end when no new insects are released into the environment. Examples are sterile insect methods (SIT or RIDL).**
- **Self-sustaining: the effect spreads throughout the population. Example: *Wolbachia.***

Oxitec has used its RIDL technology to develop a GM *A. aegypti* (OX513A) mosquito to control the spread of the dengue virus. The OX513A mosquito contains the RIDL conditional lethality and a marker gene (the DsRed fluorescent protein gene). Through the insertion of two gene constructs the mosquitoes can only survive in the presence of the antibiotic tetracycline. The marker genes are inserted to control and monitor the effectiveness of the mosquitoes.[20] The mosquitoes are 'reared' in the laboratory in the presence of tetracycline, after which only the homozygous males are released into the environment (*see Figure 3*). The male and female pupae are separated mechanically with an effectiveness of about ~99%. The male mosquitoes do not bite and so do not transmit any diseases. When the homozygous GM mosquitoes mate with wild females the resulting larvae cannot survive because of the absence of tetracycline. The RIDL technology is not 100% effective: the OX513A mosquitoes are not completely sterile and in the laboratory experiments a small proportion (3 till 5%) of the progeny of females that mate with GM males survived. The GM mosquitoes have a limited lifespan and so the effect dies out. The GM mosquitoes can be released periodically in an area to reduce the size of the mosquito population and thus curb the transmission of dengue fever. The advantage of the strategy of late or conditional lethality over the release of fully sterile mosquitoes is that the larvae do develop and therefore compete with normal larvae for food. According to the researchers, the RIDL mosquitoes are just as fit as members of the wild population. The numbers of GM mosquitoes that have to be introduced into the environment to exterminate a population is not known with precision. Computer models compiled by Oxitec indicate that a ratio of six RIDL mosquitoes to one wild female mosquito should be sufficient to exterminate a population of *A. aegypti* within a year. However, it is possible that GM mosquitoes will have to be released into the environment over longer periods or that complete extermination of the mosquitoes will not be possible in practice. Oxitec is currently establishing a production facility for GM eggs in the United Kingdom. The company has indicated that it aims to establish local production facilities in future to supply local mosquito release programmes.

FIGURE 3: PRODUCTION CYCLE OF STERILE GM MOSQUITO

(Illustration based on: thestar.com)



4.3.2 STATUS OF RESEARCH AND MARKETING AUTHORISATION

No GM insects have yet been approved for marketing. The GM pink bollworm created to control this cotton pest, also produced by Oxitec, is already being tested on a commercial basis. Oxitec's GM *A. aegypti* mosquito OX513A is in an advanced stage of development and laboratory tests have been carried out in various countries, including Brazil, India, France, Singapore, Malaysia, Thailand, the USA and Vietnam. Since 2009 field trials have been held on the Cayman Islands and in Malaysia and Brazil. Approval for field trials is given under local and national regulations, whereas the international transport and import of GM insects are governed by the Cartagena Protocol on Biosafety.

At the end of 2010 the field trials on the Cayman Islands led to public alarm and questions about the validity of the risk assessment and the public consultation procedure.[154] Oxitec released news about the field trials to the media when the initial results were known. The company stated that the number of mosquitoes in the test area had been reduced by more than 80% compared with the control area. According to Oxitec, this reduction is sufficient to exterminate the dengue virus.[155,156] In response to the public disquiet, the company announced that it had been issued with a local permit and that a risk assessment had been carried out by the Cayman Islands authorities. It also said that a public information campaign about the experiments had been held to inform the local residents and politicians.[157]

Field trials with the GM mosquitoes have also been held in Malaysia. For a month in the summer of 2010, the public were given the opportunity to make representation on the field trials (public consultation) and the Malaysian authorities organised meetings to inform the press. As a result of this consultation additional measures were imposed, including a requirement to organise a public forum to obtain consensus and approval for the trial from local residents in the area where the trials were to be held. Field trials with Oxitec's GM mosquito are currently being held in Brazil.

GMO regulations on the Cayman Islands

At the time the field trials were carried out, the Cayman Islands (a British Colony) had no adopted legislation on the use of GMOs, although the law is at an advanced stage of preparation. Moreover, the Cayman Islands are not covered by the international Cartagena Protocol on Biosafety or the Aarhus Convention on access to information, public participation in decision making and access to justice in environmental matters.[158] The United Kingdom has adopted and ratified these treaties, but this does not automatically apply to the Cayman Islands.[c] For the trials Oxitec applied for a permit from the agriculture ministry of the Cayman Islands and issued a notification of the international transport of a GMO (transport of the Oxitec mosquitoes in the UK to the Cayman Islands) under Regulation 1946/2003/EC. The Cayman Islands Mosquito Research and Control Unit (MRCU) was the implementing agency and carried out a risk assessment according to the guidelines of the draft biosafety law.

At the moment dengue does not occur in the Netherlands, but is regularly brought into the country by travellers or via international trade. There is a risk that the virus may be introduced into the warmer regions of Europe, however the good healthcare systems and access to antiviral drugs in most European countries make dengue a less urgent health risk. The likelihood that applications will be made for marketing authorisation for these mosquitoes in Europe does not therefore seem to be great. However, the use of other GM insects to control agricultural pests could be relevant. Oxitec is also using the RIDL technology to modify a number of pest insects, including the pink bollworm and the olive fly. Authorisation for placing on the market of GM insects would fall under Directive 2001/18/EC on release into the environment. The EFSA is currently drawing up detailed guidance for the assessment of GM insects.

4.3.3 ENVIRONMENTAL RISKS

The release of GM insects into the environment requires high safety standards because of the possible far-reaching or irreversible ecological or biodiversity consequences of these insects. Various biosafety agencies have prepared initial guidelines for the assessment of GM insects, including the EFSA.[56]

The environmental risk assessment focuses in particular on the consequences of releasing the GM mosquito into the environment for the ecosystem and existing mosquito

c The Aarhus Convention is a regional convention. Only countries which are members of the Economic Commission for Europe (Europe, including Asian countries that previously belonged to the USSR) and the US and Canada may be parties to the convention. The Cayman Islands are a United Kingdom colony and as such may be a party to the convention, but this is neither automatic nor compulsory. This same applies to the Cartagena Protocol.

populations. These include the impacts on the mosquito populations themselves, but also the impacts on predator species and the mosquitoes' role in the ecosystem. Any reduction in the size of an insect population can have an effect on other organisms that use the mosquitoes as a source of food. However, it is also possible that if a specific insect species disappears or its population size is significantly reduced, its function in the ecosystem can be taken over by other species. The assessment also examines worst case scenarios, especially on what the consequences would be if a non-sterile mosquito was able to reproduce and spread a transgene through the wild population.

In this case, the GM mosquitoes are self-limiting, which means that after they are released into the environment they have a limited lifespan. Because the mosquitoes are sterile and their progeny die within a short time due to the absence of tetracycline, the effect soon dies out. However, the RIDL method is not 100% effective. In laboratory experiments a small proportion (3–5% of the progeny of females that breed with GM males) still survived.[159] The researchers assert that this does not have a significant effect on the effectiveness of the RIDL technology.

4.4 ARGUMENTS AND CONSIDERATIONS

The introduction of GM insects to control vector-transmitted diseases brings with it a whole range of considerations and arguments, from ethical to social and economic considerations. This section reviews these considerations. They are not listed in order of importance, but by specificity, which means that the considerations at the top of the list relate specifically to GM mosquitoes, while those further down also relate to the control of infectious diseases in general.

Need and purpose

Dengue infections are a public health risk in large parts of the world. Children are particularly susceptible to the disease. A vaccine is not yet available and the conventional prevention and control methods are the use of insect repellents and environmental management. The spread of dengue can be curbed by releasing sterile GM mosquitoes into wild populations, a self-limiting method which makes it possible to contain any risks and make them more manageable. This technology is more specific and less environmentally harmful than other methods for controlling dengue, such as the use of chemical pesticides.

Environmental risks

The release of GM insects into the environment requires high safety standards because of the possible far-reaching or irreversible ecological or biodiversity consequences. Once the insects have been released into the environment it is not possible to recover them. In this case the strategy used is self-limiting, which means that if there is an

effect it will probably be temporary. The loss or decline of a population can in theory have consequences for the whole ecosystem.

Sustainability
Use of the GM mosquitoes is less environmentally harmful and more specific than the use of insect repellents, which target all insects.

Freedom of choice
The aim is to release the GM mosquitoes in areas where dengue is found. The public was consulted about the open field trials, which raises the question of how to respond to small groups of residents who object to the field trials. Once the mosquitoes have been released, local residents can have no further influence on whether the mosquitoes should be approved or not. A further question is the extent to which the use of GM insects is a government decision or whether individual 'informed consent' is most appropriate. The control of pests is usually a government matter (e.g., rats, cockroaches, pest insects) in view of the general public health interest. What is the appropriate response when groups of people (however small) have ethical or religious objections to the introduction of the GM mosquitoes?

Confidence
The lack of transparency and public consultation during the first field trial by Oxitec on the Cayman Islands met with criticism. Further, discussion arose about the biosafety and risk assessment of the field trial. According to opponents, the public consultations were not carried out with due care and those involved were not provided with objective information about the trial. For example, it was claimed that no explicit mention was made of the fact that GM mosquitoes were involved. Some people fear that unforeseen risks will only manifest themselves much later on, when it will be almost impossible to reverse the consequences. Another question was who could be held to account should the release of the GM mosquitoes into the environment lead to problems. This is particularly relevant in the case of the GM mosquitoes because once they are released into the environment the possibilities for controlling or managing them are limited.

Social and economic aspects
Effective control of vector-transmitted diseases such as dengue fever could have a positive effect on the quality of life and life expectancy of the population in countries where this disease occurs. However, the question of who is responsible for the costs of the technology raises the issue of the dependence of countries on the company in question. Oxitec has indicated that complete extermination of the mosquito population will probably not be possible and that the GM mosquitoes will have to be regularly released to suppress population numbers. How dependent will developing countries (where the disease mainly occurs) become on a single Western company? Will this be a more profound form of dependence than the current situation

in which developing countries are dependent on medicines produced by pharmaceutical companies?

Desirability

Consumers are generally critical of the use of genetic modification in plants and animals. This may be based on religious grounds (playing God) or issues of principle (against the misuse of animals), or simply on a general feeling of unease. However, medical and biomedical applications of genetic modification are generally considered to be an exception and are often viewed in a more positive light by the public.

Animal welfare

The GM mosquitoes are released into the environment, where they can reproduce during a brief period, but die early due to the absence of tetracycline. The larvae that hatch from eggs fertilised by GM mosquitoes die. Mosquitoes that transmit diseases are generally considered to be harmful and undesirable and the animal welfare of the mosquitoes has so far not been an item in the debate.

Alternatives

As described in this chapter, there are various options for controlling dengue of varying cost and effectiveness. The use of chemical pesticides can have adverse effects on the environment and public health, whereas environmental management is not always feasible because this requires behavioural change, and sometimes cultural changes. Other alternatives are the use of SIT and the introduction of the *Wolbachia* bacterium into the population. These techniques do not involve the use of genetic modification, but may provoke similar objections to those made against the GM mosquitoes. Although an environmental risk assessment is not required for these techniques, questions can be raised about their potential environmental risks. Another alternative would be the development of an effective and affordable vaccine. Various concepts have already been developed, but no products have yet come to market. Two vaccines are currently being tested in clinical studies, to be followed by the marketing authorisation procedures, which on average take about ten years to complete. The marketing authorisation of GM mosquitoes can also be expected to be a long process.

5

CLONED FARM ANIMALS

5.1 INTRODUCTION

The Biotechnology Trend Analysis 2009 mentions the cloning of animals, whether or not in combination with genetic modification, as an important development over the coming years.[160] Cloning does not involve genetic modification because no changes are made to the genetic material, but a genetic copy is made of the starting organism. The cloning of animals is therefore not covered by the European GMO regulations. Nevertheless, cloning technology meets with a similar response from the public. Moreover, cloning is regularly used in combination with genetic modification. For these reasons it is also discussed in this report.

Farm and other animals were first cloned as part of scientific experiments. Outside Europe animals are also cloned for other purposes, for example to maintain specific traits for breeding (breeding animals) or sport (racehorses).[161] Other uses are also mentioned in the literature, such as the cloning of endangered and extinct animal species, infertile animals and pets. The first successful animal clone, the sheep Dolly, was produced in 1996. Since then many species of animal have been successfully cloned (*see Table 10*).

TABLE 10: SUMMARY OF CLONED ANIMALS (NOT EXHAUSTIVE)

(Source: Biotechnology Trend Analysis 2009)

Sheep	**1996**	**Roslin Institute, Scotland**
Mouse	**1997**	**University of Hawaii, USA**
Cow	**1997**	**American Breeders Service, Wisconsin, USA**
Pig	**2000**	**PPL Therapeutics, Inc, Scotland**
Gaur (Indian bison)	**2001**	**Advanced Cell Technology, USA**
Cat	**2001**	**Texas A&M University, USA**
Mouflon	**2001**	**University of Teramo, Italy**
Rabbit	**2002**	**INRA, France**
Deer	**2003**	**Texas A&M University, USA**
Horse	**2003**	**Laboratory of Reproductive Technologies Cremona, Italy**
Rat	**2003**	**Genoway, USA**
Mule	**2003**	**University of Idaho, USA**
Fruit fly	**2004**	**University of Halifax, Canada**
Water buffalo	**2005**	**Guangxi University, China**
Dog	**2005**	**Seoul National University, Korea**
Goat	**2006**	**Royan Institute, Iran**
Rhesus monkey	**2007**	**Oregon National Primate Research Center, USA**
Wolf	**2007**	**Seoul National University, Korea**
Ferret	**2009**	**University of Iowa, USA & Jilin University, China**
Camel	**2009**	**Camel Reproduction Center, United Arab Emirates**
Coyote	**2011**	**Sooam Bioengineering Research Institute, South Korea**

5.2 CONTEXT: BREEDING AND SELECTION

In this report the focus is on the use of cloning in animal breeding and selection. The commercial breeding industry uses selective reproduction to maintain certain traits or to propagate them through the population. Over the years various organisations active in this area, such as herdbook associations, breeding societies, breed improvement organisations and pedigree societies, have entered into collaborative arrangements to obtain animals through selective breeding that are best suited for the purpose for which they are reared.

5.2.1 MODERN SELECTION METHODS

Various reproduction and selection methods are used in the Netherlands. The livestock industry in the Netherlands routinely uses several techniques, such as artificial insemination (AI) and semen collection, and, specifically in the pig breeding sector, estrus synchronisation and induced parturition (*see Table 11*).

The breeding of cows and pigs for milk and meat production is almost exclusively by AI.[162] AI is also used in the breeding of sheep, horses and chickens, but some reproduction takes place in the natural way. AI has become essential in turkey breeding because the male birds are so big and heavy that they would seriously harm the hens if allowed to mate naturally. Both AI and in vitro fertilisation (IVF) depend on semen collection from male animals. In the pig farming industry, in which large number of animals are often housed together, estrus synchronisation and induced parturition are used, for primarily commercial reasons. In estrus synchronisation the estrus cycles of groups of sows are synchronised; parturition induction means starting labour artificially by administering hormones. This allows sow farms to work with fully planned production systems.

Besides AI, an emerging technique is embryo transplantation (ET), in which egg cells from the best animals are harvested and implanted in surrogate animals after fertilisation. On average, cows produce four calves during their lives. Using ET the best cows can produce more progeny (up to fifty or sixty). Combining embryo selection and ET increases the chances that a certain cow will give birth to a bull calf. This technique is also used in breeding racehorses, which makes it possible to continue racing mares while breeding offspring from them by implanting embryos in surrogate mares. This technique is increasingly being used both in Europe and elsewhere. In 2009, 535,000 transplanted cow embryos were registered.[163] In the same year almost 750 cow embryos were imported into Europe for transplantation.[164] According to the official registers, in 2010 almost 115,000 cow embryos were transplanted in Europe (data from 21 countries). Most of these transplantations took place in France, followed by the Netherlands.[165,166]

TABLE 11: USE OF REPRODUCTION AND SELECTION TECHNIQUES IN THE NETHERLANDS
(Source: Raad voor Dieraangelegenheden (2010) Fokkerij & Voortplantingstechnieken [Animal Welfare Council report on Breeding and Reproductive Techniques])

Technique	Cow	Sheep / Goat	Pig	Chicken / Turkey	Horse
Reproduction					
Artificial insemination	+++	+	+++	+++	++
Embryo transplantation + IVF	+	X	+	-	-
Embryo transplantation + superovulation	++	X	+	-	+
Selection					
Cloning	**X**	**X**	**X**	**X**	**X**
Semen sexing	+	+	-	-	?
Marker assisted selection	++	+	++	++	+
Support					
Estrus synchronisation	+	+	+++	?	+
Parturition induction	+	+	+++	-	-
Ovum pick up (OPU)	+	?	+	-	+
Semen collection	+++	+	+++	+++	++
Electro-ejaculation	X	X	X	X	X

? unknown
- not used
X banned in the Netherlands
+ occasional
++ relatively frequent
+++ routine

5.2.2 ADVANTAGES OF BREEDING PROGRAMMES AND REPRODUCTION TECHNIQUES

Both conventional and modern breeding methods, or a combination of these, have over the years proved to be highly effective. This applies both to the smaller livestock farms, where breeding contributes to the maintenance of rare breeds, and to large livestock farms, where it facilitates efficient production of animal products. The amount of milk produced by dairy cows has increased considerably in recent years, while beef cattle are selected for muscle mass and chickens for the number of eggs they lay. But careful selection can also reduce susceptibility to certain diseases or genetic abnormalities and reduce undesirable traits, such as boar odour in pigs, minimising the need to castrate piglets.

The use of modern reproduction techniques has also made the breeding of farm animals and pets a more international business. For one thing, the use of AI and ET means that distance is no longer a factor when choosing a specific breeding animal, and these methods are widely used in Europe to exchange genetic material. This internationalisation of breeding practice between European countries and countries elsewhere in the world is less developed. About 2.5% of the bull sperm used in the EU comes from outside the EU, mainly from the US and Canada.

AI was developed in the first instance to control sexually transmitted diseases (STDs) in cattle. A further benefit is that the male animals can produce many more progeny, and continue to do so even after they die. AI has also stimulated the introduction of progeny testing in dairy cattle, which enables the breeding value of bulls to be estimated with considerable accuracy. Finally, AI prevents injury to animals during mating. An advantage of techniques like AI is that genetic information can be distributed throughout a population more quickly. A disadvantage is that it is limited to the genetic information from the father animal. The emergence of ET has also made it possible to obtain more progeny from valuable mother animals.

5.2.3 PROBLEMS OF BREEDING PROGRAMMES AND REPRODUCTION TECHNIQUES

As can be seen from the previous sections, reproduction techniques can make an important contribution to breeding programmes. However, breeding programmes and the reproduction techniques used in them can also have disadvantages. These may be long-term problems that appear over several generations or problems affecting the first generation offspring arising from the use of certain techniques. Generic problems include limited genetic diversity and the risk of inbreeding through the use of a limited number of parent animals, which may exacerbate certain physical deformities or susceptibility to disease within a population. These problems can sometimes be attributed to specific reproduction techniques. In 2009 the European Food Safety Authority

(EFSA) warned that ET can have negative consequences for fertility and inbreeding percentages.[167] The text box below contains some examples of health problems that have arisen as a result of breeding and selection. Breeding and selection can also have undesirable effects on animal behaviour and adaptation physiology, such as modern laying hens that are less broody, more weak piglets, and mortality due to overselection for litter size among pigs.

Examples of breeding related health effects

- **Long-term selection for high productivity among dairy cows has led to an increased risk of poor udder health, locomotion and fertility as side-effects of overselection for milk production traits.[168]**
- **85–90% of double-muscled cows can only be born by Caesarian section because they have been highly selected for muscle mass and build, but less for bone size.[169,170]**
- **Selection for the production of more piglets per litter and lean meat has led to a danger of higher piglet mortality and insufficient thermoregulation capacity.**
- **Overselection for rapid growth of broilers has led, among other effects, to more frequent occurrence of leg problems.[171]**

5.3 CASE STUDY 4: CLONES

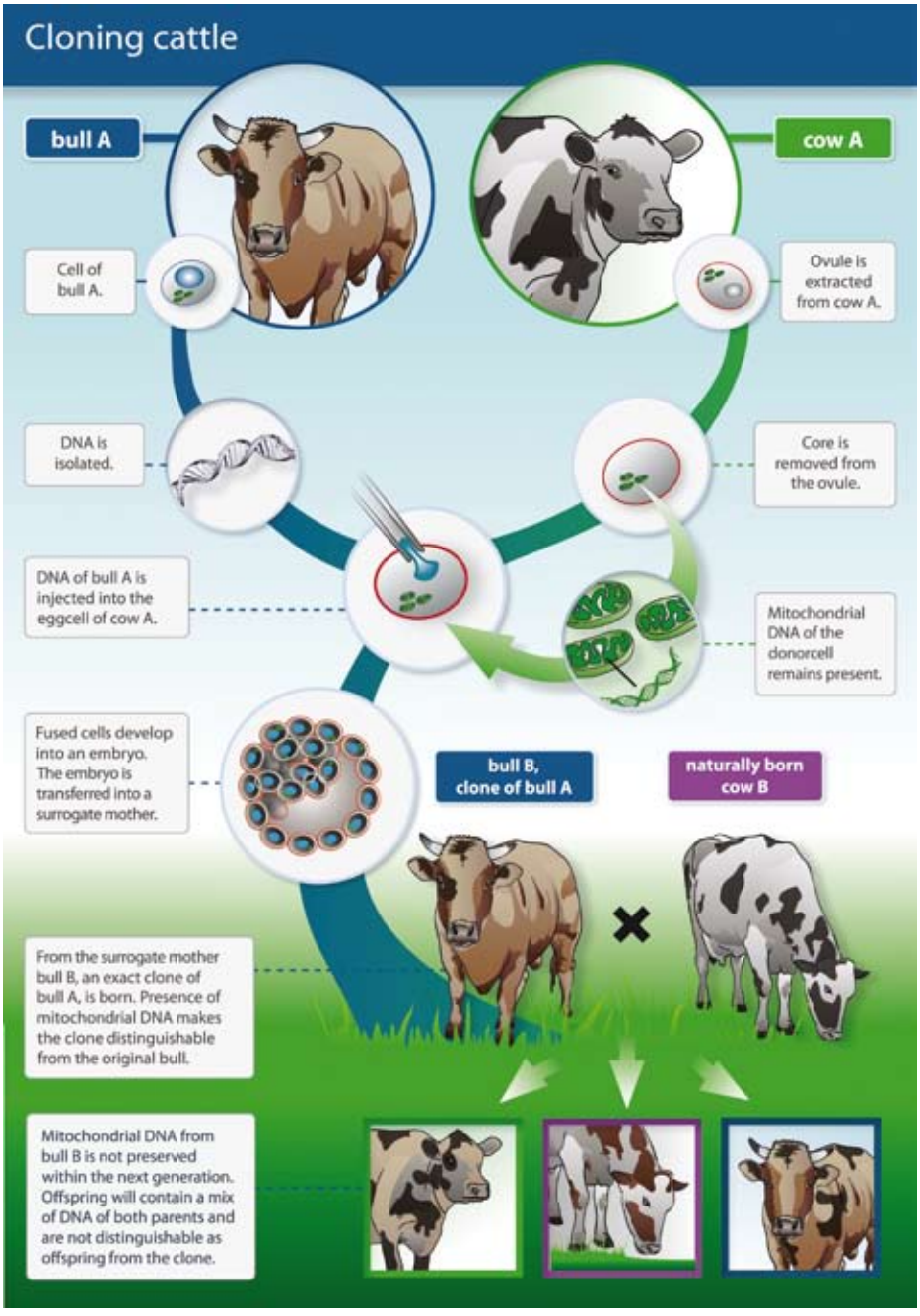
In recent years the practice of cloning animals for production purposes has become more common outside Europe. Other applications of cloning are also being investigated, such as restoring extinct animal species, preserving endangered species from extinction, cloning infertile breeding animals and cloning pets. In 2007 the EFSA estimated that there were several thousand cloned cows in the world and several hundred cloned pigs (*see Table 12*).

TABLE 12: ESTIMATED NUMBER OF CLONES PER REGION (2007)

(Source: EFSA opinion on cloned animals (2008))[172]

Country	animal	number
EU	Cow	100
	Pig	<100
USA	Cow	570
	Pig	10
worldwide	Cow	<4,000
	Pig	< 500

FIGURE 4: THE STANDARD SCNT CLONING PROCEDURE



5.3.1 THE TECHNIQUE

Cloning can be defined as the creation of genetically identical progeny from a single parent animal. The cloning of plants is widely practised in the form of cuttings and grafts. Cloning techniques are also applied to animals, including mammals. The first technique to be used was embryo division, but increasingly cloning is achieved by transplanting cell nuclei, or somatic cell nuclear transfer (SCNT).

The standard SCNT procedure consists of isolating the nuclear material from the cell of an animal to be cloned, removing the nucleus from an isolated egg cell from another animal, inserting the donor nucleus (or cell) into this empty cell and activating the reconstructed embryo, followed by culture. Finally, the embryo is transplanted into the uterus of a synchronised surrogate mother (*see Figure 4*). This technique can in principle be used in all animal species.

In practice, though, cloning is often a difficult process. Just a small fraction of attempts lead to the birth of a viable animal because losses during the development of the embryo and foetus are high.[173] The success rate – the number of living animals born as a percentage of the number of attempts – is low (around 10% for cattle and 6% for pigs) and varies considerable per species.[172] The success rate is therefore generally significantly lower than in conventional breeding and AI (40–55%). Cloning success rates are about the same as for technologies such as in vitro created embryos and ET in pigs (6%). Higher cloning success rates of 43–63% have been obtained in studies in Japan and France.[174] A limiting factor in cloning is the availability of egg cells to receive the donor nucleus. Large numbers of egg cells are generally only available from slaughter houses, which limits commercial cloning largely to farm animals. It is also possible to obtain egg cells by another method, but this is a costly process that will only be used for specific purposes.

Cloned animals that are born alive have more health problems and a shorter lifespan than conventional animals of the same species. About 1 in 3 cloned animals suffer from health complications. Health problems associated with cloning include cardiovascular failure, breathing problems, liver and kidney failure, immune deficiency, and muscular and skeletal disorders, reduced fertility, incomplete development of the vascular system and urogenital system, and brain damage.[161] Cloned cows may suffer from 'large offspring syndrome' (LOS), which can cause difficult births and health problems in the surrogate mother.

Cause of health complications in cloned animals

Defects may be caused by damage and mutations in the transferred cell nuclei in combination with epigenetic changes. The following factors need to be taken into account:

- **The use of less suitable donor cells and/or recipient egg cells;**
- **Suboptimal synchronisation between the cell cycle phases of the donor nucleus and recipient cytoplasm;**
- **Damage caused during the treatment of donor and recipient cells (mechanical, osmotic, toxic and thermal damage);**
- **Genetic transformations in the DNA of the somatic cell and**
- **Faulty 'reprogramming' of the genome of the donor nucleus. In somatic cells genes can be turned on or off for long periods through 'imprinting', which occurs during cell differentiation. Under normal conditions the differentiation specific imprinting during the formation of gametes is subsequently 'erased', followed by a maternal or paternal gamete-specific imprinting. After the nucleus is transplanted, the egg cell must therefore bring the imprinting of the genes of the somatic nucleus into line with that of the starting embryo.**

However, these complications are rarely found in the progeny of clones.[175] It is possible that epigenetic abnormalities resulting from cloning are restored in the process of gametogenesis, in which the cell is 'reprogrammed'.[176] It is expected that improving the epigenetic reprogramming during the cloning process will reduce the number of health complications.

5.3.2 CLONING OUTSIDE EUROPE

Cloning animals for food production purposes and in combination with genetic modification for the production of valuable substances is practised worldwide. As far as is known, no countries have drawn up specific legislation on cloned animals. Various environmental and food safety organisations have concluded that cloned animals pose no environmental risks or food safety issues and therefore that no separate risk assessment is needed in addition to the requirements of existing legislation. No consideration is given to any other possible aspects during the decision-making process.

Companies that clone animals on a commercial basis have been established in the US, South America and China. These companies clone mainly breeding animals for meat and milk production. Table 13 lists companies that clone farm animal on a commercial basis.

TABLE 13: COMPANIES IN NORTH AND SOUTH AMERICA THAT CLONE ANIMALS COMMERCIALLY

Country	Company	Animal	Website
USA	Cyagra Clone	Cow	www.cyagra.com
	Viagen	Cow, Horse, Pig	www.viagen.com
	Trans Ova Genetics	Cow	www.transova.com
	Viagen and Trans Ova joint venture	Cow	www.bovance.com
Argentina	Goyaike	Cow	www.goyaike.com
	Germinal Biotech	Goat, Sheep	-
	BioSidus *	Cow	www.biosidus.com
Brazil	In Vitro	Cow	www.invitrobrasil.com.br

* in combination with genetic modification (e.g. for the production of biomedical compounds)

United States and Canada

In 2008 the US Food and Drug Administration (FDA) concluded on the basis of a risk assessment that cloned animals do not pose any specific health problems, and that the existing legislation on animal production is sufficient to identify and prevent any potential risks. Animal clones must be produced according to the animal care standards developed by the International Embryo Transfer Society (IETS). With regard to food safety, the FDA has determined that products of cloned animals present no threat to public health.[177] Because the currently used analytical methods cannot show that cloned animals and products from these animals are any different from products of non-cloned animals, they do not have to be labelled in the US. For these reasons the products of cloned animals and their progeny have been approved for use since 2008. Despite this, the FDA has requested that clones and products of cloned animals are not introduced into the food chain and that steps be taken to facilitate their traceability. Two of the three companies in the US have voluntarily set up a tracking system in which each clone is given a unique identification number. These data are held by the breeding registers and are not known by the FDA. The voluntary moratorium and the tracking system do not apply to the progeny of clones.

In Canada companies and research institutes may not introduce cloned animals and their products into the food chain without applying for marketing authorisation under the Novel Foods regulations.[178]

South America

Cloning for commercial purposes is permitted in Argentina, where a register is held of cloned animals and the technique is used to produce cloned cattle, including (beef) cattle, and goats.[179] In addition, transgenic cows are cloned for the production of pharmaceutically important proteins. For example, work is progressing on the production of the human growth hormone somatropine in Jersey cows, the bovine growth hormone (BST), human insulin in Holstein cows and monoclonal antibodies.[180] In 2011 a GM cow was cloned that produces milk containing human proteins.[181] Clones are also used for other purposes. In the summer of 2011 it became known that a well-known polo player had had some of his horses cloned.[182] In Brazil the cloning of beef is also gaining ground.

Asia: China, Japan, Korea

Developments in Asia are less well known than in the US and South America. As far as is known, at the moment there are no cloned or GM animals being sold commercially in China. China is currently drawing up regulations on biosafety, but the details of these regulations are not known. It is clear, though, that cloned and genetically modified animals are being developed in China too. In 2011 news emerged that Chinese researchers at the China Agricultural University had also created cows that produce milk containing human proteins, as in Argentina. According to news reports, a herd of about 300 transgenic cloned cows that produce human milk are being kept on a farm in China.[183] In 2001 China established one of the first animal cloning companies, Yangling Keyuan Animal Cloning Ltd, to produce transgenic goats and cattle.[184]

Other Asian countries are also cloning animals, but it is not clear whether this is being carried out on a commercial basis or not. South Korea has been in the news several times in connection with the production of cloned dogs.[185,186] In Japan, cloned cattle, pigs, goats and other animals have been produced for research purposes and articles on the first cloned cattle were published as early as 1988. It is estimated that there are about 500 cloned cows and their progeny in Japan, but a voluntary moratorium on the domestic production of food products from cloned animals and their progeny is in force.[164] So far no regulatory measures have been adopted, although in 2009 the Japanese authorities concluded that food from cloned animals is safe.[187]

Australia and New Zealand

In Australia and New Zealand work is progressing on cloning farm animals for food production.[188,189] However, as far as is known there are no commercial applications yet on the market. Both the Australian and New Zealand governments have concluded that food from cloned animals is safe. However, in New Zealand there is a moratorium on cloning animals for the food chain,[190] but the labelling of cloned animals and their products is voluntary.[191] A national registration system for cloned animals has been set up, but this does not include their progeny.[192]

In March 2011 five countries, including three in South America, stated that they look favourably on the use of cloned animals for optimising the production characteristics of farm animals. Argentina, Brazil and Paraguay, as well as New Zealand and the US, have signed a document in which they express their support for the development of this technology.[193] It can therefore be expected that the development of this technology will continue in future.

5.3.3 CLONING IN EUROPE

In Europe animal cloning is largely restricted to research. In addition, valuable horses are cloned on a small scale for breeding top racehorses.[194,196]

Cloned horses

A French company, Cryozootech, has been established to clone racehorses. In cooperation with the American cloning company Viagen, the company has already cloned several horses for the purpose of breeding horses for equestrian sports.[197] Sport stallions are often castrated at a young age, especially those for use in horse jumping and dressage, which means that if they prove to be successful when older, they can no longer be used for breeding. Cloning these animals provides a solution to this problem. Cryozootech was established in 2001 and in the period from 2006 to 2011 cloned several European horses. The World Breeding Federation for Sport Horses (WBFSH) has let it be known that it will not refuse to register cloned breeding horses.[198]

In 2008 the EFSA published a report on the use of cloned animals for food production in Europe.[172] In line with the opinion of the American FDA, the EFSA concluded that food products from cloned animals are safe.[199] However, the EFSA endorsed the conclusion of the European Group on Ethics (EGE) that ethical objections can be made against the use of cloned animals and that some people consider these products to be undesirable.[200] The EGE was of the opinion that no categorical objections can be made against the cloning of animals, but was not convinced that there are sufficient 'good' reasons for dismissing the ethical objections to this technology.[200] In September 2010 the EFSA published an update on the latest developments regarding the use of cloned animals for food production,[174] but its position regarding food safety and animal welfare remained the same. It should be noted that this standpoint does not refer to the use of animal cloning for purposes other than food production, such the cloning of horses described in the example above.

In response to the EFSA report of 2008 and the report by the EGE, various proposals have been made to temporarily prohibit cloning animals for non-research purposes in Europe until agreement has been reached on specific rules on the use of this technology.[201] In

October 2010 the EC proposed banning animal cloning for food production in Europe for a period of five years, but permitting imports of food from the progeny of clones and the import of genetic material from cloned animals, such as sperm and embryos.[202]

Importing sperm and embryos into Europe

Since 2006 sperm and embryos from cloned animals have been imported into Europe from the US. The exact amounts imported are not known. What is known is that about 2% of the cattle born in Europe are fathered by American or Canadian bulls. Sperm and embryos from cloned farm animal are held in Germany.[63]

This European standpoint may possibly be revised 'when the technique has matured and problems have been partially or entirely resolved'. Allowing imports of progeny, sperm and embryos from cloned animals met with criticism from a few parties in the European Parliament because this implies that the introduction of offspring from cloned animals cannot be ruled out. On the other hand, prohibiting the import of progeny, embryos and sperm from cloned animals would lead to conflicts with WTO trade rules, because imposing restrictions on the trade in products that cannot be demonstrated to be different from the original is considered by various countries outside Europe to be improper. At the end of March 2011 the negotiations between the European Council and the European Parliament were suspended indefinitely because they could not agree on possible import restrictions and the question of whether products of cloned animals and their progeny should be labelled.[203] The result is that no moratorium has been imposed and, at least for the time being, the labelling of products and the progeny of cloned animals is not compulsory.

The Netherlands

The EU legislation also applies to the Netherlands. This means that there is no specific Dutch legislation on cloned animals, their progeny or products, or on importing these. However, cloning animals in the Netherlands for non-biomedical purposes does fall under specific Dutch legislation.

Under the Animal Health and Welfare Act (Gezondheids- en welzijnswet voor dieren) and the Animal Biotechnology Decree (Besluit Biotechnologie bij Dieren), no biotechnological procedures on animals are permitted without a permit. The definition of biotechnological procedures includes embryo technology, such as cloning. The Minister of Economic Affairs, Agriculture and Innovation can issue a permit for individual cases. Before such a permit can be issued for any non-biomedical application, advice must be obtained from the Committee on Animal Biotechnology (CBD). Under the Animal Health and Welfare Act, procedures involving animals or animal embryos are prohibited if these procedures or applications do not serve the general public interest. These rules do not

apply to the import of living cloned animals, their progeny and any products of these animals. Neither is the import of cloned animals and their products covered by the Animals Act (Wet Dieren), which will incorporate the Animal Health and Welfare Act.

Detection and tracking of cloned animals

No countries in the world have yet drawn up specific legislation on cloned animals. Various countries have concluded that products of cloned animals are safe for consumption, but do call for a voluntary moratorium. The labelling of cloned animals is also voluntary. A number of companies that produce animals on a commercial basis have responded to this call, while others have not. This inconsistency could cause problems with regard to the detection and tracking of cloned animals traded internationally. Cloned animals cannot be detected unless the DNA profile of the parent animal is known. The progeny of cloned animals can never be recognised or detected.

Detection of cloned animals

Most of the DNA of cloned animals is identical to that of non-cloned animals. Detecting, and therefore labelling, cloned animals or their products is in principle only possible if the identity of the donor and/or recipient is known. Cloning by nuclear transfer creates a new combination of the chromosomal (nuclear) DNA from the donor and the mitochondrial DNA of the recipient. Because mitochondrial DNA from different individuals is not identical, these differences could be used to distinguish the cloned animal from the donor. However, this is not possible if the identity of the donor or recipient is not known. Nevertheless, it is possible to distinguish between the clones of various donors on the basis of their DNA patterns, but it is difficult to identify individual clones.

Because animals are cloned for food production purposes outside Europe and labelling is often not required, cloned animals and their products, sperm or progeny may appear on the European market without this being known.[204] In the summer of 2010 it was discovered that products (meat, milk) from cloned cattle or their offspring entered the food chain in the United Kingdom. It is not known whether this was also the case in the Netherlands. In Great Britain there are at least 105 descendants of cloned cows. Eight embryos from an American cloned cow imported into the UK later produced 97 offspring. In 2002 at least two of these animals were processed and consumed,[205] which led to a heated public and political discussion. In response to this incident, the EU meat processing industry organisation CLITRAVI[d] stated that cloned animals or their products are processed and sold in the EU.[206]

d Liaison Centre for the Meat Processing Industry in the European Union (Centre de Liaison des Industries Transformatrices de Viandes de l'Union Européene (CLITRAVI))Breeding with clones and the legislation.

Animals are cloned mainly for breeding purposes, and, as described above, sperm, egg cells and breeding animals are sold internationally. The degree to which reproductive material is exchanged depends on the species of animal. Whether cloned animals and their progeny find their way into Dutch or European breeding programmes partly depends on the position taken by the herdbook associations, breeding organisations and breeding improvement and pedigree societies. The interests of the various organisations differ according to the type of animal and the livestock farming sector. In some sectors breeding is centrally organised and heavily controlled by the herdbook registries. In other sectors just a few companies around the world are active in breeding and maintain the registers themselves, and in yet others breeding is decentralised, with many occasional and hobby breeders and often rather confused registries. In Europe, cattle breeders must use sperm from an authorised sperm collection centre to prevent the transmission of diseases and guarantee the quality of the herd. Sperm is expensive and some illegal trade in sperm does occur.[207] For sport horses, the studbooks are of overriding importance and only approved animals may be used for breeding. Some, but not all, horse studbook associations accept progeny from cloned animals.

5.3.4 ENVIRONMENTAL RISKS

Theoretically there are few risks attached to cloning existing animals. This is because no new traits are introduced or removed, but a copy is made of an existing animal. The environmental risks associated with any escapes are therefore the same as those associated with the original conventional animal and no transgene is spread. The environmental risks of cloning an extinct animal, on the other hand, may be different. A factor to be considered in this case is how much the ecosystem into which the animal is reintroduced has changed. As far as is known, no extinct animals have been successfully restored by cloning, although efforts are being made to do this.[208,209]

The possible adverse impacts of cloning on the population of the animal in question are equally applicable to other modern reproductive techniques used in animal breeding, such as artificial insemination (AI) and embryo transplantation (ET). These include the effects on genetic diversity, disease resistance and fertility.[172]

5.4 ARGUMENTS AND CONSIDERATIONS

The discussion about the use of animal cloning involves a wide assortment of arguments and considerations, ranging from religious, philosophical and ethical principles to social and economic issues. This section reviews these considerations. They are not listed in order of importance, but by specificity, which means that the considerations at the top of the list relate to the cloned animals, while those further down also relate to animal breeding in general.

Need and purpose

Cloning can help to remove the impediments to breeding valuable animals (for example because of their sporting activities or infertility, sometimes through castration or sterilisation) and retaining the valuable traits of a parent animal after its death. Because the success rate of cloning is low and cloning is a costly process, the added value of cloning currently lies in the breeding industry (for example the cloning of top bulls or castrated sport horses) and in combination with genetic modification (for example the cloning of transgenic animals that produce pharmaceutically important proteins). In addition, cloning can be a useful technique in the reintroduction of extinct animal species or the multiplication of endangered or nearly extinct species. As far as is known, no animals in these categories have yet been cloned.

Animal welfare and integrity

The progeny of cloned animals are more susceptible to health problems than those produced by natural reproductive methods. Cloned animals face health complications and have shorter lives. Although 'cloning' does occur in nature, in the form of single-egg siblings, in general these do not suffer the same health problems as clones. The success rate of cloning is still low (around 10%), which means that a large number of donor egg cells and mother animals are needed to produce a single cloned animal. As the use of these animals is purely instrumental, some people also consider cloning, or copying, animals to be a violation of the autonomy and integrity of the animal.[210]

Freedom of choice

Producer and consumer choice are generally accepted to be important. Although cloning is not formally a type of genetic modification, many people consider them to be one and the same thing. In opinion polls, most consumers say they want food products obtained from cloned animals and their progeny to be labelled. As identifying, tracing and labelling cloned animals, their progeny and products is not always possible, consumers may come into contact with them without their knowledge. This also applies to the international trade in sperm, egg cells and embryos, which are increasingly used in modern reproductive technologies (AI and ET).

Although several countries are reluctant to permit the introduction of cloned animals into the food chain, none have imposed a complete ban and no country has adopted specific legislation or compulsory labelling of cloned animals. Several countries outside Europe have introduced a voluntary tracking system for cloned animals, but these do not apply to all countries and not to the progeny of cloned animals.

Confidence

Various food safety organisations have carried out extensive research and made statements about the safety of food products from cloned animals and their progeny. Nevertheless, some consumers fear that unforeseen risks (to the environment and food

safety) will only become manifest much later on, when it will be difficult to reverse the consequences.

Environmental risks
In principle the cloning of existing animals poses no risks to the environment beyond those associated with the conventional animals, as no new traits are introduced or removed.

Biodiversity
Animal products are produced worldwide from a limited number of breeds and commercial crossbreeds bred for optimal production under current conditions. This leads to the loss of traditional breeds, which are only kept on a small scale or have been lost entirely. In the longer term this may pose a risk to animal production and animal health, because production conditions may change. Using cloned animals does not increase existing genetic diversity and could aggravate this effect.

Social and economic aspects
Cloning animals for livestock farming and breeding delivers economic and other advantages to producers. The advantages include the retention of valuable breeding animals and maintaining a homogenous herd of cloned animals of a certain quality and a homogenous composition of edible products derived from these animals (meat, milk). In addition, having a homogenous group of animals can simplify their husbandry.

Animal cloning is an expensive technology that will not generally be used across a full herd of animals on a farm. At the moment it has certain advantages for breeding purposes. Cost is a general consideration in livestock farming, for example when deciding whether or not to go ahead with expensive or complicated operations or modern reproductive technologies.

Desirability
Consumers in Europe are critical of the use of cloning for food production. These objections may be based on religious grounds (playing God) or issues of principle (against the misuse of animals), or simply on a general feeling of unease and a fear that it will set a precedent for cloning humans. The most frequent arguments are that it is 'unnatural', that animals have intrinsic value and that people should not play God.[63]

Another consideration regarding the desirability in principle of cloning is that it further encourages or facilitates intensive livestock farming. The majority of consumers think that intensive livestock farming is objectionable for various reasons, including the instrumentalisation of animals and the adverse environmental impacts, and some people consider cloning animals to be a step further in this direction. It should also be noted that the objections to intensive livestock farming are sometimes inconsistent with consumer behaviour. Consumers often do not want to pay any more for sustain-

able products or are not prepared to reduce their meat consumption, which is at odds with their views on intensive farming. This discrepancy in outlook is also evident from the fact that cloning horses for sport has met with little opposition in Europe and the fact that people are sometimes prepared to accept extreme selection for certain features, as in some breeds of dog.

Reintroducing extinct animal species also raises ethical questions. Is it desirable to reintroduce these animals into the environment because they became extinct as a result of human activity or changes in the climate? Or is this an unnatural intervention in the natural process of evolution and selection? These considerations also apply, for example, to breeding programmes for endangered species.

Alternatives

Are there other or better alternatives available? The purpose of cloning farm animals is to improve the efficiency and quality of the production process, because increasing efficiency allows more to be produced at lower cost. Efficiency can also be increased through the use of modern reproduction techniques such as AI and ET, and also, outside Europe, by means of cloning. These techniques are used within an efficiently designed production system. AI and ET are to a certain extent alternatives to cloning, because they are also quick ways to influence the genetic composition of a population.

However, alternatives can also be looked at in a different light: as alternatives for intensive livestock farming. In this respect, reducing meat consumption and replacing animal proteins with vegetable proteins could be an alternative because it reduces the demand for more and cheap meat. Despite various promotional campaigns on this topic, reducing meat consumption appears to be a sore point for much of the Dutch and European populations. But from the growth in the number of vegetarians and flexitarians, it can be concluded that a change in behaviour is not impossible.

6

POTENTIAL PROBLEMS IN THE ASSESSMENT OF GM ANIMALS

This chapter reviews a number of problems and dilemmas that may be encountered when assessing GM animals. Several of these points have already been mentioned in the case studies and to some extent play a part in each of the cases. These problems typically concern the broader issues surrounding the use of animals and current food production systems. They do not therefore relate exclusively to GM animals. In addition, although they are endorsed by large sections of the population, individuals often perceive them differently and respond to them in different ways. Four considerations can be identified that make the more 'general' issues particularly relevant to cloning and genetic modification:

1. Genetic modification and cloning emerged at a time when people became more vocal and assertive and when environmental pollution and the controversy over animal testing in general fostered a more critical climate.
2. New technologies seem to reinforce each other and so their impacts are perceived to increase non-linearly. The combination of cloning and genetic modification seems to reinforce the objections to the individual techniques. Modern breeding techniques are only possible when used on a large scale and supported by other technological methods that in turn serve to speed up the process. Although this idea of the self-reinforcing nature of technological development can be criticised, people will still see this stacking of technologies as an alienating and autonomous process. Biotechnology therefore amplifies the workings of an existing system.
3. In the light of the current tendency of people to eat too much and too unhealthily, it can be questioned whether it is advisable to make meat production more efficient, cheaper and qualitatively better with technologies like genetic modification and cloning, thus fuelling the human tendency to consume more. Both animal welfare and human welfare are relevant to this discussion.
4. In recent years confidence in the safety assessments by scientists and the government has become strained, a point of contention being the independence or otherwise of those involved.

A distinction can be made between points derived from matters of principle or deontological questions and points of a more consequentialist nature. The first category include fundamental questions, such as whether animals should be used to meet human needs (which involve issues of unnaturalness, instrumentalisation and integ-

rity/justice). Problems of a consequentialist nature are questions about alternatives and current practice (which involve environmental risks, food safety, animal welfare and purpose/sustainability).

In addition to these ethical and social questions, the last section of this chapter discusses a few potential problems that could arise from differences in national and international legislation and regulations governing GMOs. These problems are relevant at the collective level, but can also be consequential at the individual level.

6.1 SOCIAL UNEASE FURTHER DEFINED

From the moment the first GM animals appeared in the news, one of the best known being the bull Herman, it became clear that the public reaction was generally guarded or disapproving. Over the years various public surveys have been held to gauge the attitudes of Dutch and European citizens to genetically modified and cloned animals (*see Chapter 1*). From the various opinion polls carried out among the European and Dutch populations on genetic modification and cloning of animals, it can be concluded that the public's view of these technologies has generally remained guarded and disapproving, but that people consider them acceptable under certain conditions and for certain purposes, such as medical research and the production of medicines. The use of GM animals for food production in particular is heavily criticised. A recurring element in the discussion is the general feeling of unease among some people about the use of genetic modification. This feeling of unease finds expression in a number of other concepts, such as unnaturalness, intrinsic value, integrity and species identity.

6.1.1 NATURALNESS AND UNNATURALNESS

The general feeling of unease among the public about genetic modification is often expressed through the argument that the technology is 'unnatural'. Unnaturalness is closely related to the question of when altering nature is justified and when it is not, and to what degree; this also has to do with what can be achieved. If the purpose is to improve human health, intervening in nature seems to be more acceptable than if the purpose is one of entertainment or pleasure.

The idea of unnaturalness may have its origins in religious convictions ('playing God') or intuitive or instinctive feelings, but it also has a deeper and subtler significance. It is a morally charged concept and generally refers to respect for the intrinsic value of nature: the value of nature and the organisms in it, regardless of any benefits they may have for humans. Defining exactly which interventions in nature are unnatural, or to what degree an intervention is unnatural, depends on the fundamental attitude a person takes to the relationship between humans and nature (dominator steward,

partner or participant). From the growing interest in the concept of sustainability it can be concluded that the fundamental attitude in society is shifting from domination to stewardship, although not everyone goes as far as the organic farming philosophy, which is based on a partner/participant relationship with nature. In this fundamental attitude, use can be made of nature (agriculture, livestock farming) according to the principle of 'naturalness' in three ways: 1) by using naturally degradable substances, 2) through respect for the self-regulatory capacity of living organisms and ecosystems, and 3) by respecting the integrity of life and the species-specific characteristics of living organisms.[211]

The genetic modification of animals can affect the self-regulatory capacity and the species-specific characteristics of living organisms and is therefore considered by some to be unnatural. Species boundaries may be crossed by inserting genes from one species into another and self-regulatory capacity may be altered by introducing or enhancing certain traits. However, other methods used in livestock farming also affect the self-regulatory capacity of animals, such as some reproduction techniques discussed in Chapter 5.

6.1.2 INTRINSIC VALUE AND INTEGRITY

The intrinsic value of animals is another issue that often crops up in the genetic modification debate. Some people point to concepts such as integrity, others to the 'inherent worth' of animals or to their 'subjective worth'. What they all mean is that animals have value in themselves; in other words, that they are not only valuable as a means to achieving an objective, but also in themselves or for their own sake. From this it follows that animals do not just have instrumental value and so may not be used or treated as a resource or thing, a means to an end, without good reason. This sensitivity and public resistance is one of the reasons why the search is on for alternatives and the numbers of laboratory animals and animal tests are being reduced as much as possible.

6.1.3 SPECIES IDENTITY

The species identity of animals is linked to their integrity or intrinsic value, but is not exactly the same thing. The integrity of animals can be damaged without compromising their species identity, which may refer to both the genotypic and phenotypic characteristics of animals. Introducing genes from other species by means of genetic modification can be seen as an assault on the identity of a species. If the introduced gene or genes are expressed in the physical features or the behaviour of the animal, the impact on the species identity is often considered to be more serious.

6.1.4 FREEDOM OF CHOICE

Freedom of choice is not only a practical problem, but also a morally charged issue related to the autonomy and intrinsic value of humans. The right to information and choice are important issues in genetic modification and have been an issue in all the case studies discussed in this report. The case studies have also revealed national and international differences in the ways in which the public and consumers have an opportunity to exercise their right to choose. These differences can inadvertently lead to problems in international trade.

6.2 GOALS, CURRENT PRACTICE, ALTERNATIVES AND APPRAISAL

In the previous sections a number of moral values were mentioned that play a recurring role in the forming of public opinion about the use of genetically modified animals. However, public opinion is not fixed and can change over time or vary according to the topic. This has to do with the consequentialist judgement people make on the basis of the values described above. This judgement may depend, for example, on the purpose of the genetic modification, the available alternatives or the state of current practice.

6.2.1 GOAL: THE QUESTION OF NEED AND PURPOSE

For some people the instrumental use of animals is, for ethical or religious reasons, unacceptable in almost all cases. For others, it depends on the purpose for which the animal is being used and/or the harm the animal is subjected to. For a long time, bull fighting was accepted as a cultural event, but over time has been gradually abolished because of the suffering caused to the bulls. Many people may be of the opinion that using bulls for entertainment is unacceptable, but that rearing cattle for beef production is acceptable. When making a judgement on the use of animals to meet human needs and desires, most people think that more important or worthy goals justify a higher cost (harm to the animal). Many people believe that medical applications of genetic modification (production of medicines, combating the spread of disease) have greater merit than altering animals for the purpose of sport or pleasure.

These differences of opinion about various goals can also be seen in the case of GM animals. In the Netherlands a case-by-case approach to the use of GM animals for medical purposes is no longer necessary under the current legislation. Although Dutch legislation on GM animals is based on a 'no, unless' principle, there appears to be a market for GM animals for sporting and amusement purposes. 'Glofish' (GM zebra fish that give off fluorescent light) have appeared several times on the consumer market for tropical

fish in the Netherlands. Also, some European breeding sport horses are cloned – mostly outside Europe, and then imported into EU member states – and several studbook associations have registered these horses. From this it can be concluded that there is a market for these animals, despite the official Dutch position that the genetic modification (or cloning) of animals for sporting and entertainment purposes is unacceptable. The current Dutch legislation on GM animals is based on the 'no, unless' principle, in which 'unless' refers to an interest of substantial importance. However, such interests can change over time.

The production of transgenic animals for food production purposes is prohibited in the Netherlands. When the Animal Biotechnology Decree came into force it was stated that the genetic modification of animals was only permissible in the service of an application of substantial importance. The explanatory note on this substantial importance explicitly states that the use of animal biotechnology for food production does not qualify as an application of substantial importance. The urgency of certain issues, such as the pressures on food production, can in time become such that other or additional applications previously considered unacceptable may come to be acceptable. In future, new issues and challenges will emerge that will raise questions about the purposes for which the genetic modification of animals is acceptable. For example, is it acceptable to create GM animals that contain less fat, or healthier fats, for use in the battle against the growing problem of obesity among humans?

6.2.2 CURRENT PRACTICE

A second dilemma that is found in almost all cases of GM animals is the part current practice should play in the evaluation. The descriptions of the contexts within which the GM animals have been developed reveal that current practice is often plagued by specific problems which reappear with renewed force in the arguments about GM and cloned animals.

Current practice is taken as the starting point for assessing environmental and other risks and food safety. The end product has to be just as safe or safer than the starting organism or current practice, and the animals must not suffer more health effects than under current practice. However, other aspects, such as the indirect effects or the social and economic impacts, are more difficult to determine. Current practice is often seen as the natural state of affairs (including the accepted risks and the advantages and disadvantages), whereas new developments are viewed in a critical light, a phenomenon sometimes referred to as 'status quo bias'. The dilemma of what should be considered current practice in the assessment revolves around two key questions:

What is current practice?
It is often not at all clear what current practice actually is, and there are often differ-

ent opinions on the subject. In the case of the GM pig, for example, the question is whether the assessment should take intensive livestock farming or organic farming as current practice. For the salmon, the question is whether it should be compared with other salmon in aquaculture (industrialised or otherwise), organic fish farming or wild salmon.

Should current practice also be assessed?
Some arguments put forward in the debate on GM animals are not specifically about GM animals per se, but concern issues relevant to current livestock farming practice. These arguments are put forward more forcefully in the debate about GM animals. According to some people, the GM salmon and the GM pig could encourage further intensification of the current production systems, with all the attendant problems. There is therefore a risk that the question of how the existing problems in these sectors can or should be resolved may sometimes be pushed into the background. On the other hand, the discrepancy between the stringent assessment of a new technique and the more lenient attitude to current practice can in time lead to doubts about the acceptability of current practice. For example, in the EU a major evaluation of the harmful effects of existing chemicals is now taking place in the REACH programme.

6.2.3 ALTERNATIVES

Alternatives are another recurrent dilemma in the assessment of GM animals. Again, opinions are divided on what the realistic alternatives are. Regarding GM animals for food production, some people believe that reducing meat consumption or avoiding meat altogether is a good alternative. Others think this option is out of the question. In the case of the GM pig, for example, some people think that a better distribution and reintroduction of small-scale pig farming could be an alternative. However, for the existing large pig farms, which seek to reduce costs to compete on the world market, this is neither a realistic nor a desirable alternative.

Weighing up all these different aspects and assessing often incomparable elements of alternatives makes the issue very complex indeed. When appraising alternatives, two crucial questions have to be answered: what are the alternatives and who should decide on them (individuals, the market or the government)?

6.2.4 EVALUATION

In many countries, and in Europe as a whole, the safety of new applications is a paramount consideration. Moreover, this is seen as a government responsibility that cannot be left to the individual. Many of the other aspects, such as ethical, social and

economic considerations, relate to less universal values and are therefore left to the market. However, every attempt is made to do justice to the opinions and attitudes in society, for example by facilitating labelling or making it compulsory.

Repeated public opinion surveys have shown that about half the European and Dutch populations have reservations about the genetic modification and cloning of animals. The EU institutions appear to be caught between pressures from outside Europe (e.g. the WTO) and from their own populations (public resistance), which restricts the room for political decision-making. The main question and challenge for the future is how to come to a decision given the wide diversity of aspects, such as those outlined in this report. Various laws and regulations have been drawn up to ensure aspects other than safety are also included in the assessment. The extent to which these allow room for consideration of ethical and social aspects is explored in the next section.

6.3 POTENTIAL PROBLEMS IN THE LEGISLATION

Each of the case studies includes a brief discussion of the relevant legislation. Differences can be found at the various legislative levels (national, European and international), the most salient difference being that ethical and social aspects are included in the assessment in some countries, but not or to a lesser extent in other countries. Legislation and regulations have a major influence on which applications are approved for commercial use and therefore also on the nature of research activities. This section examines the possible consequences of the national, European and international regulatory systems.

6.3.1 NATIONAL – ASSESSMENT OF ETHICAL ASPECTS IN THE NETHERLANDS

In the Netherlands the ethical and social aspects of biotechnological procedures on animals are subject to legislative provisions. Until 2010 the Committee on Animal Biotechnology (CBD) dealt with all permit applications in the Netherlands for activities involving biotechnological procedures on animals. Permits were issued by the Ministry of Economic Affairs, Agriculture and Innovation if a) the activities had no unacceptable consequences for the health and welfare of animals, and b) there were no ethical objections to the activities.

Assessment of GM insects in the Netherlands

Since 2010 biomedical tests on animals have been exempt from this licensing procedure and are assessed by the local Animal Experiment Committees (Dier Experiment Commissies, DEC). All animal tests with vertebrate animals and a few species

of invertebrates[e] are subject to an ethical assessment by a DEC.[212] Because almost no genetic modification of animals occurs in the Netherlands outside biomedical applications, much of the CBD's work is no longer necessary.

In May 2011 the Dutch Senate passed the new Animals Act.[213] This replaces a large number of provisions of the Animal Health and Welfare Act. It is not clear whether the CBD will be abolished when the Animals Act comes into force. The new law provides for an advisory body (Chapter 4, Article 2.2.3, paragraph 6) and states that the animals subject to the requirement for review are mammals, birds, fish and reptiles. The question is whether insects will also be covered by the Animals Act. The explanatory memorandum suggests that this will be the case, but it seems to contradict other provisions of the Act in which only mammals, birds and fish are mentioned.[214] The explanatory memorandum also includes a definition of 'biomedical', from which it can be deduced that a field trial with GM mosquitoes for disease control does not fall under biomedical research. A consequence of this is that if a field trial with GM insects is held in the Netherlands, it would only have to be assessed for environmental safety. There are no legal grounds for holding an ethical review, which some people would consider necessary, because these experiments do not fall under the DECs and are not included in the new Animals Act, and therefore would not appear to fall within the remit of the new advisory body.

Development not permitted, but use is permitted

The 'no, unless' policy has held up the development of GM animals in the Netherlands. From this it can be concluded that the policy has been successful in the sense that the government values the option of being able to prevent specific developments which give rise to ethical objections and social unease. However, it can also be argued that knowledge and innovation in this field have moved abroad, as the development of cloned and GM animals continues elsewhere. A further consequence is that products of these technologies can sometimes be found in the Netherlands, including cloned horses and some products of GM animals that may not be made in the Netherlands under Dutch law, but are imported into the country. In Europe two products of GM animals have been approved for placing on the pharmaceutical market. These medicines – ATryn®, which is produced from goat's milk, and Ruconest™, which is produced in rabbits – are also available in the Netherlands. ATryn® is produced in Denmark and Ruconest™ is produced in Sweden.[215, 216] The question is whether a policy which does not permit the development of certain products for ethical reasons, but does permit their import and use, is desirable and ethically acceptable. The Dutch House of Representatives has in the past debated the introduction of an import§ evaluation for GM animals and their products, but the current status of such an assessment remains unclear.

e The Experiments on Animals Act contains the following provision:
The invertebrate animal species which can reasonably be assumed to suffer distress when subjected to animal tests will be determined in a general administrative order. The following groups of animals are listed: Cyclostomata (cyclostomes, or jawless fishes), Decapoda (decapod crustaceans) and Cephalopoda (cephalopods (octopuses, squids and cuttlefish)).

6.3.2 EUROPEAN – ROLE OF THE EGE

A European advisory committee on the ethical and social aspects of biotechnology has also been established. The European Group on Ethics (EGE) gives solicited and unsolicited advice to the European Commission on the ethical aspects of new technologies. In the past the EGE has issued advice on synthetic biology and clones, and in 1996 published an advice note on GM animals.[217] The advice and recommendations of the EGE are based on sources that include interviews with stakeholders and round table discussions. This approach ensues that different views are taken into account and the most important principles, norms, values and arguments are examined. The various directives and regulations applicable to GMOs in the European Union refer to consultation with the EGE.

EU legislation referring to the EGE

Consideration 42 of **Regulation 1829/2003/EC** states:
Provision should be made for consultation of the European Group on Ethics in Science and New Technologies established by Commission Decision of 16 December 1997, or any other appropriate body established by the Commission, with a view to obtaining advice on ethical issues regarding the placing on the market of genetically modified food or feed. Such consultations should be without prejudice to the competence of Member States as regards ethical issues.

Article 33 of **Regulation 1829/2003/EC** states:
1. The Commission, on its own initiative or at the request of a Member State, may consult the European Group on Ethics in Science and New Technologies or any other appropriate body it might establish, with a view to obtaining its opinion on ethical issues.
2. The Commission shall make these opinions available to the public.

Consideration 57 of **Directive 2001/18/EC** states:
The Commission's European Group on Ethics in Science and New Technologies should be consulted with a view to obtaining advice on ethical issues of a general nature regarding the deliberate release or placing on the market of GMOs. Such consultations should be without prejudice to the competence of Member States as regards ethical issues.

Article 29 of **Directive 2001/18/EC** states:
1. Without prejudice to the competence of Member States as regards ethical issues, the Commission shall, on its own initiative or at the request of the European Parliament or the Council, consult any committee it has created with a view to obtaining its advice on the ethical implications of biotechnology, such as the European Group on Ethics in Science and New Technologies, on ethical issues of a general nature. This consultation may also take place at the request of a Member State.
2. This consultation is conducted under clear rules of openness, transparency and public accessibility. Its outcome shall be accessible to the public.

3. The administrative procedures provided for in this Directive shall not be affected by paragraph 1.

Article 31(8) of **Directive 2001/18/EC** states:
The Commission shall send to the European Parliament and the Council every year, a report on the ethical issues referred to in Article 29(1); this report may be accompanied, if appropriate, by a proposal with a view to amending this Directive.

Article 2 of **Decision 2010/1/EU/EC** states:
The task of the EGE shall be to advise the Commission on ethical questions relating to sciences and new technologies, either at the request of the Commission or on its own initiative. The Parliament and the Council may draw the Commission's attention to questions which they consider to be of major ethical importance. The Commission shall, when seeking the opinion of the EGE, set a time limit within which such an opinion shall be given.

Although various directives and regulations refer to the EGE, it is not clear when the EGE must or may be asked to give its opinion and how this advice can or should be taken into account in the decision making. Article 31(8) of Directive 2001/18/EC can be interpreted to mean that the European Commission is obliged to send a report on ethical issues of a general nature to the European Parliament and the Council each year. On the other hand, it can be inferred from Directive 2001/18/EC that the advice and opinions of the EGE cannot play an independent role in the decision making on specific cases.

This is less clearly stated in Regulation 1829/2003/EC. It is possible that the advice given by the EGE on procedures under Regulation 1829/2003/EC will be taken into account in the decision-making. This is conceivable for conditions regarding labelling when issuing permits under Regulation 1829/2003/EC, for example in cases where a food could give rise to ethical or religious concerns. Various regulations state that provision 'should' or 'shall' be made for consulting the EGE, as in Regulation 1829/2003/EC. However, this could refer to making provisions for consultation rather than the consultation itself. The various articles in the regulation do not seem to imply a duty to consult.

It may be concluded that the existing EU regulations allow for ethical and social arguments to be taken into account when assessing the manufacture or import of products from GM animals. However, it is not clear how these aspects will influence the final decision and whether these regulations also apply to products from the progeny of GM animals. An additional question is how these arguments relate to the WTO regulations.

6.3.3 INTERNATIONAL – THE WTO

Any review of the ethical issues attached to importing cloned or GM animals, or products derived from them, must not breach the regulations of the World Trade Organization (WTO), to which the member states of the EU have committed themselves.[218] A detailed examination of the many aspects of the WTO and the compatibility of any national or EU measures with WTO law is beyond the scope of this report. This section does not therefore seek to provide a legal analysis, but simply to raise a number of points that could be relevant. It must be noted that a clear distinction must been made between cloned animals and GM animals. The arguments and assessments relevant to these two groups may differ.

In response to complaints by other WTO member states, the WTO may review national measures for compatibility with WTO law under the provisions of the General Agreement of Tariffs and Trade (GATT).[f] The key provision in this case is on non-discrimination (Article III). Imported products must not be treated less favourably than 'like' domestic products. A member state of the WTO must not take domestic measures that provide protection, or any form of disguised protection, of its own products against products from other WTO countries. WTO reviews are held in response to complaints by one or more other countries.

Any import restrictions or bans on cloned or genetically modified animals (or products derived from them) are reviewed not only to determine whether they amount to protectionism, but also the degree to which they can be considered to be 'like' products. Is a GM animal comparable with its non-modified counterpart? Although cloned animals are by definition physically no different from the original animal, a distinction could be made on the basis of the production method and because cloning is considered to be unethical and harmful to animal welfare. However, in view of previous decisions by the WTO, a distinction made on the basis of production method ('non-product related processes and production methods', PPMs) would appear to have little chance of success if the physical characteristics of the products are not essentially any different.[219]

Trade restrictions in breach of Article III of GATT, such as import bans or compulsory labelling, can be imposed by appealing to Article XX of GATT.[220] This article contains a general exclusion clause and a list of non-economic values that can justify such a measure, including the protection of human, animal or plant life and health and the protection of public morals. Given previous experiences with WTO disputes over the *de facto* moratorium on GM crops and the ban on imports of 'hormone meat' into the EU, justifying import restrictions on products derived from cloned or GM animals on the grounds of environmental or food safety would seem to have little chance of success.[221, 222]

f Reviews also take account of provisions in the Agreement on Technical Barriers to Trade (TBT Agreement), the Agreement on Sanitary and Phytosanitary Measures (SPS Agreement) and the Agreement on Subsidies and Countervailing Measures (SCM Agreement).

Appealing to the protection of public morals or customs would appear to be a more obvious route, but it is difficult to predict whether such an appeal would withstand a WTO review. Numerous countries have introduced import bans under the provisions of Article XX (for example on alcohol, pigs and pork, pornography, narcotics, gambling, lotteries),[223, 224] but these bans were already commonplace before the GATT treaty was adopted in 1947. The legal precedents on 'public morals exception' are very limited. There are also several cases still under review that may be of influence, such as the dispute over the ban on the import and sale of seal skins and products in the EU on animal welfare grounds.[225, 226]

Public morals exceptions

The first decision by the WTO panel on the application of the public morals exception, in the dispute about the US ban on offshore-based gambling websites (US Gambling) introduced in 2005,[227] stated that public morals and customs vary in time and place and that countries should be able to apply their own definitions and interpretations. On the other hand, in coming to its decision the panel considered whether other countries maintained the same public morals or prohibitions on betting and gambling.[224] This would appear to suggest that an infringement of public morals is only considered to be such if it is experienced across a wider region or regions.

An appeal to Article XX must be consistent with the opening words of Article XX. This means that a country must take the measures in good faith; in other words, they must be not be arbitrary, must be proportional to the intended objective, and be necessary or without alternatives, etc.

In the theoretical case that WTO member state X takes measures which WTO member state Y objects to, a complaint can be lodged and a WTO panel established to adjudicate the dispute. Whether genetic modification of animals would be seen by a WTO panel as an infringement of public morals cannot be predicted. Genetic modification of animals appears to raise ethical objections not only in the Netherlands and Europe. For animal cloning it is debatable whether an appeal to an infringement of public morals would be accepted. In the EU, the United Kingdom has expressed opposition to a ban on cloning or labelling products from cloned animals,[228, 229] which could be construed as proof that cloning is also not widely believed to be objectionable within the EU.

It is not clear how far animal welfare can be a legitimate consideration under the public morals exception.[226, 230, 231] Earlier decisions in WTO disputes do not offer much to go on. An argument can be made that, given the large number of fatal abnormalities, deaths and adverse health effects among cloned animals,[200] an appeal can be made under the public morals exception to ban imports of cloned animals. However, it is

doubtful whether the progeny of cloned animals could fall under the same clause, because they are actually products of natural reproduction.

Labelling GMOs has long been seen as possibly being contrary to the WTO rules. However, in 2011 the Codex Alimentarius Commission adopted guidance on the voluntary labelling of GMOs. As the Codex Alimentarius Standards are recognised by the WTO, labelling is no longer considered to be a wrongful trade barrier.[232-234] In the eyes of a WTO panel, therefore, labelling GM animals and their products could be an alternative to import bans.

Within Europe measures have been proposed to prevent the cloning of animals for food purposes. The Legal Service of the European Council has drawn up confidential advice on the compatibility of the proposals with the WTO regulations. The proposals are based largely on the argument that cloning animals has unacceptable consequences for animal welfare. It should be noted that the physical and reproductive problems suffered by cloned animals do not affect all animals species to the same extent and are not always found in the progeny of GM animals. Given the rate of scientific progress, it cannot be ruled out that animal welfare problems will no longer be an issue in the future, thus undermining this argument.

7

OBSERVATIONS AND CONCLUSION

In the Netherlands and Europe, GM animals are used mainly for research purposes, especially in medical research. Outside Europe, for example in Asia and North and South America, GM animals are also created for other uses and several of these are in an advanced stage of development. An initial inventory of worldwide developments and a more thorough investigation of several cases clearly show that the GM animals being developed are not limited to attempts to increase and improve the efficiency of food production, but that the applications are much more varied in nature. This diversity of applications means that the arguments and considerations in the debate are also diverse and that a general assessment is not sufficient. The developments may require a further refinement, broadening and elaboration of the Dutch 'no, unless' policy, and raise the question of what role the various arguments can and should play in a European assessment.

The developments described in this report indicate that in future Europe and the Netherlands will be confronted with and have to deal with cloned or GM animals and products obtained from them. This may happen in various ways:

- Via applications for marketing authorisation. To date no applications have been made for the marketing authorisation of GM animals. However, the European Food Safety Authority (EFSA) is preparing a risk assessment protocol for various GM animals.
- Via trade flows. The Netherlands imports animals and animal products and this is a route which could bring in food products from cloned or GM animals. The regulations in this area vary from country to country and detecting cloned animals and their progeny or products derived from GM animals is not always possible.
- Via the environment. Cloned or GM animals that are intentionally or inadvertently released into the environment can disperse and may cross national borders.

The Netherlands and the EU will have to consider what position they wish to adopt and the measures they may wish to take in response to this new situation. In this report, COGEM has identified a number of relevant issues and problems.

OPPORTUNITIES AND THE POSITION OF RESEARCH IN THE NETHERLANDS

The current legislative and regulatory framework (the 'no, unless' policy) guarantees a measured and cautious response to a controversial technology and its use on animals, but at the same time has consequences for the R&D climate and the competitive position of biotechnology companies in the Netherlands. COGEM observes that this:

- means that some opportunities are missed, or intentionally ignored, and that companies relocate their activities abroad;
- can provide an impetus to the development of alternatives;
- gives rise to an inconsistency, because GM animals may not be developed in the Netherlands, but products from such animals may be imported and used (e.g. medicines produced in animal milk).

ENVIRONMENTAL RISKS

The EFSA is currently drawing up a detailed risk assessment method for various GM animals, such as birds, fish, mammals and insects. This would appear to adequately provide for the environmental risk and food safety assessment. In the Netherlands, COGEM and the RIKILT Institute of Food Safety will be involved in carrying out these assessments. COGEM makes the following observations:

- A case-by-case assessment of GM animals under the current legislation and procedures is possible and the regulations in this area do not need revision.
- It is important to continue to follow developments in the field of risk assessment both in Europe and countries elsewhere in the world, where the marketing authorisation stage has already been reached.

ETHICAL AND SOCIAL ASPECTS

The use of both genetic modification and cloning invokes a wide diversity of norms and values of varying degrees of importance to different stakeholders. This is apparent, among other things, from the inventory of arguments and considerations in the case studies discussed in this report. COGEM makes the following observations:

- It is important to be attentive to the diversity of different ethical and social aspects of the genetic modification and cloning of animals. For example, an ethical objection to a GM animal for food production may not necessarily apply in the same way to GM animals for sporting use or to meet public health objectives.
- Public objections to one application may not apply to other applications. From this it may be concluded that there is a degree of public approval, but that opinions are divided and sometimes ambivalent.

- Ethical arguments are mainly articulated in the form of arguments against genetic modification and cloning, which indicates the importance of differentiating these further and investigating possible arguments for as well as against these developments.
- The discussion about cloning and genetic modification cannot be divorced from the wider context of the use of animals for human purposes and the consequences for animal welfare (instrumentalisation).
- Shifting the focus of attention towards the goals for which research into GM animals is, or is not, acceptable or desirable, and under what conditions, may help to moderate and refine the discussion so that justice can be done to the great diversity of arguments involved.

Enviropig™

The Netherlands and a few other European countries are important centres of pig farming. The GM pig described in the second case study could therefore be of interest to the Netherlands. Development and production of the pig in the Netherlands would be subject to national regulations; besides an environmental risk assessment, it would also have to be subject to an ethical review by the Committee on Animal Biotechnology (CBD). When the new Animals Act comes into force an ethical review committee for GM animals will be established. It is not yet clear what the mandate and composition of this committee will be. Should an application be submitted for the marketing authorisation of the GM Enviropig™ via the import of live animals, it would have to be assessed for environmental and food safety under Directive 2001/18/EC. It is not clear whether an ethical review of such an application would be considered desirable or necessary in Europe. This will require a political decision. The existing EU directives appear to leave the door open to ethical and social arguments, but it is not clear how these should be taken into account in the decision-making. General advice by the European Group on Ethics (EGE) could be taken into consideration in the procedure, but this may not play an independent role in the decision-making. There are no procedures available for carrying out or submitting a case-specific ethical review. Do Europe or the Netherlands want ethical and social aspects to be included in the assessment process? Is there a suitable assessment framework, and who should conduct this review? How should such a review be taken into account in the decision-making on marketing authorisation? COGEM notes that it is important to companies, consumers and citizens that clear answers are given to these questions.

ETHICS AND THE LEGISLATIVE AND REGULATORY FRAMEWORK: EU AND WTO

This report highlights the fact that regulations on the assessment of GM animals differ between countries and regions of the world. A common thread is that in almost all countries a specific safety assessment is required for the approval of genetically modified and cloned animals. The differences are found mainly in the possibilities for labelling and including ethical and social aspects in the assessment. COGEM makes the following observations:

- There is an ethical advisory committee at the European level (EGE) which provides solicited and unsolicited advice on ethical and social aspects of new technologies, but this advisory committee issues generic advice, not case-specific advice.
- Existing EU regulations allow for the inclusion of ethical and social aspects in the assessment of GM animals and their products, but it is not clear how these reviews are used in the decision-making on market authorisation.
- There seems to be no standard or compulsory procedure at the European level for considering ethical and social aspects in specific cases, and there is no definitive assessment framework or import appraisal.
- There is an urgent need for a political decision on the desirability of such a procedure (and the implementation of this decision) to provide certainty to the public and to companies, and also to prevent differences of opinion between member states and assessment agencies.
- Future uses of genetically modified animals and animal cloning will be so diverse and wide-ranging that a general advice may not be sufficient. In that case, the government could consider developing a practical appraisal method, similar to the Dutch Integrated Ethical Assessment Framework (Integraal Ethisch Toetsingskader), for use on a case-by-case basis.
- If the government is of the opinion that ethical and social aspects should be taken into account in the assessment of GM animals, it is important to make clear procedural agreements on the role of ethical and social considerations in the assessment.
- Taking ethical and social aspects into account in the assessment of importing cloned and GM animals can lead to trade conflicts under WTO law. If the EU chooses to take these aspects into consideration, it should bear this in mind when drawing up measures.

Import of salmon products

Any applications for the import of tinned GM salmon will be handled under European procedures for placing on the market via import (Regulation 1829/2003/EC) and will be subject to a food safety assessment. In addition, as the products are derived from GM animals they will have to be labelled (Regulation 258/97/EC). It is not clear whether such applications made in Europe would be subject to an ethical review. The existing EU directives appear to allow for ethical and social arguments, but it is not clear how these should be taken into account in the decision-making. General advice by the European Group on Ethics (EGE) could be taken into consideration in the procedure, but this may not play an independent role in the decision-making. Imports of such products are subject to European regulations and the opinion of the Dutch Committee on Animal Biotechnology (CBD) or other organisation is not relevant. Do Europe or the Netherlands want ethical and social aspects to be included in the assessment of imported products derived from GM animals? Is there a suitable assessment framework, and who should conduct this review? How should such a review be taken into account in the decision-making on marketing authorisation?

ASSESSMENT FRAMEWORK FOR ETHICAL AND SOCIAL ASPECTS IN THE NETHERLANDS

Assessments of the environmental and food safety aspects of GM animals and their products for marketing authorisation are handled at the European and national levels. These assessments review both the possible environmental risks and the food safety implications. Research and field trials with GM animals are a national responsibility. In the Netherlands, COGEM and other agencies are consulted on the assessment of the environmental risks. Since 2010, the Committee on Animal Biotechnology (CBD) only assesses non-biomedical applications of genetic modification; biomedical experiments on animals are assessed by the Animal Experiment Committees (DECs). A special category in the Netherlands are field trials with animals, which are also assessed by the DEC for any distress they may cause to the animals (for example the drawing of blood from birds). Should these field trials have any non-medical purposes, they also have to be assessed by the CBD (if they are related to biotechnology). COGEM makes the following observations:

- It is not clear whether field trials with invertebrates such as insects (e.g. GM mosquitoes) fall under the existing legislation and/or the new Animals Act.
- It is not clear whether the CBD will continue to play a role following the introduction of the new Animals Act, or whether a new advisory body will take over its role and what exactly its remit will be.
- A new advisory committee will be established for this task, but it is not clear what exactly the terms of reference for this committee will be.
- There is a chance that ethical and social aspects relating to invertebrates will not be covered by the standard regulations.

- Eco-ethical, social, economic and sustainability issues are particularly relevant to such applications and policy-makers and politicians should give a clear answer to the question of whether these aspects should be considered and taken into account in the assessment, and if so, how.

A field trial with GM insects in the Netherlands

It is possible that in future an application will be made to carry out a field trial with GM insects in the Netherlands. This is a national responsibility; the only requirement at the European level is for notification. Under the current legislation, such a field trial would be assessed by COGEM for environmental safety. A notice would have to be published in the Government Gazette to inform the public and invite representations or objections. The CBD would review the application for ethical issues. The remit of the Animal Experiments Committees only covers biomedical experiments with vertebrate animals.

The new Animals Act only explicitly provides for the establishment of an animal ethics advisory committee. The exact composition, tasks and mandate of this committee are not specified. Moreover, only vertebrates and a few specific groups of invertebrates appear to fall within the requirement for an ethical review under the new Animals Act. Is it desirable that aspects other than the environmental risks are also included in the assessment of field trials with GM insects? Who should assess these aspects and how should they be taken into account in the decision-making? Should the public also be informed in other ways before such experiments with animals are carried out, and if so, how?

CLONES

Animal cloning does not fall under the EU legislation on GMOs, and at the moment no countries are known to have adopted specific regulations on cloned animals and their progeny or the products obtained from them. COGEM makes the following observations:

- There is public resistance in the EU to cloning animals and this resistance displays close similarities with the objections to GM animals.
- In the Netherlands, under the current Animal Health and Welfare Act, cloning falls within the definition of biotechnological procedures on animals and these applications therefore have to be assessed by the CBD (with the exception of cloning for biomedical research purposes).
- If the European authorities wish to make provisions for responding to the moral discomfort many people feel about cloning animals, they could consider subjecting cloning to the same review procedures as those that apply to the genetic modification of animals in the Netherlands. At the moment the Dutch 'no, unless' policy on the genetic modification of animals is enacted through two requirements (Article

66 of the Animal Health and Welfare Act), namely that genetic modification is only permitted if a) the treatment does not have any unacceptable consequences for the health or welfare of animals, and b) there are no ethical objections to the treatment. Requirement b) should be seen as a means of respecting the intrinsic value of animals independently of the consideration of any welfare aspects.

- The desire to take steps to introduce some sort of control over cloning in Europe may run up against problems in the international arena from the WTO.
- The ethical objections to cloning appear to be based mainly on animal welfare considerations, but welfare problems may be reduced or even largely avoided as the technology develops.
- The detection and tracking of cloned animals and their progeny is problematic, while resistance to cloning in Europe is widespread. Given the difficulties of detecting cloned animals, this problem should be tackled at the European level. For an analysis of the origins and the goal of public choice regarding genetic modification, COGEM refers to the topic report *Geboeid door Keuzevrijheid; een verkenning van de ontwikkeling en rol van keuzevrijheid rondom ggo's in Europa* [Enthused by Choice: An exploration of the development and role of choice regarding GMOs in Europe] (in Dutch only).

DETECTION AND LABELLING OF IMPORTS

There is a desire among the European population for GM animals and their products in the food chain to be labelled to allow people to choose whether to buy them or not. Detecting GM animals is in principle possible and is part of the EU marketing authorisation procedure. This obligation may be introduced in the US, but is not yet required. Detecting some products from GM animals and their progeny is more difficult, if not impossible. The same applies to cloned animals and their products. COGEM makes the following observations:

- Consumer and producer choice regarding GM and cloned animals is at least as important as in the case of food and products from GM plants.
- Not honouring promises on choice and labelling can lead to protests and loss of confidence in government and the producers of these products among consumers and the public in general.

Cloned animals

In the summer of 2010 it became known that in the United Kingdom, products from the progeny of cloned animals had inadvertently entered the food chain. Given the developments abroad, raising and using cloned animals and their offspring in Europe will become more common. At the moment there is no specific legislation in Europe on the cloning of animals, which does not fall under the regulations on GMOs. In the EU, proposals have been made to ban the import of cloned animals and to label clones, their progeny and products obtained from them. Under these proposals, importing sperm, egg cells and embryos would be permitted. However, the Council of the European Union and the European Parliament were unable to reach an agreement on these proposals.

The possibilities for detecting cloned animals remain very limited. Direct clones can be distinguished from the original animal if a DNA profile of both animals is available, but the natural offspring of cloned animals cannot be identified. A European ban on the use of the offspring of cloned animals in the food chain does not therefore appear to be enforceable. Supply chain certification is the only effective means of tracking and labelling these animals. Moreover, if importing living material (sperm, egg cells, embryos) from cloned animals were to be permitted, the chance that products from these animals will find their way (unnoticed) into the food chain would increase. Given the social resistance to cloned animals and products from cloned animals, a labelling requirement that cannot be met can undermine public confidence. COGEM points to the need to make agreements with the countries where animals are cloned on a commercial basis and can be traded internationally.

IN CONCLUSION

It would be advisable for the Netherlands and the EU to consider adopting a standpoint on the issues raised above and to take stock of the possibilities and impossibilities of certain choices from an international perspective. Developments in the genetic modification and cloning of animals appear to raise several issues and questions of policy that cannot yet be answered unequivocally. If national or European measures are difficult to maintain and enforce in an international context, other forms of management, such as labelling and tracking, could be considered. In the last instance, consideration could be given, in cooperation with like-mined countries, to reopening negotiations within in the WTO.

APPENDIX 1

COGEM TOPIC REPORTS ON GM ANIMALS

This appendix contains a brief review of a number of relevant topic reports and advisory reports previously published by COGEM on the use of transgenic animals.

Transgenic Glofish (2003)
CGM/030708-02
Reports have appeared in the media on the sale of fluorescent 'Glofish'. These are GM fish that glow in the dark for the public's amusement. The developer of the fish claims that more than 90% of the fish are sterile, which means that some of the fish are probably able to reproduce. Given that the fish are ornamental, tropical freshwater fish to be kept in aquariums, they will not generally be able to survive in outside waters in the Netherlands. The risks to human health and the environment therefore appear to be limited. Should these fish be approved for the Dutch market, COGEM considers that a scientific environmental risk assessment would be necessary. In addition, COGEM notes that genetic modification of ornamental fish raises ethical and social questions.

Transgenic salmon – A safe product? (2003)
CGM/031124-01
COGEM published this advisory report in response to technological developments in the genetic modification of salmon, advanced plans for the introduction of transgenic salmon onto the American market, and the public discussion on the subject in Europe. COGEM is of the opinion that, based on existing data, it is impossible to unequivocally identify the environmental risks associated with escaped transgenic salmon. Given the scientific uncertainty, COGEM argues for the exercise of great caution. On the other hand, COGEM considers that scientific arguments do not provide sufficient basis for declaring in advance that rearing GM salmon will always result in unacceptable environmental risks. At the very least, COGEM recommends the adoption of a case-by-case approach in which an extensive risk assessment would be carried out, depending on the specific circumstances. COGEM points out that the current European and national legislation cannot prevent any cross-border environmental consequences of rearing GM salmon. COGEM also highlights the fact that Dutch legislation concerning the ethical and social considerations of genetic modification in animals does not apply to the introduction of salmon products onto the Dutch market. Under the present circumstances there is a realistic chance that within 5 to 10 years of the introduction of transgenic salmon onto the American market, the effects of transgenic salmon could arise in the European or Dutch environment or transgenic salmon products could appear on the Dutch market.

Transgenic mosquitoes as a weapon in the war on malaria (2005) CGM/050202-05

Encouraging scientific developments in fighting malaria with transgenic mosquitoes that are unable to transmit the malaria parasite to humans bring the release of transgenic mosquitoes into the ecosystem a step closer. As a rule, when genetically modified organisms (GMOs) are released into the environment, measures are taken to limit the environmental consequences as far as possible. However, the opposite is true in the case of the release of transgenic mosquitoes to control the spread of malaria: replacing natural populations of mosquitoes with genetically modified mosquitoes is a necessary requirement for success. Their release therefore demands a new approach and the adoption of a new set of principles. The latter is an international responsibility and therefore needs to be addressed by the Dutch government, both in its role as a financer of research and development aid and as a participant in international conventions. Releasing transgenic mosquitoes into the environment is only acceptable if it does not compromise human and environmental safety and there is a good chance that the desired effect can be achieved. So far there is no evidence that releasing transgenic refractory mosquitoes is safe *and* that controlling malaria with these mosquitoes is feasible. More research is needed. A suitable method is to follow a step-by-step plan comparable to the Dutch step-by-step plan for introductions into the environment of GMOs. The last step, following laboratory and greenhouse experiments, is releasing transgenic mosquitoes into an isolated area. A subsequent step can only be justified if there are sufficient guarantees that releasing the mosquitoes is safe and will be effective.

Illegal import of genetically modified zebra fish (2006) CGM/061219-01

The VROM Inspectorate has recently tracked down a consignment of illegally imported zebra fish. Of the 1400 or more 'Glofish', 750 have been recovered. COGEM was asked to advise on any possible unacceptable environmental risks and to identify any ethical dilemmas raised by this find. The fish, which are genetically modified with a gene that codes for red fluorescent protein, glow red under short-wavelength light. The presence of this gene has been confirmed in laboratory tests. There is no risk to the environment. The fish are kept in aquariums and if they are inadvertently released into the environment are unable to survive or reproduce because they cannot withstand the low water temperatures in the Netherlands. When deciding on what to do with the confiscated fish, consideration has to be given not only to the potential environmental risks, but also the ethical and social aspects, such as animal welfare and suffering. To ensure public support for the decision on what to do when such consignments are intercepted, it is important that the policy options and judgements underpinning the decision are made public. In addition, COGEM observes that illegal imports of GM animals will probably become more frequent in future. The government could prepare specific policies to deter this. Besides enforcing policy, carrying out inspections and imposing sanctions, awareness of the legislation and regulations can be raised through better provision of information.

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P.O. BOX 578
3720 AN BILTHOVEN
THE NETHERLANDS
PHONE: +31 30 274 2777
FAX: +31 30 274 4476
INFO@COGEM.NET
WWW.COGEM.NET