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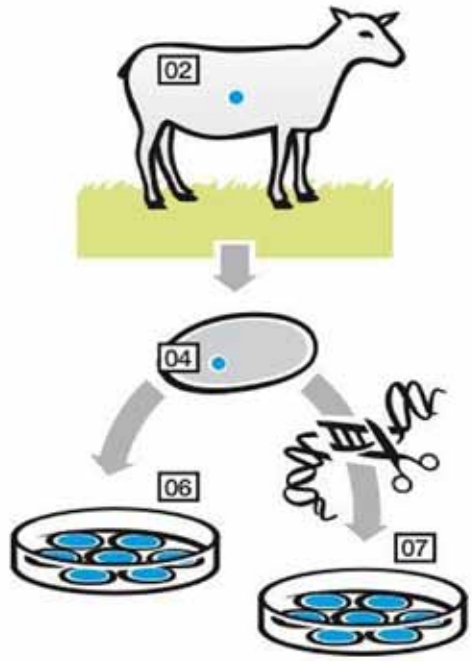

Agro-Biotechnology:

Cloning farm animals – a 'killer application'?

Risks and consequences of the introduction of cloned animals for food production

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A Testbiotech Report prepared for Martin Häusling, MEP

May 2010

The Greens | EFA
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Summary

The cloning of animals for food production has raised political discussions in the European Union. The European Commission is in favour of regulating food products derived from cloned animals under the Novel Food Regulation. The European Council recommended including food derived from cloned animals and their offspring under the Novel food regulation and later supporting a specific piece of legislation for cloned animals. On the contrary, the European Parliament is in favour of prohibiting the marketing of these products and demanding that farm animal cloning will not be allowed unless specially authorised. In March 2011, negotiations between the EU Parliament, the EU Member States and the EU Commission finished with no political solution.

This report identified several levels that are affected by cloning animals for food production and will need specific regulation:

Animal welfare: Many adverse health effects are reported in cloned animals and their surrogate mothers.[1] Further, higher productivity in farm animals is correlates with shrinking biological diversity, shorter lifespan and higher incidence of damage to health. It is likely that cloning will foster this development.

Transparency and traceability: There is some likelihood that genetic material derived from cloning farm animals (such as semen and embryos) has already reached the European market on the level of farm production. There is a high risk that this material is being disseminated throughout the populations without any transparency and traceability.

Farm production: Patents on cloned animals and their offspring will enforce new dependencies for farmers and breeders, and will foster concentration in the animal breeding business will be fostered. This can also have an impact on biological biodiversity in farm animals.

Food production: If the products from cloned animals are introduced into the food market, this can lead to high costs for labelling and segregation can arise. Consumers will need a high degree of transparency to enable them to make well-founded choices.

Food safety and food market: Further investigations concerning food safety (e.g. different milk composition) are needed. In the light of the variety of factors impacting the outcome of cloning and the broad range of observed effects, health risks cannot be excluded for the time being. Consumers risk beingturned into some 'end of pipe hostage', similar to the situation in which they found themselves with regard to the usage of genetically engineered plants. Opinion polls show substantial consumer rejection.[2]

1 Female animals carrying the cloned animal till birthing

2 http://ec.europa.eu/rapid/pressReleasesAction.do?reference=IP/08/1478&format=HTML&aged=0&language=EN

Future developments: Cloning of animals for food production could pave a way to the introduction of further biotechnologies for engineering in livestock. Future applications will combine cloning, cell culturing and genetic engineering. A further aspect of cloning farm animals is its implications in terms of encouraging cloning in humans.

From a breeder's perspective, nuclear transfer allows the propagation of genomes whose phenotypes are proven and desired. In combination with artificial insemination, these genetic conditions can spread rapidly throughout a population. But at the same time there is a risk of shrinking biodiversity. Furthermore, insofar as these genetic conditions harbour unexpected adverse effects, they can affect large populations in a short period of time. This process might be irreversible if genetic material from cloned animals is distributed throughout the population for several years. Moreover, by cloning the fastest-growing and highest-yielding animals, even higher levels of health and welfare problems than those observed in traditional selective breeding may occur.

Many of the problems created by cloning are a result of technical details in the procedure. Cloning violates the biological integrity of the egg cell and the nucleus and causes epigenetic dysfunction and further disturbances at the levels of genome and cell regulation. Its outcome depends on several technical details, but observed effects do not follow a defined cause-effect relationship. Despite all the efforts that have been put into cloning, so far it has not been possible to determine the causes and mechanisms behind the adverse health effects that have been observed. Furthermore, its implications cannot be confined to the first generation of cloned animals. The range of observed effects is broad and not clearly limited to certain organs or parts of the life cycle, although the likelihood of these effects seems to decrease in older animals and in subsequent generations. Expectations that technical difficulties will be overcome in the very near future are not based on sufficient scientific evidence. There is no silver bullet around the corner to solve these problems, simply because of its biological complexity.

The overall consequences of introducing cloning in farm animals have to be discussed in a broader context. The economic interests of a few companies in pushing their technology into markets should not lead to any hasty decisions in EU legislation with regard to open markets for products that are still subject to considerable uncertainties. The discussion should be driven from a consumer perspective so as to avoid market penetration without any authorisation, controls or transparency. It is a cause for concern that food products derived from cloned animals might have already reached the food chain within the EU without being noticed.

Given the awareness of the uncertainties regarding food safety, the adverse effects on animal welfare, the potential socioeconomic ramifications and theneed for transparency and traceability, there is a pressing need for legislation. Most nee-

ded are import regulations regarding animal material and the cloning of animals for food production. The WTO framework does not exclude these kinds of measures. Only once this level of production is fully regulated can the measures-directed at the food market be discussed. Without proper regulation regarding animal cloning and imports of semen and embryos, the attempts to put in place transparency and traceability will fail.

In view of this analysis, the European Parliament's approach of banning products and prohibiting cloning immediately is a convincing one. At least it will facilitate sufficiently detailed long-term solutions. If the issue is now brought under the Novel Food Regulation, a long time will pass before any further legal regulations are put in place and then proper segregation in breeding and animal production may become quite complicated. Thus the proposal of the European Council of Ministers risks failing to take a proper problem-solution approach.

Introduction

Cloning farm animals has been technically feasible for several years. Several techniques are used, the most well-known being somatic cell nuclear transfer (SCNT). This technology was used to create Dolly the sheep in 1996. Since then this technology has been successfully applied to several other species. In 2008, cloning animals for food production was discussed in the European Parliament. The European Group on Ethics of Science and New Technologies (EGE) released a report (EGE 2008), and the European Food Safety Authority (EFSA) published two opinions (EFSA 2008a, 2009). In September 2008, the European Parliament voted on a ban on cloning animals for food production through specific legislation. In 2009, the Parliament rejected the Novel Food Regulation being applied to this area.[3]

"The European Parliament (....) calls on the Commission to submit proposals prohibiting for food supply purposes (i) the cloning of animals, (ii) the farming of cloned animals or their offspring, (iii) the placing on the market of meat or dairy products derived from cloned animals or their offspring and (iv) the importing of cloned animals, their offspring, semen and embryos from cloned animals or their offspring, and meat or dairy products derived from cloned animals or their offspring, taking into account the recommendations of EFSA and the EGE."

But in 2010 the EU Council voted in favour of regulating products derived from cloned animals under the Novel Food Regulation (EC 258/97):[4]

"The definition of novel food and the scope of the regulation are clarified. According to the Council's position, the new regulation would explicitly apply to food produced from animals obtained by a cloning technique, and the scope of the regulation is extended to food from the offspring of cloned animals. The Council invites the Commission to report on all aspects of food from cloned animals and their offspring within one year after the entry into force of the regulation and to submit, if appropriate, a proposal for a specific legislation on this topic."

In the addendum to the Council's conclusion 24 member states noted the following:

"We also note that the majority of Member States are of the view that food produced from animals obtained by using a cloning technique and from their offspring should be regulated by specific legislation. Consequently, such foods should be excluded from the scope of the Novel Food Regulation as soon as specific legislation has become applicable. In the meantime, and in order to avoid any legislative gaps, those foods should be covered by the scope of the Novel Food Regulation."[5]

3 P6_TA-PROV(2008)0400 Cloning of animals for food supply PE410.750 European Parliament resolution of 3 September 2008 on the cloning of animals for food supply, http://www.europarl.europa.eu/

4 http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/agricult/113344.pdf

5 http://register.consilium.europa.eu/pdf/en/10/st06/st06163-ad01.en10.pdf

So far the cloning of animals affects only a very small number of animals, but the questions related to it impact a wide range of issues. Consumer choice, the economic impact on farmers, breeders and down stream markets, product safety, animal welfare and animal integrity are all affected. Many of these issues are mentioned in the European Parliament's resolution for a ban on cloning, which also mentions socioeconomic ramifications. The Parliament also justified its rejection of cloning by referring to the European agricultural model[6]:

"Whereas, in addition to the fact that the implications of the cloning of animals for food supply have not been adequately studied, it poses a serious threat to the image and substance of the European agricultural model, which is based on product quality, environment-friendly principles and respect for stringent animal welfare conditions."

Besides the EFSA and the EGE several reports and expert panels have dealt with questions related to the cloning of farm animals, including the EC project "Cloning in Public"[7]. The US FDA also released a report in 2008 pointing out that the products derived from cloned farm animals would pose no substantial health risks (FDA, 2008). This report tries to summarise some of the recent debates and published reports, and elaborates on some specific scientific, economic, ethical and legal questions. For this purpose relevant publications, proceedings and patent applications were surveyed along with additional web-based research. Direct contact was also made with some experts working in this field.

6 P6_TA-PROV(2008)0400 Cloning of animals for food supply PE410.750 European Parliament resolution of 3 September 2008 on the cloning of animals for food supply, http://www.europarl.europa.eu/

7 The project was financed by European Union and aimed to discuss technical, ethical and legal aspects of cloning of animals.
http://www.sl.kvl.dk/cloninginpublic/index-filer/Page361.htm

1. Technical development in cloning of farm animals and its relationship with biotechnology applications in livestock

The first technology used for cloning in farm animals was the splitting of embryos, using their specific biological potentials in the early stages of development. Separated cells from these early stage embryos can be used for producing additional embryos, in a similar way to how twins emerge naturally from one fertilised oocyte. This technology only has a limited capacity. In artificial embryo splitting a maximum of two to four animals can be expected (Gjerris & Vatja, 2005).

Another technology used to clone farm animals was developed by Willadsen (1986). He showed that nuclear transfer from embryonic cells into an enucleated egg cell of the same species can give rise to a whole embryo. This technique called embryonic cell nuclear transfer (ECNT) also turned out to be of only minor relevance because, in this case also, the number of embryos that can be produced from an early stage embryo is limited. But Willadsen (1986) more or less already established the technology as it was used by Wilmut et al. (1997) to create Dolly about ten years later.

In 1997 Wilmut et al. published a paper describing the successful transfer of the nucleus of somatic cells from an adult sheep which became known as 'Dolly'. This method, the somatic cell nuclear transfer (SCNT), was further developed and meanwhile successfully applied to more than a dozen mammal species (sheep, cow, pig, mule, horse, cat, mouse, rabbit, rat, buffalo, ferret, dear, dog, wolf; FDA, 2008). The SCNT meanwhile has become a matter of economic importance because a number of companies are offering cloned mammals for sale (pet animals as well as farm animals). Deregulation for food produced from cloned animals (via SCNT) is under discussion in the USA. Most of the issues discussed in this report refer to the SCNT technology. The EGE (2008) defines SCNT as follows:

"Cloning by somatic cell nuclear transfer (SCNT) involves replacing an egg's nucleus with the nucleus of an adult cell (or that derived from an embryo or foetus) to be cloned, and then activating the egg's further development without fertilisation. The egg genetically reprogrammes the transferred nucleus, enabling it to develop directly into a whole new organism."

The 'Dolly procedure' became relevant not only for propagating existing animals, but also for genetic engineering. A combination of culturing and propagation of cells from the donor animal together with genetic engineering of the cells and the selection of the most promising cells is most commonly used. The nucleus of these cells is then transferred into enucleated egg cells. As van Reenen (2009) explains, SCNT in combination with genetic engineering has already largely replaced the direct microinjection of new DNA that was used to produce the first transgenic animals (Hammer et al., 1985), because it can be more efficient.

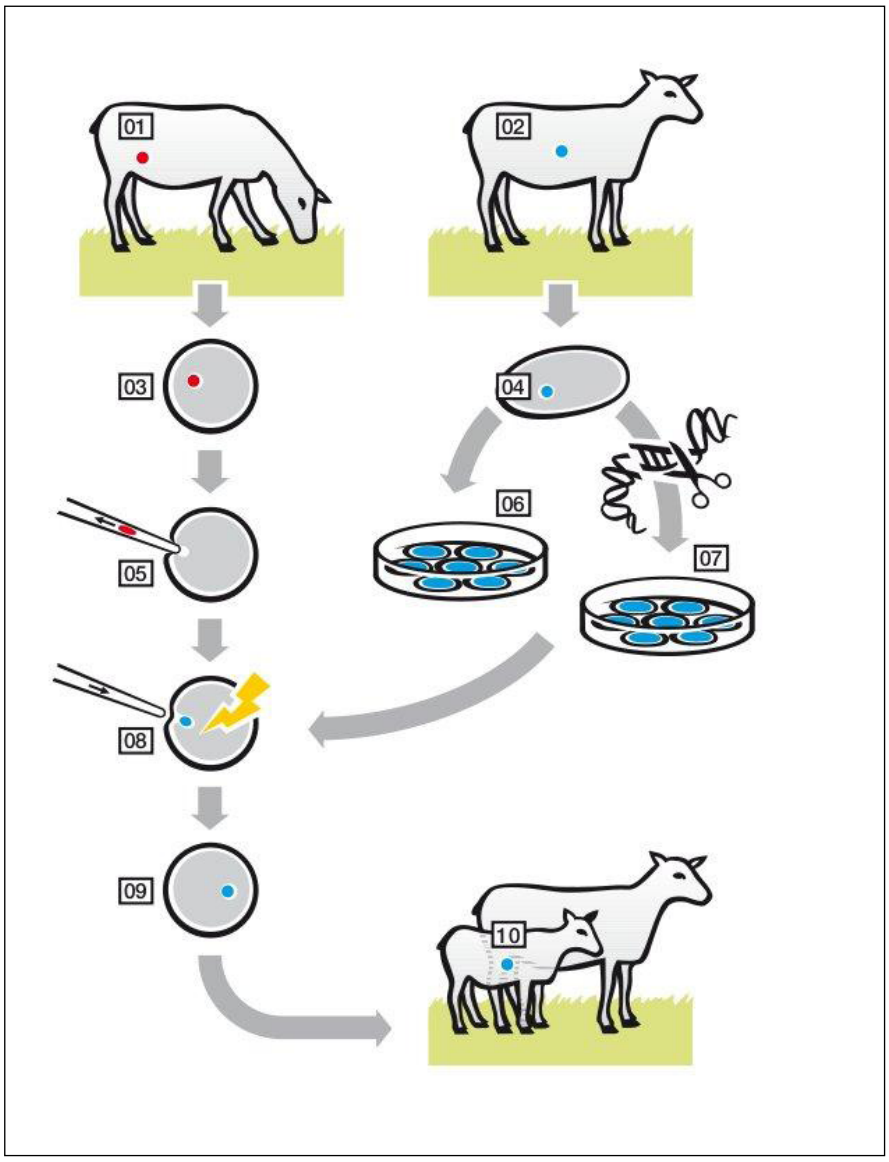

Fig 1: Procedure of cloning involving cell culturing and performing transgenesis
01: Oocyte source 02: donor animal to be clone,
03: Derived oocyte
04: Derived somatic cell
05: Enucleated oocyte
06: Culturing and propagating of the donor cells
07: Optionally genetic engineering of the donor cells can be performed at this stage
08: Fusion of nucleus of donor cell with the oocyte
09: Transfer of the artificial embryo into a surrogat mother
10: Cloned offspring

The use of genetic engineering in combination with SCNT in farm animals is somewhat restricted, because so far it has not been possible to establish lines of embryonic stem cells (ES) from larger animals. Nuclei from ES cells show the highest efficacy in nuclear cell transfer. As Suk et al. (2007) explain:

"A different means of improving gene targeting would be to use embryonic stem (ES) cells either instead of or in conjunction with SCNT, since they are more amenable to homologous recombination than somatic cells and able to differentiate into the full range of embryonic tissues. In this approach, genetic changes could be induced into an ES cell, selected for in vitro, and then returned to the early embryo to continue their normal program of development. This is a promising area, but ES cell lines for livestock species have yet to be successfully developed."

In future more advanced technologies, such as nuclear transfer from induced pluripotent[8] stem cells (iPS cells), might be available for use in this context. Some experts expect major technical progress in the combination of SCNT, cell culturing, iPS cell technology, marker assisted selection and genetic engineering, that will have an impact both agriculture and medical research. For example Niemann et al. (2009) explain:

"The convergence of recent advances in reproductive technology with the tools of molecular biology opens a new dimension for animal breeding."

And the European Group on Ethics in Science and New Technologies[9] (EGE, 2008) explains:

"In the long run, the cloning of farm animals could be combined with genetic modifications so as to have livestock with specific characteristics, for example, genetic resistance to specific diseases (bovine BSE, mastitis, brucellosis, tropical diseases etc.) or producing food products of higher value than natural ones, so-called "nutraceuticals", such as low-lactose milk, kappa casein rich milk, better beef from myostatin TG cattle etc. In this way, cloning – in combination with transgenesis – may be a potentially rich source of edible products for biomedical purposes (e.g. production of proteins, such as milk proteins, to be used for therapeutic purposes at lower cost, or providing a source of organs or tissue for xenotransplantation)."

Given this background and recent expectations by experts in the field, we need to examine the debate about the cloning of farm animals in a broader technical context. After some years of economic disappointment and only slow technical process, the proponents of genetic engineering in livestock are now hoping to reach a new stage of technical possibilities, as a result of a combination of methods such as SCNT, genetic engineering, culturing of embryonic cells (including iPS cells) and marker assisted selection (Schnieke, 2009, Niemann et al., 2009). SCNT in farm animals is practised by some institutions nowadays and is likely to be just a first step for further technical developments in engineering and propagating of livestock for commercial purposes that are around the corner. Thus taking a decision on SCNT technology for food production should keep in mind that European agriculture might be faced with further challenges in animal production that might encounter conflicts to "the European agricultural model, which is based on product quality, environment-friendly principles and respect for stringent animal welfare conditions".[10]

8 Cells, capable of differentiating into more than one cell type.

9 The task of the EGE is to examine ethical questions arising from science and new technologies and on this basis to issue opinions to the European Commission relating to the preparation and implementation of Community legislation or policies: http://ec.europa.eu/european_group_ethics/index_en.htm

10 http://www.europarl.europa.eu/sides/getDoc.do?type=IM-PRESS&reference=20080623IPR32472&secondRef=0&language=EN

2. Technical problems and adverse effects on animal health related to SCNT

Many technical problems related to current technologies used in animal cloning are reported in the opinions of EFSA (2008a, 2009), EGE (2008) and the reports of the 'cloning in public' project (Gjerries & Vatja, 2005), and in reports by the US FDA (2008) and Center for Food Safety (2007). The adverse effects observed are related to systemic disturbances in the regulation of the genome and cannot be confined to single genetic information. Various effects are summarised under the expression 'Large Offspring Syndrome' (LOS), but these effects have many differing causes and a broad range of symptoms. These technical problems and observed adverse effects give rise to questions concerning food safety, animal welfare and the biological integrity of cloned animals.

2.1 Adverse impact on animal health

The artificial embryo produced by SCNT must first be 'reset' to totipotency,[11] to enable it to start full embryonic and foetal development. This process of reprogramming interferes with epigenetic mechanisms that control gene expression.[12] Failure of reprogramming, which can occur to varying degrees, is the cause of many observed adverse health effects affecting the clones. But changes in mitochondrial functions as well as chromosomal disorders and silent DNA mutations are also observed and/or discussed as adverse factors affecting animal health. An overview is given by Gjerries & Vatja (2005), EGE (2008), EFSA (2008a), the FDA (2008) and the Center for Food Safety (2007). Possible adverse effects can be caused and observed at several steps of the cloning process and the life cycle of the animals. The US FDA (2008) uses an approach in which five critical nodes are to be assessed in regard to adverse effects, as shown in Fig. 2:

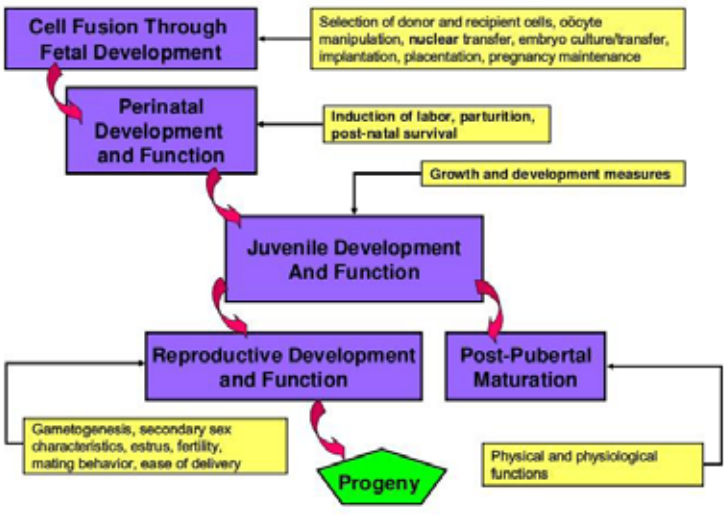

Fig. 2: Five critical nodes for assessing risks from cloning of animals for food production

11 A cell, capable of becoming any cell type in the body

12 Epigenetic processes: Alteration of gene expression by biochemical modifications (e.g. methylation) of the DNA or of DNA-binding proteins. The process does not involve changes in the DNA sequence

Many of the observed adverse health impacts are summarised as Large Offspring Syndrome (LOS). Some effects of LOS are also observed, but at a much lower rate, in animals derived from embryo transfer in cattle and sheep (EFSA 2008a, FDA, 2008). LOS has been especially observed in clones from species of cattle and sheep. They often go together with late gestation and give rise to an increase in perinatal deaths, excess foetal size, abnormal placental development (including an increased incidence of hydrops[13]), enlarged internal organs, increased susceptibility to disease, sudden death, reluctance to suckle and difficulty in breathing and standing. (EFSA 2008a)

In sheep, cows and mice the following problems were detected in sheeps, cows and mice (Gjerries & Vatja, 2005):

- Placental abnormalities
- Foetal overgrowth, prolonged gestation
- Stillbirth, hypoxia, respiratory failure and circulatory problems, lack of postnatal vigour
- Increased body temperature at birth
- Malformations in the urogenital tract
- Malformations in liver and brain
- Immune dysfunction, a malformation of related organs
- Bacterial and viral infections

In contrast to the LOS syndrome observed in cattle and sheep clones, pigs produced by SCNT are more likely to exhibit an increased incidence of intrauterine growth retardation and reduced weight at birth. (EFSA 2008a, FDA, 2008)

There is a lack of understanding of the underlying mechanisms and also there is no coherent definition for LOS. The observers agree that these effects are mostly relevant for the intrauterine[14], the perinatal[15] and the neonatal period. But at a later stage in the first three to six months a high incidence of health implications has been observed by many authors. All these effects contribute finally to a low overall rate of success. This low rate of success is also shown in some of the publications cited by EFSA (2008a) or Gjerries & Vatja (2005):

Panarace et al. (2007): of 3,374 embryo clones transferred into surrogate dams, 317 (9 % live calves were born, 24 hours after birth 278 of these clones (8 %) were alive, and 225 (7 %) were alive at 150 days or more after birth.

Wells et al. (2004): of 988 bovine embryo clones transferred into recipient cows, 133 calves were born and 89 (67 %) of them survived to weaning at three months of age.

13 Abnormal accumulation of fluid
14 During pregnancy
15 Time before and after birthing

The most precarious life period of cloned cattle seems to end at the age of six months. As FDA (2008) concludes:

"During the juvenile period (up to approximately six months of age), bovine clones continue to be at an increased risk of morbidity or mortality compared to animals produced by natural service or ARTs[16]. Estimates of mortality during this period range from 14 to 42 percent. These deaths appear to be sequelae of the initial developmental abnormalities noted in the perinatal node that persist into the juvenile period (e.g. musculoskeletal defects, prolonged recumbency, enlarged umbilicus, respiratory distress, poor thermoregulation, cardiovascular failure, gastroenteritis)."

Most cattle surviving to that age seem to be healthy. But open questions remain, since the parameters for meat and milk composition, blood parameters, and the level of gene expression are reported to be partially different from the parameters of cattle stemming from sexual propagation (for overview see Center for Food Safety, 2007). In some cases health problems in adult animals have also been reported (FDA, 2008, EFSA, 2008a). According to EFSA (2008a) the question of immunocompetence and the susceptibility of clones and their offsprings to diseases and transmissible agents under practical conditions also needs further investigation.

The FDA (2008) also mentions the immune system as potentially affected by the SCNT process. The US authority refers for example to investigations by Ogonuki et al. (2002) and Ogura et al. (2002), that show immune disorders and severe respiratory health problems in mice derived from certain donor cells.

So far only very few studies concerning animal health over whole life spans have been published. Remarkably, FDA (2008) even states that in the case of sheep there have been no published reports on the health status of live sheep clones since Dolly. Since most farm animals are used for the production of meat, it might be a challenge to identify the right scientific approach for investigating their life span and related animal health problems. As FDA (2008) states:

"Currently, it is not possible to draw any conclusions regarding the longevity of livestock clones or possible long-term health consequences associated with cloning due to the relatively short time that the technology has existed."

16 Assisted reproduction technologies such as embryotransfer

2.2 Epigenetics and underlying causes of adverse health impacts

In the EFSA opinion (2008a), FDA (2008) and the report by Gjerries & Vatja (2005), the role of epigenetics is emphasised. Epigenetics is a biological mechanism occurring in all mammals and plants. In recent years, considerable progress has been made in identifying and gaining a more in-depth understanding of the molecular mechanisms underlying epigenetic inheritance. In general, epigenetic mechanisms can be described as alterations of gene expression by biochemical modifications (such as methylation of the DNA or DNA-binding proteins). The process does not involve changes in the DNA sequence but can be transmitted to following generations.

Several epigenetic mechanisms are involved in regulation of the genome during embryonic development, growth and reproduction. These factors can be substantially disturbed by the process of reprogramming. It is due to these systemic effects that the causes of adverse impact of SCNT on animal health have not yet been able to be determined in detail and no precise predictions can be made about their consequences. This gives rise to a high level of uncertainty about adverse health effects in cloned animals and the food derived from them.

A report commissioned by the Netherlands Commission on Genetic Modification (COGEM) explains some of the molecular mechanisms shaping the epigenome of higher organisms (Nap & van Kessel, 2006). These mechanisms may be defined by specific biochemical reactions but their impact can scarcely be predicted, since they are directed not at specific genetic information but the impact of the genome regulation at a general level.

Nap & van Kessel describe four different levels of epigenetic mechanisms:

- DNA methylation (and demethylation)
- Protein (notably histone) modification
- RNA-based mechanisms
- Higher order chromatin-based mechanisms

Nap & van Kessel describe the reprogramming in SCNT as highly problematic and more or less unpredictable in its outcome:

"In contrast, reprogramming for cloning in mammals is problematic. Both the erasure of the epigenetic memory of the differentiated donor cells and the establishment of the epigenetic program of the early embryo appear highly defective in most cloned embryos. Epigenetic reprogramming during cloning is apparently a stochastic process, the outcome of which is difficult, if not impossible, to predict."

According to Gjerries & Vatja (2005) the effects observed are highly dependent on several circumstances and have to be assessed in each and every case. They differ from species to species and are influenced by the source of the donor cell and the quality of the recipient cell. But the 'craftsmanship' (experience technical skills, intuitive understanding and luck) of the person performing the

cloning can also be decisive and cannot be eradicated from the overall process. Even more relevant is the fact that there has been no proof so far of either a common origin or a common mechanism behind the phenomena, while lots of factors that influence the outcome of the process have been observed:

"Numerous experiments have shown that even small changes in the way that the reconstructed egg is activated can affect the number of transferable embryos. The types of chemical used, the parameters of the induced electric impulse, the in vitro system, and also the donor cell source and the culture medium that the cell is reconstructed in, all play an important role."

EFSA (2008a) and FDA (2008) consider epigenetic effects as the main cause of observed adverse effects and a low success rate, without being able to define the cause-effect relationships. EFSA (2008a) states that the outcome of cloning procedures also varies substantially within a single species:

"However, within a given species, success rates can vary extensively, reflecting a lack of full understanding of the role of various factors involved in the cloning process, such as somatic cell and oocyte selection, cell cycle stage, culture conditions, etc."

Other potential causes of adverse health impacts in cloned animals are unintended mutations of the DNA, caused by unspecific mechanisms. It is known that cell culturing methods can induce mutations in the cells. According to EFSA (2008), it is still largely unknown to what extent SCNT induces silent mutations in the nuclear DNA of clones that could be transmitted to later generations (through sexual reproduction).

Another issue discussed by EFSA and FDA (2008) is mitochondrial heteroplasmy. Normally the mitochondria[17] in an embryo originate only from the oocyte. In SCNT not only an isolated nucleus is transferred to the oocyte – often the whole donor cell is transferred. Thus after the fusion the embryo has mitchondria from two individuals and this might lead to genetic imbalance in the cells.

Since the mechanisms cannot be confined to single causes, the chance of predicting the health impacts of cloned animals or avoiding them by certain protocols seems quite low. There is no silver bullet around the corner to overcome these basic problems, although in recent years some research has claimed progress (Kues & Niemann, 2004, Niemann et al., 2009). Using cloning technology to produce farm animals means accepting an enormous degree of unpredictability at each level of the process. This also means that any announcements regarding significantly enhanced success rates have to be treated with caution because such improvements can vary significantly from case to case, depending on numerous factors. As Gjerries & Vatja (2005) summarise:

17 Mitochondria provide the cells' energy – they are part of the nucleus but also contain DNA.

"Although they are suspected by many, neither a common origin nor a common mechanism behind these phenomena have been demonstrated so far."

2.3 Potential impact on future generations

Another open question is the extent to which these epigenetic dysfunctions and genetic alterations can be transferred to the future generations. Many experts expect the epigenetic effects to be eliminated when cell nuclei undergo reprogramming to become germ lines[18] again, as is the case in the sexual reproduction of the next generation (Gjerries & Vatja, 2005, FDA, 2008). And EFSA (2008a) concludes that, based on the limited available data, there is no evidence that epigenetic dysregulation induced by SCNT is transmitted to the progeny (F1). But, on the other hand, EFSA (2008a) refers to experiments on rats that show that epigenetic effects can be found over three following generations:

"Transgenerational epigenetic inheritance in response to various conditions has been documented in many eukaryotes and may play an important role in mammals. In particular, environmental influences may induce a number of epigenetic modifications leading to the silencing or activation of specific genes, especially when pregnant females are maintained in conditions resulting in stress in the dam and foetus. The epigenetic modifications observed in the offspring of those pregnancies may then be transmitted to their progeny. These phenomena, which are considered as mechanisms of adaptation, have been found to be reversible after three generations in rats."

Nap & van Kessel (2006) also explain that larger epidemiological studies reveal effects of epigenetic imprinting that are stable throughout several generations in humans:

"Although most studies of fetal programming only address effects in the first-generation offspring, there are some cases in which programmed phenotypes are maintained for multiple generations. It was shown, for example, that the behavior (or the environment) of young boys could influence the phenotype of their sons and grandsons. The paternal grandfather's food supply during mid childhood was linked to the mortality risk ratio of grandsons, but not granddaughters. This indicates that in humans a one-off event is influencing the phenotype for more than one generation in a sex-specific way."

Jablonka & Raz (2009) – not assessed by EFSA – collected more than 100 cases of inherited epigenetic variations in bacteria, protists, funghi, plants and animals. In most cases the transmission of epigenetic variations over more than two generations were confirmed. Jablonka & Raz (2009) also describe mechanisms observed in mammals that allow the transmission of epigenetic changes through several generations and also persist during the reprogramming in the germ line cell:

18 A reproductive cell such as spermatocyte or an egg cell

"In sexually reproducing organisms, epigenetic variations have to survive the complex process of meiosis in order to be transmitted to the next generation, and, in multicellular organisms, they also have to survive gametogenesis and early embryogenesis – two developmental stages that involve significant restructuring of both cells and chromatin. (...) There is evidence that chromatin marks and RNAs can be transmitted in this manner, but it is not clear how this occurs. It seems likely that some footprints of chromatin marks remain and lead to the reconstruction of ancestral states, or that some remnants of ancestral states (including some RNAs) are retained."

EFSA (2009) also acknowledges publications showing that RNA can be transmitted via semen to the next generation, which is one of the possible transfer mechanisms of epigenetic effects.

Furthermore EFSA (2009) mentions heteroplasmy in mitochondria as being transferred to next generations. Here only a small number of animals was investigated.

"It has been demonstrated that donor mitochondrial DNA (mtDNA) is transmitted to clone offspring with varying efficiencies (Takeda et al., 2008). Four cows (F1) with mtDNA heteroplasmy showed normal growth, productivity and lactation characteristics and productivity."

Given awareness that the mechanisms for epigenetic changes cause a high level of unpredictability, a substantial health risk to following generations cannot be ruled out. It is fairly likely that some of the adverse epigenetic effects can escape restructuring during gametogenesis (becoming a cell in the germ line of the cloned animal).[19] The gametogenesis which is decisive for sexual reproduction of the animals already starts during the growth of the embryo. So far there seems to be some lack of understanding of whether the adverse effects observed in embryos can also impact the genesis of the male or female germ cells (FDA, 2008). It is surprising that the FDA (2008) nevertheless firmly rules out any impacts on following generations.

It is quite plausible that effects in offspring generations of cloned farm animals have hardly been observed so far due to the limited number of cases investigated. Furthermore, some adverse effects might only appear under certain environmental conditions such as stress or infectious diseases under commercial farming conditions. As Edwards et al. (2003) who were not assessed by EFSA, explain, even seemingly healthy and normal clones might be affected by deficiencies:

"However 'normal and healthy' cloned animals may appear, it is possible that undiagnosed pathologies may develop later in life as a result of subtle changes in chromatin structure and/or gene expression. Miyashita et al. noted differences in telomere lengths among cloned cattle derived from different cell types. Moreover, X-

19 The cells in the germ line are those that ultimately become the sperm and egg.

chromosome inactivation may (mice) or may not (cattle) be normal. Wrenzycki et al. noted aberrant expression of genes thought to be of importance in stress adaptation, trophoblastic function, and DNA methylation during preimplantation development in cloned bovine embryos. Yet, many mice and other animals have survived to adulthood despite widespread gene dysregulation, indicating that mammalian development may be rather tolerant to epigenetic aberrations of the genome. The ultimate consequences of epigenetic aberrations of the genome in cloned animals remain unclear but may result in an early death."

Epigenetic dysregulation is not the only possible reason for adverse effects in next generations. Other possible reasons are disturbances on the level of DNA possibly derived from the donor animals or caused by the SCNT process. FDA (2008) mentions three examples:

"Three traits that may be genetically caused were identified (cryptorchidism[20] in three calves derived from the same cell line, parakeratosis[21] in one swine clone, and sensitivity to endophyte[22] toxicity in two cattle clones). These may pose health risks to the animals, and are certainly economically undesirable."

So far it has been impossible to exclude risks for further generations. Where unexpected effects occur in the following generations, they might cause substantial damage because of the widespread use of single bulls for artificial insemination. The Center for Food Safety criticises EFSA for disregarding studies that show epigenetic effects in the F1 generation of cloned animals and warns of potential effects for further generations caused by mutations and epigenetic effects (cited from EFSA 2008b):

"Any chromosomal instability and lack of maintenance of genetic integrity (somatic mutations) in clones could have widespread consequences. Indeed, a large proportion of these putative mutations would have a recessive effect, meaning that they would be expressed, and therefore detected, only several generations after their spread in the populations. The same is true for the epigenetic status of live cloned animals."

It has to be acknowledged that epigenetic disturbances once established and spread through large animal populations have a huge potential for causing extreme damage in animal food production and agriculture.

20 The testes do not descend but remain inside the body
21 Skin Problem
22 Fungal organism

2.4. Animal welfare

Obviously, adverse effects such as LOS are also relevant for animal welfare issues. As the animal welfare group Compassion in World Farming pointed out in a hearing at the EGE (D'Silva, 2007), there are several issues involved in cloning procedures:

- Invasive medical interventions at the level of donor animals.
- Invasive medical interventions as for oocyte extraction in some animal species
- Suffering caused to surrogate mothers (complications during pregnancy and birth)
- Abnormal foetal development and late pregnancy mortality
- Postnatal mortality
- Health problems during life

The EU directive on the protection of animals kept for farming purposes (Directive 98/58/EC) states:

"Natural or artificial breeding or breeding procedures which cause or are likely to cause, suffering or injury to any of the animals concerned must not be practised."

and:

"No animal shall be kept for farming purposes unless it can reasonably be expected, on the basis of its genotype or phenotype, that it can be kept without detrimental effect on its health or welfare."

In view of the suffering caused to cloned animals and to female animals used as surrogate mothers (dams) which usually face caesarean section,[23] Compassion in World Farming calls for a ban on the cloning of animals for food production.

In their conclusion EGE opinion (2008) sees no justification for allowing cloning of animals for food production. The EGE opinion indicates that animal welfare could be seen as a general obstacle to perform cloning in farm animals:

"Considering the current level of suffering and health problems of surrogate dams and animal clones, the Group has doubts as to whether cloning for food is justified. Whether this applies also to the offspring is open to further scientific research."

While animal welfare groups such as Compassion in World Farming and the EGE regard animal welfare issues as major points of concern that put in question the use of cloning of farm animals for food production, EFSA (2008) and the FDA (2008) do not take the same view. While FDA does not discuss animal welfare in detail, EFSA acknowledges adverse effects in cloned animals and surrogate dams:

23 Birth by surgical intervention

"The welfare of both the surrogate dam and a significant proportion of clones has been found to be affected by the adverse health outcomes observed."

But EFSA (2008) does not draw the conclusion that this should be considered unacceptable. In its opinion in 2009 in particular, EFSA gives some credence to reports indicating an increasing success rate. In their conclusion, the EFSA experts even raise expectations that the success rate might be enhanced further, thus reducing animal welfare problems:

"If the success rate of the epigenetic reprogramming is improved it is likely that the pathologies and mortalities observed in a proportion of clones would decrease."

Expectations of this kind are not based on sufficient scientific evidence. There is no doubt that the success rate of cloning in some animal species has increased since Dolly the sheep was born. But a high rate of animal losses, LOS-related symptoms and other effects still occur according to all the studies published, and the causes underlying these problems have not yet been identified properly. Furthermore, the success rate in cloning still differs significantly from case to case. As we explained, differences in the technical protocol, the source and the status of the biological material as well as technical skills influence the result of SCNT. Reports of higher success rates by some experts working with distinct technical protocols and selected species cannot in any way be seen as representative of the overall success rate of the cloning of farm animals. EFSA's expectation (2009) can be seen as reflecting the perspective of those companies or institutions interested in achieving further technical progress, but it cannot be taken as a conclusion based on sufficient scientific evidence.

3. Food safety

In its opinion the FDA (2008) excludes any possible health risks:

"Extensive evaluation of the available data has not identified any subtle hazards that might indicate food consumption risks in healthy clones of cattle, swine, or goats."

Reading the FDA report (2008), there seems to be a consistent attempt to 'downplay' both the effects observed in cloned animals and deviations in the composition of food such as milk. The FDA bases its arguments on a small range of data involving many uncertainties and unexpected effects. The FDA does not consider further investigations but comes up with explanations as to why certain findings are not relevant or why missing data are not a real problem. Rather vague data have been accepted to show that milk from cloned animals does not pose any risk:

"In their Discussion, the authors point out that the discrepancies between the observed values and reference ranges may be explained by the small numbers of animals in their study, and that comparison of milk from clones to milk from a wider selection of control animals that represent more genotypes, nutrition and farming systems would put the values from clones within reference ranges for normal bovine milk. Thus from this pilot study, the authors conclude that the composition of milk from the nine clones was "broadly similar" to milk from the five comparator cows."

Where differences in the physiology of the animals are detected the FDA is dismissing these finding in regard of food safety:

"Although there may be some physiological differences between clones and their comparators during the transition between the perinatal and juvenile developmental nodes, none of these differences indicate the presence of any subtle or frank food consumption hazards."

According to the Center for Food Safety (2007) there are nearly no peer reviewed studies available so far which deal with the safety of food products derived from cloned animals. The FDA has therefore based its conclusion on the safety of milk on only three studies that were available at that time. All three studies on milk showed some differences vis-à-vis samples from other cows. The German authorities for risk assessment seem to be more cautious saying that the FDA report fails to take more recent scientific methods such as metabolic profiling into account to assess equivalence in food products.[24]

Furthermore, the EFSA does not question food safety (2008a, 2009). In its overall conclusion the EFSA (2008a) presented an opinion saying that there are no indications for specific risks attached to food derived from cloned animals:

"(...) there is no indication that differences exist in terms of food safety between food products from healthy cattle and pig clones and their progeny, compared with those from healthy conventionally-bred animals."

24 http://www.bfr.bund.de/cm/208/risikobewertung_der_food_and_drug_administration_zu_lebensmitteln_von_geklonten_tieren.pdf

These conclusions were challenged by the Center for Food Safety. In their response to the EFSA opinion (cited from EFSA 2008b), the Center for Food Safety addresses some significant differences in the composition of meat and milk and therefore it called for further investigations:

"The significant differences in cloned milk composition revealed by these studies raise serious concerns about whether milk from clones is safe for human consumption. Without more data, and standards for which 'normal variations' in protein and fatty acid compositions of meat and milk are safe, any conclusions regarding the safety of food products derived from clones and their progeny are premature."

and:

"In our opinion, this conclusion can be extended to the more general case, considering inter alia that the assessment of compositional analysis of meat and milk from clones is based on a few studies that, in general, analyse small samples."

In the discussion about food safety, we should not lose sight of the fact that EFSA (2008a) and the FDA (2008) mention a higher incidence of infections in cloned farm animals than those farm animals that are the product of conventional breeding. Thus products derived from those animals might also have a higher burden of infectious agents. For example, investigations were carried out to examine whether endogenous retroviruses (such as bovine endogenous retroviruses, BERV) are activated by the cloning process (EFSA, 2009). However, EFSA (2008a) raises some unanswered questions in this regard:

"Should evidence become available of reduced immunocompetence of clones (...), it should be investigated whether, and if so, to what extent, consumption of meat and milk derived from clones or their offspring may lead to an increased human exposure to transmissible agents."

Many questions remain unanswered since there have not been many investigations and the data presented are not generated according to any commonly approved guidelines. It seems premature to make judgements on the particular relevance of these observed differences to food safety.

Further investigations are needed to judge the safety of these products. Since effects depend on various factors such as the animal species, the protocols used for cloning and environmental effects, it will be difficult to come up with any comprehensive and final assessment.

4. Cloning in farm animals – potential benefits, products and players

Cloning animals with desirable traits will significantly raise the number of offspring with special genetic conditions and enable desirable qualities to be rapidly spread throughout the animal populations.

However, any economic advantages that might be gained by companies and some farmers in marketing food derived from cloned animals such as milk and meat has no advantages for food producers or consumers. These products have no key economic advantages that would distinguish them from other products on the market. Since SCNT can only replicate genetic material from animals already in existence, new food products with specific advantages are unlikely.

4.1 How many cloned animals exist and what is their economic relevance?

Currently the market for cloned farm animals is still small. There are three companies in the USA that are known to market cloned animals for food production. These are ViaGen (pigs), TransOva (cattle) and Cyagara (cattle) (Fox, 2008). The number of animals available on the market is comparatively low although there are some precise figures available for the USA and the EU. US officials estimate the number of cloned farm animals at 600 (Fox, 2008). According to industry, about 120 cloned cattle are available within the EU (as quoted by the EGE, 2008).

The EGE (2008) gives some information on the number of research institutions involved in animal cloning but does not reveal its source. It is also still unclear how many of these institutions are working on farm animals meant for food production and which of these institutions are working on livestock meant for upstream production, pharming or other medical purposes:

"At present, more than 160 laboratories in about 37 countries are working on SCNT. Most of the resources are directed towards livestock cloning (around 75% of cases), whereas less than 30% of the work is directed at laboratory animals. Cattle are most efficiently cloned by SCNT, which is practised in around 80 laboratories (50% of total cloning labs) in 24 countries."

Since the cloning of farm animals is also performed in Japan, New Zealand, Brazil, Argentina and China, the actual number of animals involved is thought to be several thousand. These figures do not seem to be based on any empirical study, peer-reviewed publication or registration. EFSA estimates that the number of cloned animals is just below 4,000:

"There is no world-wide register of clones; similarly no register is available in individual countries and therefore the number of living clones is difficult to estimate. From information gathered by EFSA it is estimated that in 2007 in the EU there were about 100 cattle clones and fewer pig clones alive. The estimated number in the USA is about 570 cattle and 10 pig clones. There are also clones produced elsewhere e.g. Argentina, Australia, China, Japan and New Zealand. EFSA estimates

that the total number of clones alive world-wide in 2007 was less than 4000 cattle and 500 pigs." (EFSA 2008a).

Until 2010 there were still no peer reviewed publications available based on empirical systematic research. For example, Heiner Niemann, who works for a governmental research institute in Germany[25] and was involved in the EFSA opinion in 2008 and 2009, told Testbiotech by direct communication that so far about 4,000 cloned cattle and between about 1,000 and 1,500 pigs had been born. He said that this was just an estimate but upon request he could not present peer-reviewed publications. In addition he mentioned EFSA and the FDA as relevant sources, but neither of these institutions cite sufficiently reliable sources. This means that the actual number of cloned farm animals meant for food production cannot be pinpointed exactly.

The news agency Reuters reported in 2009 that there were around 600 cloned cattle in Japan.[26] Adding to that the 120 cloned cattle in Europe and 600 in the USA, it is hard to believe that the quoted figure of 4,000 cloned cattle is actually correct. Moreover, substantial numbers of cloned pigs and cattle are meant for medical purposes (see Schnieke, 2009).

There might be some vested interests in cultivating the impression that many more cloned animals for food production have already been produced than is actually the case. This might put pressure on EU authorities to allow market authorisation. For example, ViaGen told Reuters in 2009 that 6000 cloned cattle already existed in the USA[27] – just one more figure that cannot be verified since no registration is available. There is also some confusion about which cloning technologies (SCNT or ECNT or embryo-splitting) are taken into account. Yang et al. (2007), for example, reported that in the USA about 2,000 bulls had come from embryo-splitting.

Compared to the relatively low number of animals, the propagation and dissemination of the genetic material throughout the populations via artificial insemination (using semen from cloned bulls) is much more relevant. This is also explained by FDA, 2008:

"SCNT has the potential to impact animal breeding in as fundamental a manner as artificial insemination. Given its current high costs (approximately $20,000 for a live calf) and relatively low success rates (< 10 %), SCNT will likely be used to improve production characteristics of food producing animals by providing breeding animals, just as any breeding program would select the most elite animals for breeding, and not as production animals."

25 Friedrich Loeffler Institute, Institute of Animal Genetics, belonging to Federal Ministry of Food, Agriculture and Consumer Protection, BMELV

26 http://www.reuters.com/article/idUSTRE50J1SV20090120

27 http://www.reuters.com/article/idUSN12788712009113?loomia_ow=t0:s0:a49:g43:r1:c1.000000:b30344402:z0

A single cloned bull can be used to generate tens of thousands of semen portions. This issue is highly relevant to traceability and transparency on the level of farm and food production discussed below.

4.2 Weighing up potential commercial benefits

Since cloned animals cannot have superior genetic conditions to the original donor animals, the overall economic advantages can only be expected if specific features are introduced more quickly and on a larger scale in agriculture than is possible by using methods of sexual reproduction. This potential economic advantage on the level of animal production is highlighted by Yang et al. (2007). However, the potential economic advantages of multiplying animals of a certain value must be counterbalanced by potential adverse effects that are likely to be correlated if genetic material from cloned animals is used on a large scale (for example in artificial insemination): If cloning prevails on a large scale there is a substantial risk of shrinking genetic diversity in farm animal populations. This risk already exists without cloning. Cloning has the potential to exacerbate these problems.

Higher productivity in farm animals generally correlates with a trend towards a higher incidence of distress, illness and shorter lifespan of the animals (Rauw et al., 1998, Knaus, 2009) – with and without cloning.

Both trends are already aspects of current breeding. Cloning can substantially increase the problems depending on the extent to which the technology is used. The EGE (2008) and EFSA (2008a) both mention this problem. However, EFSA does not seem to recognise the additional negative impact of cloning compared to current breeding:

"Cloning does not appear to have a direct effect on genetic diversity in that no new genetic modifications are introduced, but there could be an indirect effect due to overuse of a limited number of animals in breeding programmes. An increased homogeneity of a genotype within a population may increase the susceptibility of an animal population to infection and other risk factors. This would also be the case in conventional breeding schemes and is not caused by cloning as such."

In contrast, Compassion in World Farming states that cloning is likely to add to existing problems and may become a driving force in this area, leading to loss of genetic diversity as well as affecting animal welfare beyond current levels (cited from EFSA, 2008b):

"To correctly assess the long-term impact of cloning on the welfare of cattle and pigs, Compassion in World Farming believes that it is important that EFSA pays more attention to the ways in which cloning is likely to be used within the livestock sector. The likelihood is that it will be used to multiply the most high-yielding and productive animals for breeding purposes. Yet research shows that it is these very animals which are most likely to suffer from the metabolic and physiological disorders associated with fast growth and excessive muscle or udder development."

The risk of further losses in genetic diversity is also mentioned by the EGE (2008) and in a report of the US National Academy of Sciences (NAS 2002) which states:

"*(...) disease could spread through susceptible populations more rapidly than through more genetically diverse populations. This concern is well documented and several studies illustrate the susceptibility of species with low genetic diversity to infectious disease.*"[28]

Given the technologies available for the propagation of farm animals (such as artificial insemination), an awareness of the steady progress made in breeding during recent decades and the problems inherent in current breeding (such as loss of genetic diversity and health problems), it is hard to believe that there is any justification for introducing cloned farmed animals.

Companies interested in the technology are looking for a 'killing application' (as it is called by the pharmaceutical industry) to introduce the technology on a wide scale. A review of all the arguments and stories being used in favour of the technology shows that arguments put forward range from combating world hunger to the reintroduction of the mammoth and overcoming illnesses in animals (such as BSE). For example, FDA (2008) summarizes some arguments in favour explaining that cloning can even help people in developing countries:

"Cloning has the relative advantage of allowing for the propagation of animals with known phenotypes to serve as additional breeding animals. This is critically important in breeding programs (...). Second, it allows the propagation of animals whose reproductive function may be impaired. (...). Third, it allows the propagation of valuable deceased animals from which tissue samples have been appropriately collected or preserved, which may have profound implications for species or breeds nearing extinction. Finally, for the first time, cloning allows for the careful study of the "nature-nurture" interactions that influence breeding programs by allowing a large enough sample of genetically identical animals to be raised in different environments, or with different diets. Such studies have been impossible to perform prior to the advent of SCNT and are likely to yield important information for developing livestock species to live in areas that have, until this time, been marginal for food animal production. This is of particular importance to the developing world, where even slightly increased wealth generally favours the incorporation of animal-based agriculture."

Most of these kind of arguments are not based on a sound problem-solution based approach in relation to food and farm production. Thus the EGE (2008) after weighing up several arguments did not find sufficient justification for the introduction of animal cloning for food production, concluding:

28 Cited from statement of ICTA in EFSA 2008b

"At present, the EGE does not see convincing arguments to justify the production of food from clones and their offspring."

4.3 Who benefits from the cloning of farm animals?

Some companies marketing cloned farm animals were listed by Suk et al., 2007. Among those are four US companies, one from Australia, New Zealand and one from China. Companies in Japan and Europe are not listed. ViaGen and its partner TransOva is said to be responsible for most of the cloned animals in the USA.[29] They hold the rights on the patent that was originally granted for the creation of Dolly. According to ViaGen it costs at least US $15,000 to clone a cow and US $4,000 to clone a sow.[30]

Company	Location
ViaGen	Austin, TX, USA
Celentis	Auckland, New Zealand
Clone International	Melbourne, Australia
Cyagra/in vitro Brazil/Goyaike	Elizabethtown, PA, USA/Mogi Mirim, Brazil/Escobar, Argentina
Yangling Keyuan Cloning	Yangling, China
Trans Ova Genetics	Sioux Center, IA, USA
Minitube USA	Verona, WI, USA

Table 1: Livestock biotech companies applying animal cloning for food production (Source: Suk et al., 2007). The list of companies is based on contact with the companies and Internet searches. The industry dynamics in this sector is rapidly changing and this table should not be considerd either definitive or fully up to date.

Taking a closer look at the expectations of the companies involved in cloning it becomes clear that their interest is not only in selling certain animals at high prices. Cloning is largely driven by intellectual property rights that give control over access to genetic material such as semen, embryos and animals. Analyses of patents show that patents filed on cloning technology also cover the animals and their genetic resources as part of the so-called invention. Therefore cloning goes hand in hand with the introduction of exclusive intellectual property rights in animal breeding.

29 http://www.reuters.com/article/idUSN12788712009113?loomia_ow=t0:s0:a49:g43:r1:c1.000000:b30344402:z0

30 http://www.reuters.com/article/idUSN12788712009113?loomia_ow=t0:s0:a49:g43:r1:c1.000000:b30344402:z0

The underlying pattern of introducing patents into animal breeding can be studied examining the patent on the cloned sheep Dolly. A worldwide patent application was filed by Roslin Institute in 1996 (WO1997007669) claiming the methods, the embryo and the cloned animals:

Claim 1 reads: *"A method of reconstituting an animal embryo, the method comprising transferring the nucleus of a quiescent donor cell into a suitable recipient cell."*

Claim 11 reads: *"A method for preparing an animal, the method comprising:*

a) reconstituting an animal embryo as claimed (...)"

b) causing an animal to develop to term from the embryo; and

c) optionally, breeding from the animal so formed."

Claim 14 reads: *"A reconstituted embryo prepared by transferring the nucleus of a quiescent donor cell into a suitable recipient cell."*

Claim 19 reads: *"An animal prepared by a method as claimed."*

This patent was granted by the European Patent Office in 2001 (EP849 990). The wording of the European Patent as granted does not claim the embryos and the animals, but the method for producing them (see claim 1 as cited) and performing breeding of further generations (see claim 11 as cited).

In fact the European Patent is not reduced in its scope. EU Patent Directive 98/44 EC states that a patent on a process for production of plants or animals also covers all biological material hat is derived from them. According to Article 8 (2) of 98/44 EC the exclusive rights as conferred by such a patent can even be transmitted to further generations:

"The protection conferred by a patent on a process that enables a biological material to be produced possessing specific characteristics as a result of the invention shall extend to biological material directly obtained through that process and to any other biological material derived from the directly obtained biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics."

Thus in general a patent on a process for the cloning of animals does not only cover the process but also any derived embryos and animals. The implications for the broad scope of patents can result in far reaching dependencies for farmers and breeders. There may even be an impact on downstream markets such as food processing.

Recent research shows that several patents have been granted by the European Patent Office since the patent on Dolly. The patents as listed do include cloning of farm animals, some of them might also be used for medical purposes.

Patent/ year of granting	Title	Proprietor	Claims
EP 849990 B1 2001	Quiescent cell population for nuclear transfer	Roslin Institute	Method of reconstituting a non-human animal embryo by cloning. Breeding from the cloned animal.
EP 739412 B1 2002	Ungulate embryonic stem cells as nuclear donors and nuclear transfer techniques to produce chimeric and transgenic animals	Infigen Inc.	Method of nuclear transfer using ES cells as nuclear donors. These cells may be transgenic.
EP 972017 B1 2004	Efficient nuclear transfer using fetal fibroblasts	Agrobiogen	Process for the production of ungulate embryos by cloning; process wherein ungulate is bovine, and/or transgenic.
EP 1229784 B1 2005	An improved method for production of porcine clone embryos via somatic cell nuclear transfer	Korea Research Institute of Bioscience and Biotechnology	Method for mass production of porcine clone embryos by nuclear transfer.
EP 1131409 B1 2005	Method of cloning porcine animals	Infigen Inc.	Method for preparing cloned porcine embryo; method for preparing a live-born cloned porcine animal.
EP 938550 B1 2006	Cultured inner cell mass cell lines derived from ungulate embryos	University of Massachusetts	Method for producing ungulate cultured inner cell mass (CICM) cells from of pig or cow, cell lines.
EP1313849 B1 2006	Methods for producing cloned avians	Avigenetics Inc	Method of enucleating recipient avian (chicken) oocyte, wherein oocyte is injected.
EP 1015572 B1 2007	Nuclear transfer with differentiated fetal and adult donor cells	University of Massachusetts	Method of cloning a bovine mammal; method of producing a chimeric bovine embryo.
EP 1127112 B1 2007	Method for cloning animals	Trustees of Tufts College	Method of cloning a non-human animal, as mice, rats, pigs, horses, ruminants: method of producing a non-human transgenic animal, and recombinant protein.
EP 1238584 B1 2007	Method for producing livestock individuals from cells of established cell line	Administrative Agency National Agriculture and Bio-oriented Research Organization; National Livestock Center	Method for producing cloned livestock, preparing a blastocyte and selecting an embryo
EP 1590435 B1 2008	Depletion of endogenous primordial germ cells in avian species	North Carolina State University	Method of modulating primordial germ cells, for producing chimeric animals, as chicken, turkey, duck, quail, sand hill crane;
EP847237 B1 2008	Unactivated oocytes as cytoplast recipients for nuclear transfer	Roslin Institute	Method for reconstructing a mammal as ungulate, cow, bull, pig, goat, sheep, horse; rodent, rat, mouse.
EP1141265 B1 2008	Double nuclear transfer method and results thereof	Revivicor Inc.	Method of cloning ungulate species, as cow, bull, pig, sheep, water buffalo,..: developing foetus and animal, breeding from that animal; with and without genetic engineering
EP1053897 B1 2008	Efficient nuclear transfer using primordial germ cells	Agrobiogen GmbH	Method for cloning animal embryo, ungulate, cattle; method wherein germ cell is also transgenic, method wherein product is secreted into milk.

Patent/ year of granting	Title	Proprietor	Claims
EP1071321 B1 2008	Source of nuclei for nuclear transfer	Consorzio Incremento Zootecnico S.R.L.	Method of reconstructing a embryo, blastocyst, fetus, animal; method wherein animal is ungulate; method of preparing ES cell lines and genetic engineering on this cells.
EP1661456 B1 2009	Tokyo University of Agriculture Educational	Method of constructing nuclear-transplanted egg, parthenogenetic embryo and parthenogenetic	Method of constructing a nucleus-implanted egg wherein egg is haploid; method wherein mammal is mouse, pig, cow, sheep, goat, rat, rabbit; method of constructing parthenogenetic embryo;
EP1049372 B1 2009	University of Hawaii	Full term development of animals from enucleated oocytes reconstituted with adult somatic cell nuclei	Method for cloning non-human mammal; method wherein mammal is primate, ovine, bovine, porcine, ursine, feline, canine, equine, rodents, mouse.
EP1159415 B1 2009	Revivicor Inc.	Genetic modification of somatic cells and uses thereof	Method of nuclear transfer; transgenic non-human embryo, fetus, cell, animal, as sheep, cow, bull, goat, pig, horse, camel, rabbit, rodent; bred animal; clonal pluripotent or totipotent cell population.

Table 2: Examples of granted European patents relating to cloning of farm animals

In 2007, the League for Pastoral Peoples and Endogenous Livestock Development published a report explaining that technologies such as cloning are the entry points for companies to claim monopolies on animal genetic resources, thereby fostering concentration in animal breeding (Gura, 2007):

"The livestock breeding industry has experienced an enormous degree of concentration in recent years, and cloning and gene transfer as well as other emerging technologies including proprietary arrangements can be expected to further speed up concentration. These developments are not in the interest of the general public and will exacerbate prevailing problems associated with high performance breeds and industrial production: large public expenditure caused by animal diseases, environmental pollution, and human diet-related diseases, as well as animal welfare problems."

This aspect was not touched upon by the EFSA (2008a and 2009) and only vaguely addressed by EGE (2008). Patents on farm animals and their offspring can have substantially adverse economic impacts for farmers and breeders as well as they introduce new dependencies for downstream markets. This issue should be taken into account when the Commission, the Member States and the European Parliament discuss and decide on further legal regulation in this context.

There are numerous further patent applications pending in this area. Some of them include further steps such as cell culturing of embryonic stem (ES) cells to enhance efficiency and perform transgenesis in the cloned animals. Even some of the experts involved in the EFSA opinions from 2008 and 2009 are involved in patent applications which mostly address medical purposes (such as Andras Dinnyes, Louis-Marie Houdebine, Heiner Niemann, Jean-Paul Renard and Eckhard Wolf).

But some of the patents also concern livestock and food production. For example, a patent application which names Heiner Niemann as one of the inventors (WO2005038014, patent applicant Innovative Dairy Products Ltd, Australia) aims to raise efficiency in cloning procedures by using stem cell-like cells, including animal species such as kangaroo, wallaby, whales, dolphins, elephants, horses, giraffe, cows or bulls, sheep, camels, llama, pigs and hippos (as listed in claim 14 of this application). According to the patent application cells from these animals would be used for performing transgenesis and cloning for medical purposes as well as in agriculture.

Since the EFSA has a responsibility to act independently of vested interests, it is highly questionable that experts like Niemann were invited to work on EFSA's expert opinion on cloning. Experts who are developing new technologies for cloning and are even involved in their commercial application can hardly be seen as independent when the potential impacts of the technology have to be assessed. Gjerries & Vatja (2005) even explicitly name Heiner Niemann as being one of the experts who are "'cultivating' (...) a river of optimism that tends to reduce the unanswered questions within farm animal cloning to mere technological problems that will soon be fixed (...)".

5. Need for regulation

The European Commission has started a process designed to regulate products derived from cloned animals under the Novel Food Regulation[31]. Transparency and measures for the effective control of possible entry points into the markets for farm and food products derived from cloned animals and their offspring should be in place before such products come to the market. However, there are how-ever serious doubts whether the Novel Food Regulation can meet this challenge.

5.1 Which products are already on the EU market?

Suk et al. (2007) compiled an overview of potential products that could hit the markets within the next few years.[32]

2005 to 2010: semen and offspring from cloned cattle and milk, meat and derivates from offspring of cloned cattle; semen and offspring from cloned pigs, and pig meat and derivates from offspring of cloned pigs

2010 to 2015: cloned cattle and milk, beef and derivates from cloned cattle; cloned pigs, pig meat and derivates from cloned pigs.

The question arises as to whether these products have already reached the EU market without being noticed. On the whole this is very likely. The import of semen from cloned animals or even the import of embryos is not prohibited. Currently, the EU buys $23 million worth of bull semen from the US every year.[33] Testbiotech questioned Heiner Niemann, ViaGen and customs authorities in Germany about imports of semen from cloned animals. They did not provide any answers apart from the information that imports were possible. In 2007 it was discovered that in the UK, offspring of cloned cows had been born after cloned embryos had been imported.[34] Government authorities said that the import of cloned embryos was legal because EU regulations do not draw any distinction (Idel, 2007). Swiss authorities are convinced that semen from cloned cows has reached the country and that several hundred offspring are alive and their products are likely to have reached the food market.[35]

It is quite probably that material from cloned farm animals has already reached the EU and has been disseminated within the EU. Such products might even have entered the food chain in European markets. This situation needs to be redressed urgently by a new European legislation. Effective measures are needed to prevent products penetrating the markets without control and transparency.

31 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2007:0872:FIN:EN:PDF
32 Table, taken from EGE 2008, citing Suk et al, 2007
33 The Wall Street Journal Online, January 2008
34 http://www.dailymail.co.uk/news/article-1024578/Eight-clone-farm-cows-born-Britain--meat-sale-months.html
35 http://www.bag.admin.ch/themen/lebensmittel/04861/05316/index.html?lang=de

5.2 A broader perspective

The market for cloned animals for food production seems to be quite small but its overall impact goes far beyond The niche market of producing and selling cloned animals. Animal cloning for food production will impact farm and food production, animal welfare, biological diversity, transparency, traceability and food safety. It is likely to go further and pave the way for genetic engineering in livestock. One other aspect in the context of SCNT is its potential for encouraging human cloning. These specific concerns were important for the national legislation in Norway (see below).

Introducing controversial products (such as products derived from the cloning of farm animals) into the chain of European food production without any transparency is unacceptable to civil society. In the context of the ethical aspects of livestock engineering Kaiser (2009), for example, points out that:

"When it comes to evaluating the ethics of livestock engineering, science and technology alone cannot provide the answers, and neither can surveys that simply mirror emotional reactions of sectors of the public. We need a broad social debate about the paths that we choose, in particular a debate that pays respect to ethical arguments and is informed by science."

Decision making cannot only focus on technical aspects but must take into account a broader range of concerns. As Gunning (2006) explains this approach is also required by EU law:

"Risks to human health and the environment posed by animal cloning obviously raise concerns that need to be addressed. However, in addition to scientific uncertainty there remains uncertainty about the acceptability of products from cloned animals. That acceptability may be linked to a number of other important concerns such as animal welfare, animal integrity, consumers' rights and, more generally, an interest in promoting the basic values underpinning the EU (e.g. sustainability, biodiversity) and in promoting the precautionary principle."

Recital 19 of Regulation 178/2002/EC concerning basic European regulations of food safety and consumer protection explicitly mentions that societal, economic, traditional and ethical factors should be taken into account:

"It is recognised that scientific risk assessment alone cannot, in some cases, provide all the information on which a risk management decision should be based, and that other factors relevant to the matter under consideration should legitimately be taken into account including societal, economic, traditional, ethical and environmental factors and the feasibility of controls."

Animal closing raises a number of fundamental concerns. Gunning (2006) mentions animal integrity as an example of the questions connected with the debate about cloning and SCNT. Animal integrity is a concept which goes beyond animal welfare. It was also discussed in the context of legislation in Denmark:

"Another type of concern is animal integrity. This was raised in connection with the Danish legislation on farm animal cloning. Integrity can be defined in a number of ways, but here it implies that more is at stake than animal welfare: that is, integrity demands that we ask whether animal cloning technology conflicts with what is considered permissible human utilisation of animals, regardless of reduced welfare or not."

Basic ethical concerns directed at animal welfare and animal integrity as well as socio-economic impacts must not be ignored when decisions about the regulation of SCNT are made. Compared to issues regarding food safety these issues might be harder to assess, but nevertheless they are accepted as being relevant under legislation within the EU. Ignoring widespread concerns and consumer rejection can jeopardise the EU's legitimacy. A Eurobarometer poll published in October 2008[36] showed that 58% of the European citizens thought that cloning for food production could never be justified. A big majority of 83% said that special labelling should be required if food products from the offspring of cloned animals became available in the shops. 63% stated that it was unlikely that they would buy meat or milk from cloned animals, even if a trusted source stated that such products were safe to eat. Similarly, in the USA, 77% of the American consumers are "not comfortable" with eating cloned animal products, and 81% of the American consumers believe that cloned foods should be labelled.[37]

Consumers might be turned into some kind of 'end of pipe hostage'. They are already trapped in the usage of genetically engineered plants. There is a high risk that in the case of cloned farm animals the food market will simply provide products from extreme industrial agricultural production without respecting the wishes of a broad majority of consumers who reject those kinds of products.

If the EU decides not to have a general ban on the cloning of animals for food production, at least a high degree of transparency and traceability should be implemented in order to enable sufficient choice at the level of farm and food production as well as within the food market. These mechanisms might generate high costs and confine the economic advantages to small niche market in animal production.

36 http://europa.eu/rapid/pressReleasesAction.do?reference=IP/08/1478&format=HTML&aged=0&language=EN

37 US Food Marketing Institute, May 2008
http://www.fmi.org/news_releases/index.cfm?fuseaction=mediatext&id=935

6. Framework legislation

So far there is no specific legislation within the EU that deals with the cloning of farm animals. However the existing EU regulation touches on several related aspects such as animal welfare, food safety, health protection, the zootechnical sector and patent law (Gunning, 2006, EGE, 2008)

Some national legislation dealing specifically with animal cloning is in place in Denmark, the Netherlands and Norway. These laws mainly concern the cloning procedure but do not legislate on products derived from cloned animals (semen, embryos or food products).

The European Council is currently planning to include food products from cloned animals into the Novel Food Regulation until specific legislation takes effect. The European Parliament voted for a general ban. The following paragraphs describe some of the existing legislation and new approaches that can meet current needs for regulation.

6.1 National legislation

Denmark:

The law only allows animal experiments involving cloning and genetic engineering for certain purposes such as basic research, health issues and environmental benefits. Furthermore, a license from the national authorities is required in each case. These requirements also apply to the breeding of cloned or genetically modified test animals and in cases where a previously cloned or genetically modified animal is used for research purposes. In practice, this can be seen as a barrier to the cloning of farm animals for food production. On the other hand it does not cover the import and breeding of cloned or genetically modified animals for purposes other than animal experiments (e.g. food production, etc.) (Gamborg et al., 2005, Gunning et al., 2006, EGE, 2008).

Germany

Under German law on animal welfare, permission must be sought for animal genome experiments that might cause pain, suffering or damage. Subsequent breeding is also covered by legislation. Such legislation pertains to cloning since it interferes with animal genomes and is not seen as an established breeding process. There are no laws that concern the import of cloned animals or semen or embryos derived from cloned animals. The same is true for food products.[38]

The Netherlands

There is no specific legislation. Like Germany, the cloning of animals is regulated via the Animal Health and Welfare Act. All biotechnological animal experiments, including cloning by nuclear transfer, have to be approved by the

38 http://www.gesetze-im-internet.de/tierschg/

Ministry of Agriculture. It is a requirement that experiments do not solely follow scientific research purposes – they must have substantial societal relevance. Moreover, there should be no alternatives to achieving the aim of the research or application, and the importance of the research or application must outweigh the possible damage to the health, welfare and integrity of the animals. (Gamborg et al., 2005)

Norway

In May 2004, Norway became the first European country to issue legislation on animal cloning. The main provision prohibits the cloning of vertebrates although it is possible to have a dispensation for basic biological and medical research and other medical activities. The cloning of primates is prohibited without exemption. The restrictions on animal cloning do not cover cloning processes which could take place in nature (embryo splitting). The Norwegian law, like the Danish law, emphasises respect for animal integrity as an independent value that goes beyond welfare. The Norwegian legislation only covers the production of cloned animals. One of its principal aims is to prevent human cloning, and it is silent both on the import of cloned animals and imports of their products. (Gamborg et al., 2005, Gunning et al., 2006)

Gamborg et al., 2005 summarize the situation regarding national legislation as follows:

"To summarise, in most countries there is no legislation directly prohibiting the cloning of animals, and hence farm animals. Instead – where it is regulated at all – cloning is indirectly regulated through laws on the protection of animals and animal research legislation. As with other types of animal experimentation, experiments connected with the cloning of animals have to be approved by the relevant authorities. To date Denmark and Norway are the only two European countries to have taken legislative initiatives on animal cloning and to have passed cloning legislation."

6.2 EU legislation

The EU has comprehensive regulations that deal with animal welfare[39], traceability in food markets[40] and labelling[41], risk assessment[42], food safety[43], import of animals and material for breeding[44] and patents[45]. Gunning et al. (2006) and EGE (2008) provide a further overview, but they differ in part in their interpretations.

6.2.1 Animal welfare

As national legislation shows, authorisation to perform research involving cloned animals can be regulated by animal welfare legislation. Since cloning of farm animals causes additional suffering compared to normal breeding, it is legitimate to prohibit cloning of farm animals for food production. Paragraph 20 of the Annex to Directive 98/58 for example prohibits the use of breeding procedures (natural or artificial) that cause or are likely to cause suffering or injury to animals. This provision could be a starting point for regulating the use of cloning in farm animals. EU legislation places a great deal of emphasis on animal welfare. Consequently, a clear, prohibitive regulation which is in accordance with or goes beyond existing national legislation, as is the case in Norway, would not pose any conflict with the EU's legal system and its internal market. The Directive 2010/63/EC takes into account the protection of animals used for scientific purposes. It requires a mandatory review of ethical aspects of animal experiments in all Member States.

6.2.2 Imports of genetic material and food products

As shown above the imports of animals, semen, oocytes and embryos from animals and their offspring produced by SCNT is a crucial issue. Imports of semen and embryos are the starting point for broader distribution of cloned animals and their progenies, and regulation at this level is critical for transparency, traceability and effective controls. From the perspective of consumers in particular, food derived from cloned animals or their offspring needs to be regulated, *inter alia* for ethical reasons.

39 such as Directive 98/58/EC, 86/609/EEC
40 such as Regulation 1830/2003/EC
41 such as Regulation 258/97/EC, Directive 2000/13/EC
42 such as Regulation 1829/2003/EC and Directive 2001/18/EC
43 Regulation 178/2002 EC, Regulation 1829/2003
44 Directive 77/504 EEC, Directive 94/28EC, Directive 89/556/EEC and Directive 88/407/EEC
45 Directive 98/44 EC

6.2.2.1 Scientific reasons for an import ban

Legislation in this sphere deals with import regulations and free movement of goods and is therefore of a complex nature. But there are some legitimate reasons to prohibit the import of genetic material derived from cloned farm animals and their offspring. The arguments can be deduced from mechanisms of genetics and epigenetics and the effects observed in cloned animals. As explained, cloned animals show a broad variation of health problems which can include the immune system. Potential risks concern animal and human health. The possibility of transmitting agents posing risks to human health is discussed by EFSA (2008a). Since no definitive causes for adverse health impacts are known, it is difficult to define a reliable risk assessment for the safety of genetic material from cloned animals.

Furthermore, the risks cannot be confined to the first generation of cloned animals. Mechanisms are known that in principle allow the transfer of epigenetic effects and genetic defects to the next generations. For example RNA can for example be transmitted via semen, as discussed by EFSA (2009). Epigenetic imprinting is not completely deleted by the process of reprogramming during sexual reproduction (Jablonka & Raz, 2009). Mitochondrial heteroplasmy is also found in F1 generations.

Food products derived from cloned animals will also always imply a certain level of uncertainty emerging from the various factors that can impact the result of SCNT. There is no history of safe use in this technology and its products. Further risk assessment of food products derived from cloned animals produced under certain technical procedures can hardly be transferred to other cloned animals (and their products) because of the broad range of factors impacting SCNT.

The WTO agreements such as the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and the Agreement on Technical Barriers to Trade (TBT Agreement) allow market measures, if they are based on the precautionary principle, only to be applied only for a limited period of time. If these agreements are seen as relevant,[46] any period of time should cover at least several full life spans of animals derived from SCNT. Furthermore concerning technical uncertainties a much larger number of animals and derived products needs to be tested.

The risk assessment should be performed case by case. Any change in technical procedure with SCNT might impose further market bans related to products

46 The TBT Agreement does not apply to SPS measures - see Article 1(4) of the TBT Agreement. Annex A of the SPS Agreement defines four types of SPS measures according to their purpose. If SCNT food products are seen as (a, c, d) "pests, diseases, disease-carrying organisms or disease-causing organisms" or (b) "additives, contaminants, toxins or disease-causing organisms" the SPS Agreement would be relevant.

derived by a new or altered technical method. Thus, market measures based on the precautionary principle should be understood as applying for a longer period of time, taking into account the complexity of scientific issues.

6.2.2.2 Should cloned animals be considered as genetically modified?

In the context of international trade, a relevant question is whether genetic material from cloned farm animals should be defined as genetically modified as defined in Directive 2001/18. While the EGE (2008) is of the opinion that this legislation cannot in general apply to cloned animals, other scientific opinions might be justified. Arguments can be based on the recent understanding of biomolecular mechanisms. The SCNT process interferes with epigenetic mechanisms on several levels of the genome. This can be seen as technically induced modification of genome regulation. Furthermore, combining the mitochondrial DNA of the donor animal with the mitochondrial DNA of an oocyte from another animal can be seen as technical modification of the animals' DNA. Edwards et al. (2003) warn of effects of mismatching nuclear and mitochondrial genes.

The notion that some genetic modification is caused by the process of cloning cannot, as a rule, be dismissed. As the EGE (2008) clearly points out, a clone is not a copy. Since most of the differences between the original animal and its clone are caused by the SCNT procedure, clones can be defined as animals with non-targeted, technically derived genetic modifications. Gunning et al. (2006) summarize some open questions concerning the issue of genetic modification:

"However, it is also necessary to consider whether SCNT in itself involves genetic modification. If that is the case, all SCNT-cloned animals will fall under the scope of the GMO regulation. In connection with Article 2(2) in Directive 2001/18 there is disagreement among the scientific experts as to whether the use of SCNT in itself involves 'alteration' of genetic material."

Gunning et al. (2006) discuss several options in relation to the definition of the EU Directive 2001/18:

"If non-transgenic clones were included, it would need to be decided whether they fell into the definition under Annex IA(2), because the nuclear DNA, which is heritable material, is prepared outside the organism (if an egg can be called that) and is introduced by micro-injection. It might also fall under the definition given in Annex IA(3). While SCNT does not form new combinations of genetic material through the fusion of two cells, nuclear DNA from a somatic cell forms a new association with the mitochondrial DNA in the enucleated egg cell in which it is placed. Both types of DNA are heritable, and the method by which they are brought together is not natural." [47]

47 Annex IA, defines genetically modified organisms for example as a result of a cell fusion: (3) „cell fusion (including protoplast fusion) or hybridisation techniques where live cells with

If clones derived from SCNT are considered as genetically modified, not only does GMO legislation like 2001/18 and 1829/2003 come into play, so does the Cartagena Protocol. As Gunning et al. (2006) explain:

"The Cartagena protocol may be relevant here. If there is any possible adverse effect on biological diversity, or on human health, trans-boundary protection may be needed. For GMOs there is a system for notifying and exchanging information on GMO exports to third-party countries, and specific procedures govern the way exporters and importers must notify the Biosafety Clearing House set up by the Cartagena protocol."

6.2.2.3 Moral reasons for import ban

Many observers believe that a general ban on food products from cloned animals might raise problems with the WTO, if ethical reasons are put forward. Gunning et al. (2006) for example discuss these questions:

"If the EU were to ban animal cloning (or even just farm animal cloning) from a moral standpoint, it would follow that it should not allow imports of products from cloned animals from other countries. This would put the EU in a difficult position with regard to international trade agreements and the WTO, since moral grounds for embargoes on goods or products from other countries are prohibited."

The view presented by Gunning et al. (2006) is a good example of the 'chill effect'. 'Chill' or 'chilling effect' means to state something which is obviously wrong, incorrect, or at least very controversial and should be subjected to a trade dispute settlement with the aim of preventing any trade restriction. Contrary to the view presented in Gunning's statement on Article XX (General Exceptions) of the main WTO agreement, the General Agreement on Tariffs and Trade (GATT) declares that

"nothing in this Agreement shall be construed to prevent the adoption or enforcement by any contracting party of measures [which are] (a) necessary to protect public morals and names tene additional reasons among them, (b) necessary to protect human, animal or plant life or health... [or] (g) relating to the conservation of exhaustible natural resources if such measures are made effective in conjunction with restrictions on domestic production or consumption."[48]

In addition another WTO agreement, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), allows measures necessary to protect ordre public or morality. Article 27 (Patentable Subject Matter) says

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new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally."

48 For environmental related WTO cases refering to GATT Article XX (b), (d) and (g) see http://www.wto.org/english/tratop_e/envir_e/edis00_e.htm
http://docsonline.wto.org/imrd/directdoc.asp?DDFDocuments/t/wt/cte/w203.doc

" (2) Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law."[49]

The third example showing that morality is a relevant category under the WTO is taken from a speech by the Director General of the WTO, Pascal Lamy. While speaking about the moral and ethical responsibility to preserve the flora and fauna Lamy said:

"Today, more than ever before, we have become conscious of the fact that we do not simply live on a planet, but live on what is itself a "living planet". There are many reasons why that planet needs to be kept alive. First, is the wellbeing of the human race – which cannot itself thrive in an unhealthy ecosystem. But, second, is our moral and ethical responsibility to preserve the flora and fauna on whose habitats we intrude as we construct our own. The preservation of our biological diversity is a responsibility that we owe not only to this generation, but to future generations too."[50]

While the history of WTO dispute settlement cases and the interpretation of existing trade laws by the WTO member states shows that environmental, health or ethical concerns are not favoured, there is nothing in general in the WTO rules prohibiting "moral grounds for embargoes on goods or products from other countries". On the other hand "moral grounds" are not mentioned in two other WTO agreements which are in general relevant for food products: the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and the Agreement on Technical Barriers to Trade (TBT Agreement).

The legitimacy of the WTO to force-feed markets with products that are matters of deep ethical concern and imply a high level of technical uncertainty is not set in stone. The discussion about food imports from cloned animals is likely to add to the demands and discussions about strengthening consumer rights with respect to the interests of international markets. In any case, European risk managers must take socio-economic and ethical aspects into account. The European Commission should have the courage to undertake non-discriminatory trade restrictions and not use the WTO 'chill effect' as an excuse for avoiding any regulation.

Even if products are banned from the EU market, traceability has to be organised in international markets. Companies in the US have already developed a

49 http://www.wto.org/english/docs_e/legal_e/27-trips.doc

50 WTO DG Pascal Lamy at the Ministerial Segment — Panel on Biodiversity and Trade - Convention on Biological Diversity 8th Meeting of the Conference of the Parties (Cop-8)26-29 March 2006, http://www.wto.org/english/news_e/sppl_e/sppl22_e.htm

system of tracking cloned animals.[51] These systems have to be expanded to the level of food production. Relevant genetic markers to identify products from cloned animals together with a system of comprehensive documentation and registration have to be implemented. Existing registers could, for instance, be expanded to include information on whether an animal was cloned or was the offspring of a cloned animal (Gunning et al., 2006). Several announcements have been made by companies such as ViaGen and TransOva saying they will establish mechanisms to track their animals used in farming,[52] and companies such as IndentiGen are able to provide DNA technologies for tracing meat from specific sources.[53]

6.2.3 Patents

European Directive 98/44 does allow patents on animals and plants – something which has been the subject of controversy for years. There is growing political determination within the EU to prohibit patents on animals and plants. The German government follows the political goal of avoiding patents on plants and animals in general[54]. Since new dependencies for farmers and adverse impacts on research and food security have to be expected if patents on seeds and farm animals are granted, patent law should be changed to define clear prohibitions concerning patents on genetic material from plants and animals.

The current legislation might already allow patents on the process of cloning animals for food production to be ruled out in some cases. Article 6 of Directive 98/44/EC prohibits patents on the process for modifying the genetic identity of animals in case it is likely to cause suffering without substantial medical benefit. Since medical benefits can not be expected from animals cloned for food production, and the suffering of animals caused by SCNT cannot be denied, patents might be challenged. In cases where patents cover both – medical and farm purposes – a disclaimer could be introduced to exclude patents for cloning of animals for food production.

51 See for example: http://www.medscape.com/viewarticle/570297

52 Cloning Companies Promise to Track Their Animals, 20 December 2007m http://www.wired.com/wiredscience/2007/12/cloning-compani/

53 http://www.identigen.com/

54 Aigner fordert Änderung des europäischen Biopatentrechts, 10 Juni 2009 http://www.bmelv.de/SharedDocs/Pressemitteilungen/2009/120-AI-Biopatente.html

Conclusions and Recommendations

Following the analysis made in this report, the most urgent sector for EU regulation is the production, import and usage of semen, embryos and animals and their offspring derived from SCNT. These products have a high potential for infiltration and dissemination in markets. Transparency, traceability and segregation on this level of production, import and usage is a prerequisite for all other downstream markets of farm and food production.

These problems cannot be solved by the Novel Food regulation. They need regulating at other levels of legislation, such as the import of breeding material and animal welfare legislation. This can be seen as a decisive reason for following the approach of the European Parliament in imposing a ban on the production, import and usage of cloned animals for food production and related genetic material. In this way further risks of infiltrating the markets could be avoided, thus providing enough time for appropriate long term solutions to be found and further developments monitored.

The legal mechanisms for imposing a ban can be deduced from existing animal welfare legislation and the regulation of zootechnical issues and animal breeding. The regulation on genetically engineered organisms can also be taken into account. Ultimately, a specific regulation on cloning animals covering all aspects seems to be the best solution, in order not to create legal uncertainty by having an overly fragmented regulatory framework.

A specific legislation to clarify the legal situation in Europe is a matter of high urgency, not only from the point of view of European farm and food production and the interests of the consumers, but also for the international markets. Companies from outside the EU need legal certainty in order to implement segregation and traceability as necessary, and thus safeguard the free movement of breeding material which is not derived from cloned animals.

Regulations concerning the markets for food production are matters of high urgency as well, but measures on this level can only be applied successfully if upstream production is sufficiently regulated by specific legislation. From the perspective of the precautionary principle, a ban on food derived from cloned animals might be introduced for several years at least, since the necessary data have to be the result of a systematic approach and need to be based on sufficiently detailed guidelines. Potential guidelines for the risk assessment of cloned animals have to define a proper time frame covering several generations of farm animals during their whole life span. Further to this, a high number of animals derived from the various technical protocols have to be investigated thoroughly, on a case-by-case basis, before decisions regarding food safety can be taken.

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