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Biotechnology in Animal Agriculture: Status and Current Issues

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Summary

Animal agriculture is being transformed by rapid advances in biotechnology — a term that encompasses a variety of technologies, including genetic engineering (GE), genetic modification, transgenics, recombinant DNA techniques, and cloning, among others. Producers are interested in the application of biotechnology to improve productivity, consistency, and quality; to introduce new food, fiber, and medical products; and to protect the environment. Potential human health applications of transgenic animals include producing biopharmaceuticals and generating organs, tissues, and cells for xenotransplantation. Criticisms of such applications involve issues ranging from food safety and social resistance to potential negative impacts on animal welfare and on ecosystems. Questions also have arisen about the adequacy of the current regulatory structure to assess and manage any risks created by these technologies.

A final risk assessment and industry guidance on the safety of meat and milk from cloned cattle, pigs, and goats and their offspring were released January 15, 2008, by the U.S. Food and Drug Administration (FDA). The documents generally echoed the FDA's December 28, 2006, draft risk assessment, which found that such products are as safe to eat as those of conventionally bred animals. The FDA also concluded that cloning poses the same risks to animal health as those found in animals created through other assisted reproductive technologies — although the frequency of such problems is higher in cloning. (Scientists stress that cloning is an assisted reproduction technique that does not involve any transfer or alteration of genes through GE.) The agency said it was no longer asking industry to refrain voluntarily from marketing the products of cloned animals and their offspring, although the U.S. Department of Agriculture (USDA) has since asked that it be continued for products from clones (but not from the offspring of clones).

The European Food Safety Authority (EFSA) on January 11, 2008, released for public consultation its own draft scientific opinion on the food safety, animal health, and environmental aspects of animal clones and their progeny. EFSA also concluded that food products from healthy cloned cattle and pigs and their offspring are no less safe than food products from conventionally bred animals. EFSA's findings on animal health were similar to the FDA's, and EFSA predicted no environmental impacts, based on the limited data available. Meanwhile, a different European agency is charged with providing an opinion on the ethics of cloning.

The Senate-passed version of the pending omnibus farm bill (H.R. 2419) would have delayed the final risk assessment and continued the marketing moratorium until completion of newly mandated studies on the safety and on the market impacts of introducing such products. The impact of this language, if it survives a House-Senate conference on H.R. 2419 in early 2008, is now less clear. Other pending bills on animal cloning include S. 414 and H.R. 992, to require all food from cloned animals or their offspring to be labeled; and S. 536, to prohibit food from cloned animals from being labeled as organic.

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Introduction

The U.S. Food and Drug Administration, on January 15, 2008, released a final risk assessment and industry guidance on the safety of milk and meat from cloned animals and their offspring. Its finding — generally, that such products from cattle, pigs, and goats are as safe as products from their non-cloned counterparts — has renewed public interest animal biotechnology in general and animal cloning in particular. (Cloning by itself is not considered to be genetic engineering; see discussion later in this report).

Biotechnology is a broadly defined term of relatively recent origin describing the range of modern knowledge, applications, and techniques underlying advances in many fields, notably health care and agriculture. Animal biotechnology has been defined as "that set of techniques by which living creatures are modified for the benefit of humans and other animals."[1] By its very nature, agricultural development is the history of humans modifying plants and animals to maximize desirable traits. For example, domestication and selective breeding of animals date back many thousands of years. Artificial insemination of livestock, notably dairy cattle, is another, more recent, biological technology, first finding wide commercial acceptance in the 1950s.

Discovery of the genetic code in the 1950s gave birth to modern techniques of biotechnology. One of the first commercial products of this new biotechnology in

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[1] National Research Council (NRC), *Animal Biotechnology: Science-Based Concerns*, (Washington, DC, National Academy Press, 2002). (Hereafter cited as NRC, *Animal Biotechnology*.) Unless noted, this CRS report is based on material in that document and the following additional sources: Institute of Medicine (IOM) and NRC, *Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects* (Washington, DC, National Academy Press, 2004). (Hereafter cited as IOM-NRC, *Safety of Genetically Engineered Food*.); Council for Agricultural Science and Technology (CAST), *Biotechnology in Animal Agriculture: An Overview* (Issue Paper 23) (Washington, DC, February 2003). (Hereafter cited as CAST, *Animal Agriculture*.); Pew Initiative on Food and Biotechnology, *Issues in the Regulation of Genetically Engineered Plants and Animals*, (Washington, DC, Pew Initiative April 2004. See [http://pewagbiotech.org/research/regulation/].) (Hereafter cited as Pew, *Issues in Regulation*.); Pew Initiative on Food and Biotechnology, *Post-Market Oversight of Biotech Foods* (Washington, DC, Pew Initiative April 2003) (and other Pew materials); information accessed through the websites of the Biotechnology Industry Organization at [http://www.bio.org/]; the Center for Food Safety, at [http://www.centerforfoodsafety.org/]; the Union of Concerned Scientists, at [http://www.ucsusa.org/]; and the Consumer Federation of America, at [http://www.consumerfed.org/].

animal agriculture was bovine somatotropin (bST), a naturally occurring metabolic modifier that is now being manufactured in larger quantities through the use of recombinant DNA technology. Manufactured bST came onto the market in 1994 and is now administered to as many as half of all U.S. dairy cattle to increase per-cow milk output. Although bST is being used commercially in approximately 20 countries, it is banned in the European Union (EU).

Other agricultural biotechnology developments include pigs that have been engineered for increased sow milk output to produce faster-growing piglets. Cloned cattle also have been developed to resist mastitis, and transgenic salmon with enhanced growth characteristics are under regulatory consideration for possible commercialization. Output traits such as drugs recovered from animal milk ("pharming"), milk that lacks allergenic proteins, and animal organs for human transplant (xenotransplantation) that resist rejection are other contemporary objectives of animal biotechnology research. In March 2006, researchers at the University of Missouri announced the creation of transgenic pigs whose tissue contains omega-3 fatty acids.[2] The consumption of omega-3 fatty acids, found primarily in fish, has been linked to lowered incidence of heart disease in humans. Similar research is also under way to produce omega-3 fatty acids in cow's milk and in chicken eggs.

This report describes several scientifically emerging animal biotechnologies that are raising a variety of questions concerning risks to humans, animals, and the environment, as well as ethical concerns. The report examines applications of the technologies and discusses major issues that may arise. Consumers, agricultural producers, the biotechnology industry, and federal regulatory bodies are debating the relative costs and benefits of these technologies. As technologies move toward commercialization, Congress is being asked to examine these issues and possibly to refine the current federal regulatory structure governing the technologies and their agricultural products.

Animal Biotechnologies

Given the breadth of the term "animal biotechnology," one might reasonably define it to include thousands of years of humans selectively breeding animals: observing desirable animal traits and attempting to breed those traits into successive lines of animals. One of the first modern forms of assisted reproductive technology (ART) was artificial insemination (AI). AI has been long established as a technological advance in traditional selective breeding and an important adjunct to the development of modern industrial animal production, especially in dairy and poultry. AI was adopted by producers and accepted by the public with virtually no controversy.[3] Estrus synchronization, a related technology that improved the efficiency of AI by more accurately controlling when a female was in heat, is also an important animal biotechnology.

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[2] *New York Times*, March 27, 2006.

[3] For example, more than 70% of all U.S.-bred Holstein cows, by far the most widely used milk producers, are artificially inseminated. FDA, "A Primer on Cloning and Its Use in Livestock Operations," at [http://www.fda.gov/cvm/CloningRA_Primer.htm].

With the development in the 1970s and patenting in the 1980s of recombinant DNA techniques, and the subsequent analysis of genes, their resulting proteins, and the role played by the proteins in animal biochemical processes (functional genomics), modern biotechnology is increasingly equipped with a set of sophisticated tools holding the promise of transforming the selective breeding of animals. The range of new techniques and technologies is only now beginning to transform animal biotechnology in ways that plant biotechnology was transformed in the 1980s and 1990s.

Modern animal biotechnology is developing against the background of public experience with plant biotechnology, and controversy over the technologies may be a continuing feature of animal biotechnology development, not least because of the closer connection between humans and some animals and the belief that techniques developed for animals are only a step away from application to humans. Some of the better known animal biotechnologies follow. A number of them are types of assisted reproductive technology (ART).

Embryo Transfer. After AI and estrus synchronization, embryo transfer (ET) is the third most commonly used biotechnology. In ET, a donor cow of superior breeding is chemically induced to superovulate. The eggs are then fertilized within the donor, the embryo develops and is then removed and implanted in a recipient cow. Between removal and implantation, embryos may be frozen for safekeeping. Because of the relatively high costs, ET is used mostly within registered cowherds.

In Vitro Fertilization. With in vitro fertilization (IVF), a technician removes unfertilized eggs (oocytes) from the donor cow's ovaries, usually recovering 6-8 useable oocytes. The oocytes mature in an incubator and are fertilized with sperm. The resulting zygotes incubate and develop in the laboratory before being placed into the recipient cow. While IVF can produce many fertilized embryos, the added expense of ET makes the procedure prohibitive in most cases.

Sexing Embryos. The dairy industry prefers heifers and the beef industry prefers bulls. Embryo sexing methods in cattle have been developed using a bovine Y-chromosome probe. Technicians remove a few cells from the embryo and assess the DNA in these cells for the presence of a Y-chromosome. Presence of a Y-chromosome determines the embryo is male. Research is also developing in sperm sexing technology.

Transgenics. A prominent area of contemporary animal biotechnology research is the development of *transgenic animals* through genetic engineering (GE) technology.[4] Transgenic animals are produced by introducing an isolated DNA fragment into an embryo so that the resulting animal will express a desired trait. Transgenic animals may be generated by the introduction of foreign DNA obtained through animals of the same species, animals of different species, microbes, humans,

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[4] *Genetic engineering* (GE) here refers to the use of molecular biology to alter cells by inserting or removing genes. GE is a form of *genetic modification*, which refers more broadly to the practices of altering an organism's genetic composition by both GE and non-GE methods.

cells, and *in vitro* nucleic acid synthesis. The only currently routine use of transgenic animals, primarily mice, is in the area of human disease research. Potential agricultural applications for such genetic engineering, however, include improved feed use and faster growth; more resistance to disease; meat that is leaner or that has more of some other desirable quality; and possibly even animal waste that is more environmentally benign. **Table 1** provides examples of various objectives of animal biotechnology involving genetic modification.

Table 1. Agricultural Applications of Animal Transgenics

Purpose	Animal model	Transgenic source
Faster growth/leaner meat	Cattle, swine, rabbits, sheep	Growth hormones/factors: *Human, Bovine, Porcine, Rat, Chicken*
Altered milk composition (higher protein)	Cattle	Extra copies of casein genes; disruption of lactoglobulin gene: *Cow*
"Biosteel" production in milk[a]	Goat	Spider
Reduced phosphorus in swine feces	Swine	Phytase gene; *Bacteria*
Increased wool production	Sheep	Cysteine synthesis gene: *Bacteria* Growth factor: *Sheep*
Disease resistance	Swine, sheep, rabbit	Monoclonal antibodies: *Mouse* Viral envelope genes: *Sheep*
Xenotransplantation: Developing animal organs for human transplantation	Swine	CD55 (DAF-decay activating factor: *Human* CD59: *Human*

Source: GeneWatch UK, April 2002.

a. "Biosteel" is the trade name for spider web material intended to be produced in the milk of a transgenic goat. Said to be twenty times stronger than steel, "Biosteel" has an envisioned breaking strength of about 300,000 pounds per square inch and could produce microscopically fine, super strong fibers for industrial use.

Cloning. Cloning, discussed at greater length later in this report, is a biotechnology developing rapidly and with significant public controversy. Most people think of cloning as the creation of an organism that is genetically identical to another one. However, scientists use the term more broadly, to refer to production not only of such organisms but also of genetically identical cells, and to replication of DNA and other molecules. It also refers to a form of reproduction found naturally

in many single-celled organisms, as well as plants and animals. Those differences in meaning and usage have caused some confusion in public debate about cloning, where the main area of controversy relates to artificial cloning involving higher organisms, including humans.[5]

Gene Knockout. This is a technique where researchers inactivate, or "knock out," a gene by replacing it or disrupting it with an artificial piece of DNA in order to determine what that particular gene does — e.g., cause or protect against some disease, alter metabolism, and so forth. A knockout mouse is a laboratory mouse subjected to this technology.[6]

Regulation and Oversight

The basic federal guidance for regulating the products of agricultural biotechnology is the Coordinated Framework for Regulation of Biotechnology (51 *Fed. Reg.* 23302), published in 1986 by the White House Office of Science and Technology Policy (OSTP). A key principle has been that GE products should continue to be regulated according to their characteristics and unique features, not their methods of production, that is, whether or not they were created through biotechnology. The framework provides a regulatory approach intended to ensure the safety of biotechnology research and products, using existing statutory authority and previous policy experience.

Some newer applications of biotechnology did not exist when the current regulatory framework was enunciated. The NRC animal biotechnology report concluded that this regulatory regime "might not be adequate to address unique problems and characteristics associated with animal biotechnologies" and that federal agency responsibilities are not clear.[7]

Food and Drug Administration (FDA). Within the Department of Health and Human Services (HHS), the FDA regulates food, animal feed ingredients, and human and animal drugs, primarily under the Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S.C. §301 *et seq.*). The FDA has stated that most — although probably not all — gene-based modifications of animals for production or therapeutic claims fall within the purview of the agency's Center for Veterinary Medicine (CVM), which regulates them under the FFDCA as new animal drugs. A new animal drug (NAD) must be approved by the agency after it is demonstrated to be safe to man and animals, as well as being effective. Regulation of transgenic animals as NADs, however, suggests to some observers (e.g., the Center for Food Safety, Union of Concerned Scientists) the inherent weakness of existing regulatory structures to respond adequately to the complexities that arise with animal biotechnology innovations.[8]

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[5] See archived CRS Report RL31358, *Human Cloning*, by Judith A. Johnson and Erin D. Williams.

[6] National Institutes of Health, National Human Genome Research Institute, "Knockout Mice," accessed January 17, 2008, at [http://www.genome.gov/12514551].

[7] NRC, *Animal Biotechnology*, p. 14.

[8] See Center for Food Safety website [http://www.centerforfoodsafety.org/geneticall7.cfm], (continued...)

Primarily under the FFDCA, FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for assuring that domestic and imported foods are safe and properly labeled. Generally, FDA does not review new foods themselves for safety before they enter commerce but does have enforcement authority to act if it finds foods that are adulterated under the act. All food *additives*, whether or not introduced through biotechnology, must receive FDA safety approval before they can be sold; the exception to pre-market approval are those on a list the FDA has determined to be "generally recognized as safe" (GRAS).[9, 10]

Sections of the FFDCA and of the Public Health Service Act (42 U.S.C. §262 *et seq*.) provide the authorities for FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research to regulate the safety and effectiveness of human drugs and other medical products, including those produced by GM animals. Under these laws, the FDA requires pre-market review and licensing of such products, and requires that their production conditions ensure purity and potency.[11]

U.S. Department of Agriculture (USDA). Several USDA agencies, operating under a number of statutory authorities, also have at least potential roles in the regulation of transgenic and cloned animals and their products. As several critical reviews have indicated, USDA has not had a clearly spelled out policy in this area, including whether it intends to exercise these authorities to regulate GE animals.[12] However, USDA's Animal and Plant Health Inspection Service (APHIS) intends to publish an advance notice of proposed rulemaking (ANPR) on GE animals, possibly early in 2008.[13]

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[8] (...continued)
and the Union of Concerned Scientists [http://www.ucsusa.org/food_and_environment/genetic_engineering/genetically-engineered-salmon.html].

[9] The FDA, as of early 2008, has not granted approval for any human foods from transgenic (or cloned) animals, although a "very limited number have been approved for rendering into animal feed components." The only FDA-approved product of biotechnology in wide commercial use is bST, and an application is pending for a GE salmon. (*Questions and Answers about Transgenic Fish*, at [http://www.fda.gov/cvm/transgen.htm]).

[10] Also see CRS Report RL34247, *Federal Regulation of Substances Generally Recognized As Safe (GRAS) and the Use of Carbon Monoxide in Packaging for Meat and Fish*, by Vanessa K. Burrows and Cynthia Brougher.

[11] NRC, *Animal Biotechnology*, p. 163.

[12] See, for example, Pew, *Issues in Regulation*. Beginning on p. 139, the report contains an extensive discussion on how these and several other USDA authorities might be utilized for oversight of animal biotechnology.

[13] "USDA promises ANPR on transgenic animals next month," *Food Chemical News*, December 17, 2007. APHIS in 2007 established an Animals Branch within its Biotechnology Regulatory Services "to develop a regulatory framework for the possible regulation of genetically engineered animals." Source: APHIS website, "Regulation of Genetically Engineered Animals," accessed on January 11, 2008, at [http://www.aphis.usda.gov/biotechnology/news_transgenic_animals.shtml].

APHIS has broad authority, under the Animal Health Protection Act (AHPA; 7 U.S.C. §8301 *et seq.*) to regulate animals and their movement to control the spread of diseases and pests to farm-raised animals. APHIS also administers the Viruses, Serums, Toxins, Antitoxins, and Analogous Products Act (21 U.S.C. §151-159), aimed at assuring the safety and effectiveness of animal vaccines and other biological products, including those of GM origin, and the Animal Welfare Act (7 U.S.C. §2131 *et seq.*), portions of which govern the humane treatment of several kinds of warm-blooded animals used in research (but generally not agricultural animals). Elsewhere at USDA, the Food Safety and Inspection Service (FSIS) is responsible for ensuring the safety to humans of most food animals and meat and related products derived from them under the Federal Meat Inspection Act (21 U.S.C. §601 *et seq.*) and Poultry Products Inspection Act (21 U.S.C. §451 *et seq.*).

Other Authorities. Reports and studies have cited a number of other authorities and federal agencies that are or could be relevant. The National Environmental Policy Act (42 U.S.C. §4321 *et seq.*) requires federal agencies to consider the environmental impacts of their actions. The Environmental Protection Agency derives its authority from, among other laws, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA; 21 U.S.C. §301 *et seq.*); pesticides derived from living organisms, including those of biotechnology, are within its purview. The Interior Department's Fish and Wildlife Service and the Commerce Department's National Marine Fisheries Service have also been cited.

Cloning Policy Developments

In 1997, scientists at the Roslyn Institute in Scotland used nuclei from the mammary cells of an adult sheep to clone "Dolly." Such nuclear transfer (NT) techniques were first developed in amphibians in the 1950s. They were first used in sheep in 1986, with the production of clones using nuclei taken from sheep embryos. The significance of Dolly was that she was cloned from differentiated cell types obtained from an adult (called "somatic cell nuclear transfer" or SCNT), rather than undifferentiated cells from an embryo ("embryonic NT").

Cloning in animal agriculture is generally not applied in isolation from other biotechnologies such as genetic engineering. Scientists note that cloning does not require fertilization and is not, by itself, a form of genetic engineering, i.e., altering, removing, or inserting genes into an animal's existing DNA. However, cloning can involve transgenic as well as non-transgenic cells.

Currently, SCNT is not yet a notably efficient technique ready for widespread commercial adoption. For example, only about 6% of the embryos transferred to recipient cows resulted in healthy, long-term surviving clones, according to a 2005 report.[14] The European Food Safety Authority (EFSA) recently reported that overall success rates vary by species, ranging from 0.5% to 5%.[15]

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[14] D. N. Wells, "Animal Cloning: Problems and Prospects," *Review of Science and Technology*, 24(1): 251-264, 2005.

[15] European Food Safety Authority. *Draft Scientific Opinion on Food Safety, Animal Health and Welfare and Environmental Impact of Animals Derived from Cloning by Somatic Cell*
(continued...)

What Is Cloning?

Cloning, or somatic cell nuclear transfer, is a process by which animals are reproduced asexually ..... In cloning, a differentiated somatic cell (a non-germ line cell from an existing animal) is introduced to an oöcyte (a cell that is the immediate precursor of a mature egg) that has had its nucleus (and thus its genome) removed, and then, following some manipulations, is induced to start replicating. If all goes well, the dividing cell is implanted into a female animal (dam), continues to develop normally, and is delivered just as any newborn.

— Animal Cloning: A Risk Assessment, p. 20

Success rates are said to be improving, however. As more efficient cloning technologies, which can overcome the range of cloning abnormalities that have resulted from SCNT, are introduced, they could provide new opportunities in human medicine, agriculture, and animal welfare. This is the focus of much of the current international animal biotechnology research.

The EFSA draft scientific opinion estimated the number of live clones worldwide in 2007 to be less than 4,000 cattle and 1,500 pigs, of which about 750 cattle and 10 pig clones were in the United States.[16] EFSA reported that life span data were limited, with only a few reports on cattle of six to seven years of age and no data available in 2007 on the full natural life span of livestock clones generally.[17]

FDA Risk Assessment. The FDA in July 2001 began asking companies to refrain voluntarily from marketing the products of cloned animals and their offspring until it could fully assess the scientific information on their safety. It subsequently issued two draft risk assessments on the matter, culminating in the release of a final risk assessment — and industry guidance that effectively lifts the voluntary moratorium — on January 15, 2008.

Some stakeholders, including several Members of Congress, wanted a continuation of the moratorium until more studies are completed on safety and other aspects of animal cloning. Their views were reflected in nonbinding language to accompany the omnibus spending measure for FY2008, which passed in late 2007, and binding language in the Senate version of the pending farm bill (H.R. 2419); see "Congressional Action," at the end of this report, for details.

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[15] (...continued)
Nucleus Transfer (SCNT) and their Offspring and Products Obtained from the Animals, Enorsed for public consultation December 19, 2007 and released January 11, 2008. Hereinafter cited as EFSA draft scientific opinion. Accessed on the Internet at [http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178676922939.htm].

[16] According to FDA and USDA, approximately 600 cloned animals exist in the United States, most of them breeding animals and most beef cattle.

[17] Ibid.

In an October 2003 draft risk assessment, the FDA had concluded that "the current weight of evidence suggests that there are no biological reasons ... to indicate that consumption of edible products from clones of cattle, pigs, sheep or goats poses a greater risk than consumption of those products from their non-clone counterparts."[18] However, shortly after the assessment's publication, many members of the FDA's Veterinary Medicine Advisory Committee stated that there were not enough data to fully understand any potential risks from this relatively new techonology.[19]

On December 28, 2006, the FDA's CVM released another long-awaited risk assessment — also in draft form, along with a proposed risk management plan and draft guidance for industry — on the safety of animal clones and their offspring.[20] The lengthy risk assessment examined two important questions: the safety of food from cloned animals and their progeny, and the effects of the process on the health of these animals. FDA officials stressed that the risk assessment did not address any other issues, such as the social and ethical aspects of cloning or consumer acceptance of cloned animal products. The risk assessment also focused only on cloning from non-transgenic cells. This risk assessment is now final.[21]

The final risk assessment concluded — as had the December 26, 2006 draft — that the meat and milk of clones of adult cattle, pigs, and goats, and the meat and milk from the offspring of these clones, were as safe for human consumption as the food from conventionally bred animals. The FDA added that not enough data were available to reach the same conclusions about sheep clones (or other species) and recommended that they not yet be used for human food. The risk assessment arrived at these conclusions after analyzing physiological, anatomical, health, and behavioral data on the animals and evaluating available information on the chemical composition of their milk and meat. FDA said its final assessment was peer-reviewed by an independent panel of experts, who agreed with the findings. The final assessment also took into account many thousands of public comments and additional data that became available since the draft was prepared, the agency said.

The agency said it would not require any special measures (including labeling) relating to the use of food products or animal feed derived from cloned cattle, goats, and pigs because they are "no different from food derived from conventionally bred animals. Should a producer express a desire for voluntary labeling (e.g., 'this product is clone-free'), it will be considered on a case-by-case basis to ensure compliance

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[18] See [http://www.fda.gov/cvm/Documents/CLRAES.pdf].

[19] "Panel Calls for More Data on Animal Cloning Risks," *Food Chemical News*, November 10, 2003.

[20] Availability of the draft documents was formally published in the January 3, 2007, *Federal Register* (72 FR 135-137; FDA docket no. 2003N-0573); comments were accepted until May 3, 2007.

[21] FDA documents were posted on the Internet at [http://www.fda.gov/cvm/cloning.htm] on January 15, 2008. They are the Risk Assessment, Risk Management Plan, and Guidance for Industry.

with statutory requirements that labeling be truthful and not misleading."[22] The industry guidance states that products from the offspring of cloned animals of any species are suitable for food or feed consumption.

Upon release of the 2006 proposed assessment, FDA officials said they were continuing to ask livestock breeders and producers to keep food products from cloned animals and their offspring out of commerce. This moratorium was announced in July 2001 and remained in effect until the final guidance was released in January 2008. Although the FDA moratorium is no longer in effect, USDA is now encouraging technology providers to maintain the voluntary moratorium, but for products from cloned animals only. Food products from cloned animals' offspring would not be similarly constrained. During a continuation of this moratorium, USDA said it wants to "work closely with stakeholders to ensure a smooth and seamless transition into the marketplace for these products."[23]

Officials emphasized that, at least initially, almost all cloning-related foods will come not from the clones themselves but rather from their sexually reproduced offspring. Cloned animals — like other "elite" breeding animals such as a prized bull — are too valuable to use for food production, except possibly when they reach the end of their productive lives. The FDA observed that it can cost $20,000 or more to produce one such animal.

The risk assessment did conclude that some animals involved in cloning (notably cattle and sheep surrogate dams) and some clones are at greater health risk than conventional animals. While the types of animal health problems observed in cloned animals are no different than those found with other assisted reproductive technologies, these problems appear more frequently in cloning than in the other technologies. Such problems include late gestational complications in the surrogate mothers, and increased risk of mortality and morbidity in calf and lamb clones that are apparently caused mainly by large offspring syndrome (LOS). Swine and goat clones and their mothers do not appear to experience any additional cloning-related problems, FDA reported.

FDA found that livestock clones as a group tend to have more health problems and death rates at or right after birth. However, the risk assessment added that most animals surviving the neonatal period appear to grow and develop normally, and that no increased risk of adverse health effects have been reported in clones approaching reproductive maturity. The agency said that the technology was too new to draw any conclusions on the relative longevity of livestock clones.

European Draft Opinion. The European Food Safety Authority (EFSA) on January 11, 2008, released its own draft scientific opinion on the food safety, animal health and welfare, and environmental impacts of animals derived from cloning (SCNT). The EFSA opinion was limited to cattle and pigs, but its findings generally

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[22] "FDA Issues Documents on the Safety of Food from Animal Clones," FDA press release, January 15, 2008.

[23] Statement by Bruce Knight, Under Secretary for Marketing and Regulatory Programs on FDA Risk Assessment on Animal Clones, January 15, 2008.

do not appear to be substantially different from those in the FDA assessment. According to EFSA, currently available data indicate that meat and milk from healthy cattle and pig clones and their offspring are as safe as food products of animals derived from conventional breeding — provided that unhealthy clones would be detected and their products kept out of the food chain. As with FDA, the EFSA conclusion is based on an examination of compositional and nutritional data, the probability of novel constituents to be present, the health status of the animal, and available data on toxicity, allergenicity, and microbiology.

EFSA agreed that SCNT can be a successful reproductive technique, although death and disease rates of clones are significantly higher than those of conventionally reproduced animals. "The health and welfare of a significant proportion of clones have been found to be adversely affected," EFSA concluded, but added that this proportion is likely to decline as the technology improves. The agency cautioned that its overall opinion is based on interpretation of limited available data, studies with small sample sizes. Because the technology is relatively new, observations are not yet available the cover the full natural life spans of the animals.[24]

Comments were being accepted on the EFSA draft until February 25, 2008, with a revised opinion expected by May 2008. The findings are to be used by the European Commission (EC), the European Parliament, and member states in any policy decisions they make regarding animal cloning. Cloning currently is not in commercial use in Europe, nor is there any specific authorization procedure in the European Union for products from cloned animals.[25]

Other Views. Critics, including a number of consumer advocacy and animal rights groups, oppose the use of cloned animals and their offspring for food. In October 2006, a coalition formally petitioned the FDA to impose a moratorium on producing foods from cloned animals, and to establish rules for mandatory pre-market review and approval of cloned foods by regulating clones as new drugs under the food and drug act. These consumer and animal welfare groups contend that FDA has ignored or minimized a number of food safety and animal welfare problems. These include the treatment of surrogate mothers with high doses of hormones and their clone offspring, who often have severely compromised immune systems, with large doses of antibiotics, which could enter the human food supply; imbalances in clones' hormone, protein, or fat levels that could compromise meat and milk safety and quality; the possibility of increased foodborne illnesses; and a wide variety of health problems and abnormalities in the animals themselves. Consumer advocates assert that there are no consumer benefits from cloning.

FDA disagrees, citing the potential to breed livestock that meet consumers' changing tastes for traits like leanness, tenderness, color, size of meat cuts, and so forth. These would be in addition to potential producer-related benefits such as

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[24] EFSA draft scientific opinion.

[25] "EFSA launches its draft opinion on animal cloning for public consultation," EFSA press release, January 11, 2008. Also, "Animal Cloning FAQs," accessed January 14, 2008 at [http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_AnimalCloningFAQs.htm].

disease resistance, climate suitability, fertility, and improved physical qualities, FDA states.[26]

Opinion polls have suggested that the general public may not yet be ready for widespread animal cloning. A 2006 poll commissioned by the Pew Initiative on Food and Biotechnology, for example, found that Americans generally were not well informed about animal cloning, but 64% of those questioned are "uncomfortable" with it. Forty-three percent of Americans believed that foods from clones are unsafe, the survey found. Cloning opponents cite these types of findings to argue that products from cloned animals should be labeled so that consumers could avoid them if they wanted to. Some critics have urged the President to halt all FDA actions on cloning until a national panel that includes ethicists and religious leaders can consider the ethical and other social issues that they believe the technology has raised.

The NRC animal biotechnology report had stated that embryonic splitting and nuclear transfer using embryonic (not adult) cells were performed with some dairy cows to successfully produce genetically valuable offspring that were milked commercially and whose milk and meat did enter the food supply. Few concerns were raised by NRC authors about using these types of cloned animals for food, since they are generally believed to pose a low level of food safety concern. However, evaluating cloned-animal food composition "would be prudent to minimize any food safety concerns. The products of offspring of cloned animals were regarded as posing no food safety concern because they are the result of natural matings."[27] Other issues, notably consumer acceptance, social values, and animal welfare, could eventually overshadow any lingering questions about human health.

Other Policy Concerns

The following are among the policy concerns that have arisen along with the development of new biotechnologies in animal agriculture. Some may be more applicable to GE-related technologies than to cloning *per se*, although others, like social acceptance and animal welfare concerns, may apply to both.

Environmental Issues. Environmental concerns arising from emerging animal biotechnologies are largely speculative at this time because few products have been commercialized. For example, although the EFSA draft scientific opinion foresaw no environmental impact, it also noted that limited data were available on this aspect of animal cloning.

Industrial developers of agricultural biotechnology might argue that more efficient production of animal-based feeds could reduce the resources necessary to produce food and, thereby, reduce the environmental burden of animal production. Should the development and widespread adoption of the "EnviroPig" (tm), which produces less phosphorus in its waste, occur, it might be considered by some to be a positive environmental benefit of agricultural biotechnology.

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[26] "A Primer on Cloning and Its Use in Livestock Operations," at [http://www.fda.gov/cvm/CloningRA_Primer.htm].

[27] CAST, *Animal Agriculture*, p. 8.

The 2002 NRC animal biotechnology report noted potential negative environmental impacts of genetically altered animals. Escape, survival, and gene flow into wild populations were identified as major concerns. Of most concern to the NRC committee was the escape into the environment of "super" salmon that have been genetically modified for rapid growth, and the likelihood that they could then breed with wild populations in the environment.[28] Other genetically altered animals such as fish, insects, and shellfish could also potentially escape into natural environments and become feral, disrupt ecosystems, or introduce novel genes in a natural population.

Food Safety. Unexpected and unintended compositional changes arise with all forms of plant and animal genetic modification, including GE, concluded the IOM-NRC report on genetically engineered foods.[29] The report added that, so far, no GE-related adverse human health effects have been documented. However, the report's authors cited "sizeable gaps" in the ability to identify compositional changes caused by all forms of genetic modification — whether GE or conventional — and their relevance for human health, and they recommended new approaches for assessing the safety of new foods both before and after they enter the market.

Previous research and experience with commercializing transgenic plants suggested that negative effects on human health were virtually nonexistent. While not asserting that genetically modified organisms necessarily generate health problems, more recently reported research in peer-reviewed scientific journals has suggested that GMOs may raise food safety concerns:

- Australian researchers have published an article explaining that the transfer from a bean to a pea gene that expresses an insecticide protein has resulted in antibody production in mice fed the transgenic pea. The antibody reaction is a marker of allergic reaction.[30]
- Italian researchers at the University of Urbino had previously shown that absorption of transgenic soy by mice induced modifications in the nuclei of their liver cells. Recent research showed that a return to non-transgenic soy made the observed differences disappear.[31]

- Norwegian scientists at the University of Tromso demonstrated that the catalyst 35S CaMV, an element of the genetic structures used to modify a plant, can provoke gene expression in cultured human

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[28] NRC, *Animal Biotechnology*, p. 73.

[29] IOM-NRC, *Safety of Genetically Engineered Food*, p. 1.

[30] V. E. Prescott, P. M. Campbell, et al., "Transgenic Expression of Bean-Amylase Inhibitor in Peas Results in Altered Structure and Immunogenicity," *Journal of Agriculture and Food Chemistry*, 53(23); 9023-9030, November 2005.

[31] M. Malatesta, C. Tiberi, et al., "Reversibility of Hepatocyte Nuclear Modifications in Mice Fed on Genetically Modified Soybean," *European Journal of Histochemistry*, 49(2):237-242, July-September 2005.

cells. This catalyst was previously believed to operate in this way only in plants.[32]

In the NRC animal biotechnology report, experts observed that the scientific principles for assessing the safety of GE animals are "qualitatively the same" as for non-GE animals.[33] However, because GE can introduce new proteins into foods, the potential for allergenicity, bioactivity, and/or toxicity responses should be considered, they said. Others have remarked that animals genetically engineered for nonfood products like pharmaceuticals or replacement organs might be of concern if such animals entered *or* affected the food supply.[34]

Consumer and Social Acceptance. Criteria for selecting desirable traits to be produced through transgenic animals will likely be based on the demand for specific commercial characteristics. Even if scientific evidence is convincing that GE and cloned animal products are safe and beneficial for human consumption or economically valuable to producers, other concerns may limit marketplace and consumer acceptance.

Polls in recent years in the United States indicate that public knowledge about food and biotechnology generally remains limited. In two 2005 surveys, approximately half of those surveyed expressed opposition to the use of biotechnology in the food supply.[35] More than half of those in a 2005 Pew-sponsored poll said they opposed research into genetically modified animals, although opposition declined with increased knowledge. Many Americans have heard about animal cloning; two-thirds expressed discomfort with it — more of them out of religious or ethical concerns than food safety concerns. A majority of respondents to the Pew survey believe that regulators should take into account ethical and moral considerations. (See also the 2006 Pew findings on cloning, under "Cloning Policy Developments," section on "Other Views.")

Consumers may be less willing to accept the practice of genetically modifying animals than plants, some have argued, observing that people relate differently to animals, which many recognize as sentient beings. Some observers have expressed the concern that cloning farm animals might lead more quickly to human and pet cloning, which those observers oppose. Others believe that modifying animals, for example, to save human lives through xenotransplantation or the production of some important drug, might be more acceptable than doing so simply to produce more or cheaper food.

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[32] M. R. Myhre, K. Fenton, et al., "The 35S CaMV Plant Virus Promoter Is Active in Human Enterocyte-like Cells," *European Food Research and Technology*, 222(1-2):185-193, January 2006.

[33] NRC, *Animal Biotechnology*, p. 65.

[34] See CRS Report RS20507, *Labeling of Genetically Modified Food*, by Donna U. Vogt.

[35] Gallup poll on biotechnology and food safety, July 2005; Mellman Group/Public Opinion Strategies Poll Conducted for the Pew Initiative on Food and Biotechnology, October 2005. See [http://www.pewagbiotech.org] (Accessed March 20, 2006).

Further, science alone cannot resolve ethical views that appear to vary widely:

> Some people, irrespective of the application of technology, consider genetic engineering of animals fundamentally unethical. Others, however, hold that the ethical significance of animal biotechnologies must derive from the risk and benefits to people, the animals, and/or the environment. Yet another view focuses on the right of humans to know what they are eating or how their food or pharmaceuticals are being produced and therefore labeling becomes an issue to be addressed.[36]

Food industry leaders appear sensitive to consumer unease with animal biotechnology in general and cloning in particular. Many companies are not yet ready to process and sell meat and milk from transgenic and cloned animals because, they believe, consumers may view the products as less safe than more conventionally produced food products. The food industry also does not want to be portrayed as overstepping any widely held ethical or moral concerns about the new technologies.[37]

Such observations led some skeptics of animal biotechnology to propose that the FDA not only consider the science and safety issues, but also these broader concerns. In the area of human reproductive health, for example, the FDA and other federal agencies have invoked particular moral arguments either to reinforce scientific arguments or to counterbalance scientific evidence. Others believe that the FDA should base its decisions only on scientific evidence, and perhaps some other body should be established to consider the ethical and cultural questions. As the NRC animal biotechnology report observed, regulatory decisions and enforcement involving animal biotechnology "are difficult in the absence of an ethical framework."[38]

Labeling. Some believe that segregating and labeling the products of biotechnology in agriculture, including meat and milk, would enable the consumer to choose whether or not to buy such products. Either segregating and labeling biotechnology products or failing to do so could contribute to public suspicion that these products are flawed or different in some negative way, which may lead to contradictory policy decisions.[39] Opponents of labeling argue that biotechnology products essentially are the same as more conventional products — and are subjected to the same rigorous safety standards — and therefore should be treated no differently in the marketplace. A study by USDA's Economic Research Service reported that

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[36] NRC, *Animal Biotechnology,* p. 13.

[37] These concerns were explored in depth at an October 2006 symposium, "Animal Biotechnology: Considering Ethical Issues," sponsored by the Pew Initiative on Food and Biotechnology and by Michigan State University. Also reported by *Food Chemical News*, October 23, 2006.

[38] Ibid.

[39] C. T. Foreman, *Can U.S. Support for Food Biotechnology Be Salvaged?*, paper prepared for the American Enterprise Institute for Public Policy Research Conference on Biotechnology, the Media and Public Policy, June 12, 2003.

consumers' willingness to pay for a food item declines when the food label indicates that it was produced with the aid of biotechnology.[40]

In December 2007, two leading U.S. livestock cloning companies announced they were creating a voluntary system for tracking cloned animals. The program, which they asserted "is designed to facilitate marketing claims," is to involve a national registry providing for the individual identification of each cloned animal, affidavits that owners will sign committing to proper marketing and disposal of such animals, and monetary deposits to be returned when such commitments are fulfilled. Consumer organizations immediately criticized the initiative, noting that it would not track the offspring of cloned animals and was not mandatory.[41]

Meanwhile, USDA has reminded stakeholders that products from cloned animals are not eligible to be labeled as organic, under its National Organic Program (NOP). While cautioning that the organics program is a marketing, not a food safety, program, USDA also noted: "Cloning as a production method is incompatible with the Organic Foods Production Act and is prohibited under the NOP regulations."[42] However, the status of products from clone offspring is less clear. The Department noted that USDA's Agricultural Marketing Service, where the NOP is located, is preparing rulemaking to address the organic status of such offspring.[43]

Animal Welfare. Some aspects of gene transfer, and of cloning, have the potential to create infectious disease hazards and/or impaired reproduction. Looming large in the ethical debate are questions about whether genetic modifications, cloning, and other technologies stress animals unnecessarily, subject them to higher rates of disease and injury, and hasten death.[44] The NRC animal agriculture report noted, for example, that ruminants produced by *in vitro* culture or nuclear cell transfer methods tend to have higher birth weights and longer gestation periods than those produced by artificial insemination, creating potential calving problems. Nuclear transfer techniques to propagate genetic modifications may increase risks to the reproductive health and welfare of both the surrogate female animals and their transgenic offspring. The report cited other evidence of problems such as anatomical, physiological, or behavioral abnormalities in many transgenic animals.[45] Some scientists have countered that animal welfare problems have been exaggerated and

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[40] A. Tegene, W. Huffman, et al., *The Effects of Information on Consumer Demand for Biotech Foods: Evidence from Experimental Auctions*, USDA, Economic Research Service, Technical Bulletin 1903, March 2003.

[41] Sources: "Top U.S. Cloning Companies Announce New System to Track Cloned, Livestock," December 19, 2007, Viagen press release, and "Consumer Groups Displeased with Voluntary Animal Clone Registry," *FDA Week*, December 21, 2007.

[42] USDA, Questions and Answers, FDA's Final Risk Assessment, Management Plan and Industry Guidance on Animal Clones and their Progeny, January 2008.

[43] Ibid.

[44] See also H. P. S. Kochhar, G. Adlakha-Hutcheon, and B. R. Evans, "Regulatory Considerations for Biotechnology-Derived Animals in Canada," *Review of Science and Technology*, 24(1):117-125, 2005.

[45] NRC, *Animal Biotechnology*, p. 11.

tend to recede, particularly as the technologies are perfected. Most appear to agree, however, that animals originating from some forms of genetic modification or from cloning may require closer observation and care. (See also the section of this report on cloning.)

In Europe, officials are expected to consider the ethical dimensions of animal welfare in formulating their own cloning policies. The EC has charged a separate panel, the European Group on Ethics in Science and New Technologies, with drafting an opinion. This group was to discuss its opinion at a January 15-16, 2008, meeting.[46]

Genetic Diversity. Could the introduction of a few genetically altered or cloned "superspecies" bring too much genetic uniformity to herds? As genetic diversity declines, herds could be more susceptible to diseases, leading to large production losses and/or much heavier use of antibiotics and other animal drugs to treat them, some have argued. A related concern is that a relative handful of "elite" producers or breeders might hold the proprietary rights to these species, to the disadvantage of many farmers and ranchers. Some animal biotechnology researchers have pointed to the potential importance of preserving unaltered germlines in domestic animals because they could prove to be an invaluable "gene bank" in the event that novel infectious diseases or inheritable genetic defects were inadvertently introduced into modified subpopulations as a consequence of genetic modification.

Trade Issues. If the United States becomes the first country to approve food products from cloned animals, how might the decision affect U.S. exports? Any exports of the products of animal biotechnology would presumably encounter a wide spectrum of foreign regulatory regimes, some more restrictive than the U.S. system. For example, the current European Union restriction on new biotechnology products is likely to encompass various restrictions on animal biotechnology as it does on plant biotechnology. On the other hand, researchers in a number of other countries, including some EU members, have been producing clones, and one — France — has published its own risk assessment on clones that, FDA has observed, generally agrees with the U.S. assessment.[47]

International guidelines pertaining to exports of animal products derived from biotechnology are being considered. The Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology held an initial meeting in September 2005 in Chiba, Japan, to determine the new work projects. Almost every country, except for the United States, proposed an animal biotechnology project. The task force agreed to move forward with a recombinant DNA (r-DNA) animal project, specifically to develop guidelines for how countries would assess the safety of foods derived from r-DNA animals.[48] At its next meeting in November-December 2006 in Chiba, the task force, among other things, reviewed the developing guidelines,

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[46] The group's website is at [http://ec.europa.eu/european_group_ethics/index_en.htm].

[47] Stephen F. Sundlof, then Director of FDA Center for Veterinary Medicine, transcript of a December 28, 2006, teleconference on the draft risk assessment.

[48] Codex is recognized by the World Trade Organization (WTO) as the body that sets food safety standards for facilitating international trade of food products. The WTO cites Codex texts as a benchmark in the Agreement on Sanitary and Phytosanitary Measures (SPS).

agreeing to limit their scope to food safety and nutritional issues (while recognizing the importance of others like animal welfare, environmental, and ethical concerns).[49]

USDA has said it would consider "discussion with industry on possible verification of its supply chain management plan to ensure that trading partners are aware of whether or not they receive cloned or non-cloned products."[50]

Congressional Activity

Members of Congress in the past have proposed various bills aimed at more closely regulating the products of agricultural biotechnology, requiring such products to be labeled, and providing a means to recover any damages caused by the technology. None of these past bills appears to have focused on transgenic animals or cloned animals specifically, although bills have been offered to prohibit human cloning. As with human cloning, ethical issues concerning animal clones and other animal biotechnologies also may continue to be visible public issues. Congress could be asked to play a larger role in weighing the benefits and costs of these evolving technologies, and to refine existing government oversight.

The release of the FDA draft risk assessment in December 2006 made it a focal point for some Members of the 110th Congress with interest in the numerous consumer and production issues surrounding animal biotechnology in general and cloning in particular. During the first session, this interest culminated in nonbinding language, in explanatory notes to accompany the Consolidated Appropriations Act, 2008 (P.L. 110-161), strongly encouraging FDA to continue the voluntary moratorium on marketing products from cloned animals until the agency can evaluate the need for additional studies. The report language takes note of the "thousands" of public comments received on the risk assessment, many of which asked FDA to first obtain additional information, and scientific peer review, on potential health, economic, and trade impacts. More specifically, the explanatory notes state:

> The [House and Senate Appropriations] Committees strongly encourage FDA to continue the voluntary moratorium on introducing food products from cloned animals into commerce until FDA completes a review and analysis of comments and evaluates the need for additional studies recommended during the public comment period. The Committees direct the Food and Drug Administration to enter into an agreement with the Economic Research Service at USDA to study the domestic agricultural and international trade economic implications of

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[49] The collaborative document is entitled *Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals*. For a more detailed description of the meeting, see "Report of the U.S. Delegate, 6th Session of the Codex ad hoc Intergovernmental Task Force on Foods Derived From Biotechnology, Nov. 27 - Dec. 1, 2006, Chiba, Japan," on the USDA-FSIS website at [http://www.fsis.usda.gov/regulations_&_policies/Delegate_Report_6FBT/index.asp].

[50] Questions and Answers, FDA's Final Risk Assessment, Management Plan and Industry Guidance on Animal Clones and their Progeny.

> permitting commercialization of milk and meat from cloned animals and their progeny into the food supply.[51]

The FDA obviously did not heed this nonbinding language — although USDA officials said they will proceed with the study of domestic agricultural and international trade economic implementations of commercialization.

The Senate-passed version of the pending omnibus farm bill (H.R. 2419, in Section 7507) contains statutory language that would be binding — although its outcome and potential policy effect appeared to be unclear as of early 2008. A conference with the House, whose bill lacks the language, was pending in January 2008. This Senate provision would require the FDA both to postpone publication of its final risk assessment until the completion of several newly mandated studies, and also to maintain the voluntary marketing moratorium until then.

It is conceivable that conferees might endorse a part of Section 7507 that directs the HHS Secretary to contract with the National Academy of Sciences to conduct a study on the safety of food products from cloned animals and the health effects and costs attributable to milk from cloned animals, with a report to Congress due within one year of enactment. The study is to address whether there were a sufficient number of studies to support the FDA draft assessment, and whether there were other pertinent ones that were not taken into account. The study would include an evaluation of potential public health effects and associated health care costs, and an evaluation of any consumer behavior and negative health and nutrition impacts resulting from a decrease in dairy consumption if milk from cloned animals and their offspring is commercialized. The Senate language also directs USDA to study and report within 180 days "on the state of domestic and international markets for products from cloned animals, including consumer acceptance."

The first animal cloning-related bills (S. 414 and H.R. 992) in the 110th Congress were introduced in early 2007, both of which would amend federal food safety laws to require that foods from cloned animals and their offspring be so labeled. Also introduced in early 2007 was S. 536, which would prohibit the use of the "organic" label on food products from cloned livestock or their offspring. These bills were pending in January 2008.

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[51] Joint explanatory statement to accompany H.R. 2764, published in the December 17, 2007 *Congressional Record*.