

Law, Ethics, and Gender**A Brave New Beef: The US Food and Drug Administration's Review of the Safety of Cloned Animal Products**

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ABSTRACT

To meet its public mandate, the US Food and Drug Administration (FDA) collected studies on the potential health hazards of eating or drinking cloned food products. Based on an earlier National Academy of Sciences study that, on closer analysis, was not nearly as sanguine, the FDA's report found no evidence of a health risk from the public's ingestion of cloned food products. This article analyzes the risks the FDA considered, and concludes that there is a disconnect between the risks the FDA assessed in these studies and the risks that might arise from cloned food products. The FDA should consider instituting effective tracking mechanisms and other diagnostics that would permit scientists and the public to answer the question of health risks posed by cloned food products. (*Gend Med.* 2009;6:402–409) © 2009 Excerpta Medica Inc.

INTRODUCTION

The first chapters of the story of the US government's approach to the issue of what health risks, if any, attend the consumption of cloned food products could be caricatured by the delightful vignette of the drunken man explaining that he was looking for his lost keys under a light pole, not because he dropped them there, but because that was where the light was. In discharging its public duty, the US Food and Drug Administration (FDA) duly examined the health risks posed by the novel but growing use of cloning in the preparation of food products for human consumption. Yet, to many observers, when the FDA sought to identify and assess the risks associated with this wholly unknown phenomenon, it chose to use known risk profiles rather than to determine whether the novel technology would beget new risks. The FDA's conclusion that there are no known risks from the consumption of cloned foods tells us less about the risks than about the methodology used to answer the question. Worse, because of the FDA's pronouncement of no evidence of known risks, there is no data collection mechanism in place to evaluate issues over broader populations and time periods. We believe the FDA should consider modifying its approach so that it can lead the debate on what may become an important public health issue.

BACKGROUND

In 1997, Scottish researchers stunned the world by announcing the first successful cloning of an animal from an adult donor cell.¹ Because the cell used for the cloning was taken from a mammary gland, the cloned sheep was named Dolly, after the famously busty country western singer, Dolly Parton. The production of Dolly-the-clone proved that a cell taken from a specific part of the body could be used to recreate a whole individual. Since this historic announcement, many more animal species have been cloned by somatic cell nuclear transfer (SCNT), including livestock animals such as cows, pigs, and goats. There are an estimated 600 individual cloned livestock animals in existence in the United States,² though the number could be much larger.

In 2008, the FDA published its animal cloning risk assessment.³ This significant document approved meat and milk from cloned animals for human consumption. Based on the FDA's Risk Assessment, cloned animal products need not be labeled for consumers. As a result, these products are not required to be systematically tracked or monitored.

Animal Cloning

SCNT is a relatively recent technique for cloning animals. The process entails transplanting the nucleus of a terminally differentiated adult animal cell (such as a skin cell) into a recipient egg cell (oocyte) whose own nucleus has been removed.³ Some as-yet unidentified combination of factors inside the recipient oocyte causes the DNA of the transplanted nucleus to undergo the process of dedifferentiation, reverting the cell to a state of totipotency, such that it is able to give rise to daughter cells of any lineage or cell type. In this way, the reprogrammed nucleus of the newly formed oocyte can direct the development of an entire organism. Successive cell divisions of the oocyte with the foreign reprogrammed nucleus produce daughter cells that differentiate into the appropriate tissues and organs. In successful cases, embryonic development directed by the reprogrammed nucleus results in a fully formed animal having the same DNA as the animal who provided the transplanted nucleus (ie, a clone).

Animal cloning is currently an inefficient process, resulting in high rates of embryonic, fetal, perinatal, and neonatal deaths, as well as the birth of clones with various physiologic abnormalities. A significant percentage of clones exhibit respiratory distress, cardiovascular abnormalities, and abnormalities of the immune system, brain, and digestive system.⁴ These defects are thought to be the result of epigenetic changes, such as histone modifications and altered DNA methylation patterns of the reprogrammed donor nucleus that can result in faulty gene expression by turning genes on or off at inappropriate times.

Owing to this high frequency of failure, the number of clones in existence remains low—approximately 6000 worldwide.⁵ At the same time, the cost of producing clones remains high—a single cloned cow, for example, costs approximately \$15,000 to \$20,000 to create.⁶ Therefore, it would appear that, to date, it is not economically feasible to use cloned animals for meat consumption; instead, they are used primarily for breeding. Thus, it is still unlikely that any meat in grocery stores comes from a cloned animal itself. However, because the number of offspring or products produced by animal clones is unaccounted for, products derived from the progeny of these animals are certain to have already entered the US food supply.⁷

The FDA's Role

The FDA is the federal agency responsible for ensuring food safety in the United States. The agency's self-described mandate is the protection of public health by ensuring that information about food products is accurately represented. Even though the FDA's specific responsibilities include the labeling of foods and the safety of food products, meat and poultry technically do not fall under FDA jurisdiction, but are regulated instead by the US Department of Agriculture (USDA), which is responsible for inspecting meat from slaughtered animals.⁸

Despite the USDA's jurisdiction, on January 8, 2008, the Center for Veterinary Medicine of the FDA released a 968-page report entitled "Animal Cloning: A Risk Assessment," approving the consumption of food products derived from cloned

animals and their progeny.³ The Risk Assessment concluded that cloned animal products posed no increased food consumption risks to humans. However, the FDA's conclusion was based on a review of the scientific literature, not on independent investigation by the FDA itself. Furthermore, the available scientific literature contained no data on the effects of routine consumption of cloned food products. Finally, although the Risk Assessment purported to concur with a 2002 independent report by the National Academy of Sciences (NAS) on the safety of cloning,⁹ that report had expressly cautioned about unknown risks.

An Absence of Evidence of Hazard Is Not the Same as an Absence of Hazard

In its preface, the FDA's Risk Assessment noted the period of study, beginning in the late 1990s with information gathered from clone producers that culminated in the commissioning of the 2002 NAS study on the safety of cloning.⁹ The NAS report comprised new animal biotechnologies in general, including genetically engineered animals. In its discussion of cloned animal-derived food products, the NAS committee highlighted the difficulty of drawing conclusions regarding safety, in view of the limited sample size and health and production data, as well as the rapidly changing cloning protocols. The committee observed that "direct effects of any abnormalities in patterns of gene expression on food safety are unknown." Because the NAS study found no scientific data linking abnormal gene expression patterns in adult clones to food safety risks, nor any analytical data comparing the composition of meat and milk of clones to that of conventionally bred animals, the report offered the correct but unremarkable conclusion that there was no current evidence that food products derived from adult somatic cell clones or their progeny presented a food safety concern.

The report, however, was careful to explain that the NAS committee's concerns could be described as a rather "uneasy state of blended interest, uncertainty, and apprehension," and noted that for some applications of animal biotechnology, scientific uncertainty would be of particular con-

cern, due in part to the lack of established scientific methods for answering some of the novel health questions posed.⁹ With regard to animal cloning, the committee identified the key scientific issue as whether the genomic reprogramming in clones could result in gene expression that might raise food safety concerns, and found that it would be "difficult to characterize the level of concern without further supporting evidence regarding food product composition." The NAS report devoted an entire section to a discussion of scientific uncertainty in the context of agency decision-making: "...if we are ignorant of the potential existence of a particular hazard, we might fail to consider it at all when attempting to estimate the potential harms or benefits of an activity...Attempts to estimate the probability of harm (or benefit) from such a fundamentally uncertain activity must be undertaken with great care since ignorance-of-ignorance might lead to serious errors."

By contrast, the overall tone of the FDA Risk Assessment is much more optimistic than the NAS report. The FDA states, for example, that "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."³ The FDA Risk Assessment concludes that "edible products from healthy clones that meet existing requirements for meat and milk in commerce pose no increased food consumption risk(s) relative to comparable products from sexually-derived animals." In arriving at this determination, the Risk Assessment cites the 2002 NAS report: "The results of this comprehensive risk assessment agree with the preliminary findings of the NAS (2002a) conclusions...there is no current evidence that food products derived from adult somatic cell clones or their progeny present a food safety concern."

Methodology of the Risk Assessment

What prompted this increase in confidence over the 2002 NAS report that would lead the FDA to approve cloned animal foods as safe for human consumption in 2008 with such unqualified statements concerning the absence of risk? As explained

by the study's risk assessment methodology development, the FDA's initial analysis of food safety was based largely on the health status of the cloned animals, as there were no studies explicitly evaluating the safety of food products from animal clones.³ This initial approach, founded on the "critical biological systems hypothesis," assumes that cloned animals that appear healthy are likely to produce normal meat and/or milk with no attending food consumption risks. The health risks to cloned animals are examined at distinct developmental stages: pregnancy and parturition, perinatal period, juvenile development, reproductive development and function, and postpubertal maturation and aging. According to the critical biological systems theory, if the cloned animal survives to at least the juvenile stage and appears otherwise normal, it is presumed to be healthy, and its meat or milk are considered fit for human consumption. This approach additionally relies on the regulatory meat inspection process to prevent cloned animals that exhibit visible abnormalities from entering the food supply: "Animals found to have a disease or condition that would render them adulterated (eg, unfit for consumption, unhealthful, unwholesome) are prohibited from entering the human food supply..."

When data on the composition of edible products from clones became available later in the multiyear study, the FDA Risk Assessment began to use an additional approach to evaluate cloned food for safety. This second approach depends on a compositional analysis of the meat and milk produced by cloned animals and assumes that, if no major differences in the composition of milk and meat between clones and nonclones can be found, the cloned meat and milk are safe for human consumption.³ Similar to the critical systems approach, the compositional approach relies on the assumption that if meat and milk from cloned animals meet all local, state, and federal regulatory requirements, and are not materially different from conventional meat and milk, they pose no additional risk to human consumption. To make this safety determination, the Risk Assessment evaluated select nutrients in milk and meat that make "major" or "moderate" contribu-

tions to human nutrition (eg, vitamin B₁₂, riboflavin, calcium, selenium). The FDA acknowledged that limited numbers of cloned specimens and uncertainty as to what analyses should be performed created some uncertainty in the assessment's conclusions, but apparently not enough to prevent the agency from concluding that cloned food is safe for human consumption.

Epigenetic Reprogramming and Subtle Hazards

The primary food safety concern with epigenetic reprogramming of the donor nucleus was not that it may result in gross deformation of cloned animals. The FDA's implied conclusion was not that food from *any* cloned animals is safe to eat, but rather that food from normal, healthy-looking clones is safe to eat. The rub here, unfortunately, is that it may not be safe to assume that abnormal clones will always be identified and kept out of the food supply. Clones with gross morphologic abnormalities can reasonably be expected to fail regulatory inspection.³ Of much greater concern, however, might be that epigenetic changes causing "subtle hazards" can elude detection by conventional means.

The epigenetic reprogramming that may go awry in cloned animals can result in the global disruption of normally tightly regulated gene expression patterns during development of the growing organism. For example, it has been reported that some bovine clones inappropriately express a cell surface antigen (MHC I) in the chorion, rendering the cloned embryos at increased risk of immune rejection by their mothers.⁴ Another study noted that the brain cells of a bovine embryo cloned from an adult immune lymphocyte contained the genetic rearrangement normally found only in lymphocytes.¹⁰ While this genetic rearrangement did not allow the embryo to survive to birth, it is conceivable that less profound epigenetic changes producing only subtle shifts in cell identity of tissues would allow abnormal clones to survive into adulthood. Such subtle cytologic manifestations of epigenetic changes could evade detection by conventional meat inspection procedures, for example, if faulty epigenetic reprogramming caused a cloned cow to

express neuronal genes in its muscle cells that changed the cells' membranes to become partially like those of brain cells. Eating steak from such a clone, then, would be akin to eating brain tissue. Detecting such changes would likely require molecular or cytologic techniques and could be easily missed in common meat inspection. In addition, because it is known that epigenetic transformation can induce normal cells to become tumor cells,⁴ meat from cloned animals could harbor precancerous changes that are not detectable by conventional means.

The FDA has acknowledged that the "[m]echanisms of epigenetic reprogramming are complex and not fully understood." It has further acknowledged that "various factors influence the success rate of SCNT...factors that have not yet been identified."³ Others have suggested that no clone can be completely "normal." As a well-known leader in the field of mouse transgenics said: "You can't tell me that 95 percent [of clones] die before birth and the other 5 percent are normal."¹¹ Indeed, a 2004 NAS report found that epigenetic changes in the genome may "lead to changes in expression of one or more genes in a manner that may be analogous to gene expression changes observed in transgenic animals"; the report concluded that cloned animals should initially be evaluated in a manner comparable to that for "animals in which genetic engineering has been used to make specific genetic modifications."⁴

As previously mentioned, in addition to the risk assessment approach based on the assumption that healthy-appearing clones able to survive to slaughter age are safe to eat, the FDA also employed compositional analysis to determine the safety of cloned food. The 2004 NAS report on assessing unintended health effects of genetically engineered food provided thoughtful and detailed guidance on the evaluation of potential unintended composition changes of cloned animal products.⁴ The NAS report divided the compositional analysis strategies into targeted or nontargeted categories. Whereas the FDA Risk Assessment discussed the targeted analytical approach in which known individual compounds are quantified, the NAS report noted that, with the targeted

approach, it would be possible to miss some unexpected compositional changes because the list of compounds selected for assay was not all inclusive. To enhance the likelihood of detecting unintended compositional changes, the 2004 NAS report recommended that the targeted approach be supplemented with nontargeted analytical approaches, or profiling methods, such as DNA array, proteomics, and metabolomics. These high-throughput approaches allow the rapid analysis of many compounds simultaneously. For example, DNA microarray technologies can be used to examine global patterns of DNA expression in cloned food products that later could be associated with toxicity. Likewise, proteomics and metabolomics can survey global changes in the structures and functions of cellular proteins and assess the small-molecule metabolite profile of cells, respectively. According to the 2004 NAS report, these profiling methodologies have the potential to provide a more extensive or global quantification of mRNA, protein, and metabolites to determine whether changes have occurred as a result of the cloning procedure.

Curiously, the FDA Risk Assessment is silent on the topic of nontargeted compositional analyses. Instead, the accompanying FDA document entitled "Animal Cloning: Risk Management Plan for Clones and Their Progeny" confidently pronounces that "the Risk Assessment has also determined that there is sufficient information to determine that food from cattle, swine, and goat clones is as safe to eat as that from their more conventionally-bred counterparts. We therefore do not believe that meat or milk from cattle, swine, and goat clones would require any additional controls compared with meat or milk from cattle, swine, or goats currently entering the food supply today..."¹²

In contrast to the FDA's cheerful assessment of absence of risk, the 2004 NAS report emphasized the importance of identifying each gene product affected by cloning to establish its biological function.⁴ This would allow the gene product to be evaluated for hazard potential as a defined chemical food constituent. However, the report also recognized that, inasmuch as the expression of numerous genes could be affected by the cloning

event, this type of evaluation could become costly and burdensome. The 2004 NAS report concluded its section on the assessment of methods to detect unintended health effects with this cryptic statement: "Since there is no evidence that food from cloned animals poses any increased health risk to the consumer, it could be concluded that food from cloned animals should be approved for consumption. However, the paucity of evidence in the literature on this topic makes it impossible to provide scientific evidence to support this position."

Tracking and Animal Identification

The 2004 NAS report also urged the implementation of effective programs to monitor the presence of cloned animals.⁴ It acknowledged that if subsequent scientific review established an increased risk to human health associated with the consumption of food products from cloned animals, it would be necessary to distinguish cloned animals from noncloned animals before entry into the food chain. This recommendation, too, has apparently been ignored by the FDA, as neither tracking nor monitoring systems are required by the Risk Assessment. While the FDA risk management plan contemplates the review of additional animal health and food composition data on animal clones or their progeny as the data become available, any active monitoring envisioned by the FDA consists of little more than attending seminars: "Our monitoring will consist of surveying the literature, maintaining our attendance at such scientific and professional meetings that address epigenetic reprogramming, including the International Embryo Transfer Society, and others as appropriate."¹²

Reaction to the Risk Assessment

When the FDA released its report, members of the public reacted with great concern. Most of the outcry was focused on the idea that cloned food could enter the marketplace without being labeled as such. A 2008 poll by the Consumers Union found that 89% of Americans wanted cloned food to be labeled, and 69% had concerns about cloned food entering the food supply.¹³ About half of the more than 30,000 public comments received

about the Risk Assessment concerned labeling.⁶ To ease this fear, and to facilitate tracking of cloned food products, the FDA should mandate labeling for cloned foods, or at a minimum, allow producers to label food as not cloned.*

One difficulty inherent in not requiring that cloned food be labeled is that there is no single post-market test that will be able to distinguish cloned food from conventional food. Although buying products labeled as organic will avoid the issue (organic foods cannot contain cloned products), not having cloned foods labeled as such does not provide full information, thus restricting freedom of choice for consumers.⁶ A degree of labeling is mandatory for foods under the Nutrition Labeling and Education Act of 1990, and foods must bear information about serving size, servings per container, calories, and nutrients including fat, cholesterol, sodium, carbohydrates, sugars, fiber, and protein.¹⁷

The FDA should address public concerns over cloned food labeling instead of ignoring the issue. Not having a labeling or tracking system in place for cloned food products could lead to disastrous results if it is later discovered that some cloned food products harbor a previously unknown and unidentified risk to consumers. In the event of such a discovery, the FDA would be unable to recall the products because they cannot be tracked or located. In addition to requiring labeling, the FDA might consider mandating a safety assessment to identify potential unintended effects, similar to the framework proposed by the 2004 NAS report. At a minimum, this should entail both the integration of targeted and nontargeted methods to establish compositional profiles of food derived from cloned animals, and the implementation of animal identity preservation systems to allow the tracking of animals and their products through the food chain.

*A tracking database is in the process of being created that would allow marketers, but apparently not individuals, to track clones as they progress through sale and processing.¹⁴ This system has been criticized because it will not include data on the progeny of clones.¹⁵ The cloning industry has been criticized for resisting the release of clone DNA to tracking companies, given that it will be exceedingly difficult to track animals without DNA verification once they are processed.¹⁶

CONCLUSIONS

The American public, as well as members of Congress and the USDA, have reacted with skepticism to the FDA's Risk Assessment.⁶ In 2008, the Senate passed legislation, as part of its farm bill, attempting to stop the FDA from approving cloned food until further studies could be conducted and to force the FDA to consider consumer approval of cloned food products. The USDA has asked for a *voluntary* ban on cloned foods in the public marketplace.¹⁸ The two NAS reports have addressed the scientific uncertainties regarding the safety of cloned food products and have recommended the mandatory tracking of cloned food products. To date, however, the FDA's Risk Assessment is taken as a persuasive argument for the safety of human consumption of cloned animal products, when the reality is far less clear.

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