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Initial Comments Concerning the Food and Drug Administration's Animal Cloning Risk Assessment

by

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The Center for Food Safety (CFS) is a national non-profit membership organization with offices in Washington, DC and San Francisco, CA. CFS works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and other forms of sustainable agriculture. CFS engages in legal, scientific and grassroots initiatives to guide national and international policymaking on critical food safety issues. CFS provides the following initial comments to the Food and Drug Administration (FDA) concerning its Animal Cloning Risk Assessment.

Critical Lack of Scientific Rigor in FDA's Risk Assessment

CFS believes that the conclusions reached by the FDA in its Animal Cloning Risk Assessment are scientifically unsupported and run contrary to the agency's mandate to protect the safety of American consumers and the food supply. Rather remarkably, the FDA basis its initial safety conclusions on the milk and meat from cloned animals upon only one study. The FDA's admits:

> Information on the composition of clone meat or milk is extremely limited. Very few of the bovine clones are old enough to have been bred, given birth and lactating. One study has been identified on the composition of milk from clone cows; no studies on the composition of meat from clones have been identified.[1]

Similarly, the Risk Assessment's conclusions rely upon one study on the milk from progeny of clone and no studies on the edible products from cloned animals.[2]

Regulatory agencies throughout the world have only recently begun to analyze the human health and safety issues associated with cloned animals and their progeny. However, to the extent the issue has been addressed, the FDA's safety conclusions are based upon data that falls woefully short of assuaging food safety concerns. In the fall of 2002, the United Kingdom Agriculture and Environment Biotechnology Commission recommended that its regulatory agencies require welfare records of two generations of animal living full life spans before assessing the discharge of cloned animal products into any commercial markets.[3] The National Academy of Sciences (NAS) has pointed out that "it is difficult to identify [food safety] concerns without further supporting evidence regarding food product composition."[4] While the NAS has found that more studies were necessary to begin identifying the areas of risk associated with cloned animals, the FDA has come to initial conclusions based upon single studies in several categories of products and no studies concerning cloned meat. Unfortunately, rather than protecting consumers the FDA seems to be engaged in a race to the regulatory bottom by putting forth a scant risk assessment designed to justify the commercial marketing of cloned milk and meat.

Accordingly, CFS calls on the FDA to institute a mandatory moratorium on the marketing of milk and edible products from animals created by somatic cell nuclear transfer (hereinafter "cloning") and their progeny. This moratorium should remain in place until the agency has: (1) engaged in a far more rigorous scientific review of data related to cloned animals and their edible products; (2) held several additional advisory panel meetings to analyze and discuss this data; (3) held public field hearings on the issue similar in nature to the Year 2000 FDA meetings on agricultural biotechnology; (4) fully integrated and assessed ethical and animal welfare concerns into its risk analysis; and (5) proposed and established an inter-agency mandatory pre-market regulatory approval process complete with mandatory labeling.

Numerous Issues of Concern Associated With Cloned Animals

The widespread commercialization of cloned animals poses numerous issues that need to be further addressed prior to the completion of any risk assessment and conclusions concerning commercialization. These issues include animal welfare issues, in-depth edible product analysis, study of novel herd management issues that might arise because of cloned animal health and novel slaughter issues. The FDA's draft risk assessment fails to adequately analyze these issue.

1. Issues of Animal Welfare

The cloning of animals represents a fundamental change in our relationship with animals. The relationship changes human interaction with animals from an assistant in reproduction to a wholesale creator of genetic "replicas" of existing animals. The results of his relational change manifest themselves in the abhorrent animal suffering, a cruelty that will grow should cloning become a widespread commercial venture.

Ian Wilmut and his team of scientists implanted 277 cloned sheep embryos in surrogate ewes, from which only thirteen pregnancies resulted and Dolly was the only successful birth.[5] Even after several years of additional research and the development of new methods for extracting and transferring genetic material, well over 99% of all cloning attempts still fail.[6] Even when nuclear transfers produce embryos that are successfully implanted in surrogates, only 3% to 5% of these pregnancies produce offspring that live to adulthood.[7]

In one case, researchers at Texas A&M University set out to compare the development rates of cloned cattle derived from somatic and fetal cells. Only 17% of 322 adult SCNTs and 12% of 332 fetal cell

nuclear transfers developed into embryos. Of these, 26 adult-cell-derived embryos and 32 fetal-cell-derived embryos were successfully implanted in surrogate mothers. After 40 days of pregnancy, six of the adult-cell-derived fetuses and three of the fetal-cell-derived fetuses survived. After 290 days of pregnancy, the experiment's only viable calf was born—a clone derived from an adult somatic cell. The project's 654 total nuclear cell transfers and 58 pregnancies had resulted in only one viable offspring.[8] But even this meager success rate was tainted. "The cloned calf produced in this experiment possessed significant metabolic and cardiopulmonary abnormalities similar to those observed in previous studies," the researchers reported. In addition, the calf was born with diabetes mellitus and was found to be susceptible to severe immune-system deficiencies.[9]

Cloned livestock that manage to survive birth tend to require more care than those sexually reproduced. Cloned calves, piglets, and lambs often require neonatal glucose infusions to treat hypoglycemia or oxygen treatments to offset hypoxia.[10] Jonathan Hill, who has worked on cattle cloning at Cornell University, suspects that 25% to 50% of clones are born having been deprived of normal levels of oxygen. The neonatal condition of most clones is so poor, Rebecca Krisher, an animal reproduction specialist at Purdue University, says, "Almost all of these animals, if born on a farm without a vet hospital, . . . probably wouldn't survive."[11]

The tremendous suffering of animal clones also impact their surrogate hosts. Most cloned livestock also exhibit a condition known as "large-offspring syndrome," which results in overly stressful deliveries for the surrogate mothers. Because of their large size, a higher than normal percentage of clones are delivered via cesarean section.[12] In one documented cattle cloning project, three out of 12 surrogate mothers died during pregnancy.[13]

Even the cloned animals that survive to be born are likely to suffer a wide range of health problems. One example is a sheep cloned by Ian Wilmut and his team, the same group who brought Dolly into the world. This much less heralded sheep, born not long after Dolly, had a malformed respiratory tract and was soon euthanized.[14] In fact, such abnormalities are common. Late in 2002, scientists at the New Zealand government's AgResearch reported that 24% of the cloned calves born at the facility died between birth and weaning. This compares to a 5% mortality rate for non-cloned calves. Another 5% of cloned calves died after weaning, compared to 3% of sexually reproduced calves.[15] One review of scientific literature, authored by executives at the commercial cloning lab Advanced Cell Technology, found that nearly 25% of cow, sheep, swine, and mouse clones showed severe developmental problems soon after birth. However, the vast majority of the studies considered for this review had follow-up periods of only a few weeks or months.[16] Many later-developing health problems would not be reflected.

These results clearly indicate that cloning has a significant and overwhelming impact on the animals involved in the process. Consumers and the public have consistently rejected the animal suffering caused by cloning based upon moral grounds.[17] While the FDA Risk Assessment makes cursory note of the aforementioned impacts, it provides no discussion on whether society views such animal suffering an acceptable risk or cost of producing edible cloned products. CFS believes that this issue must be addressed before the FDA makes any decision on allowing clone milk and meat on the market.

2. Issues of Food Safety

In addition to the animal welfare issues, data concerning the health of adult clone animals raises the specter of significant unresolved issues of food safety. Recent research shows that even clones seeming

healthy at birth may not be as normal as they appear. Scientists at Tokyo's National Institute of Infectious Diseases found that cloned mice had significantly shorter life spans than normal mice. The research team raised 12 apparently healthy cloned mice and seven sexually reproduced mice in a controlled laboratory environment. At about 300 days after birth, the first cloned mouse died. Within 800 days of birth, 10 of the 12 clones had died, while six of the seven sexually reproduced mice were still thriving. Autopsies revealed that the clones died from a variety of maladies, including liver failure, pneumonia due to weak immune systems, and cancer.[18]

Late-developing health problems are not confined to mouse clones. In fact, Dolly, often touted as livestock cloning's greatest success story, developed premature arthritis.[19] Even more seriously, in February this year veterinarians at the Roslin Institute decided to euthanize Dolly after diagnosing her with a progressive lung disease. Dolly was only six years old. Researchers said that her normal life expectance would have been 11 or 12 years.[20]

The most likely causes of clones' prenatal and postnatal defects are genetic abnormalities that arise during fetal development. Rudolf Jaenisch and colleagues at Massachusetts Institute of Technology's Whitehead Institute determined that cloned mice in their study had hundreds of improperly expressed genes. These resulted in a wide variety of abnormalities, ranging from the very subtle to the catastrophic. With so-called "imprinted genes," those that in a normal offspring only one copy—either from the mother or the father—is "switched on," Jaenisch found that nearly half "were incorrectly expressed." Though his experiments dealt only with cloned mice, Jaenisch concluded that genetic abnormalities were most likely responsible for the dismal success rates of cattle, sheep, and swine cloning efforts. "There is no reason in the world to assume that any other mammal . . . would be different from mice," he said.[21] Davor Solter of Germany's Max Planck Institute for Immunobiology says it is likely that few if any clones are completely free of genetic abnormalities. "Whether the clone dies next day or next year depends on how badly it misses," he said.[22]

In normally reproduced animals, a methylation switches certain genes off as the animal matures and the functions encoded by those genes are no longer necessary. Methylation also plays a role in the proper expression of imprinted genes. Because SCNT cloning uses genetic material from mature cells, the methylation pattern in these clones is often quite different than in animals that develop as normal embryos. While scientists try to "reprogram" the adult genetic material to act as if it were embryonic DNA, a group of South Korean scientists who studied SCNT cloned cow embryos detected no indications of methylation; they found this resulted in unusual patterns of genetic imprinting. The research team concluded that this incomplete genetic reprogramming could be one reason for the high failure rate of animal cloning.[23]

A second study, presented in the June 2001 issue of *Genesis*, also showed abnormal methylation in clones, leading to unpredictable health problems, including overgrown placentas, increased body weight, and respiratory, blood or immune system problems. "No matter what you do, cloning changes these methylation flags," said one scientist.[24] Jaenisch and his colleagues at the Whitehead Institute concluded that improper methylation caused the abnormalities they found with imprinted genes in their cloned mice. "Even apparently normal clones have an abnormal regulation of many genes," Jaenisch said. "Completely normal clones may be the exception."[25] In fact, improper methylation may be cloning's fatal flaw. Writing in *Science*, Wilmut and Jaenisch state that there is no way now or for the foreseeable future for scientists to detect whether these reprogramming errors have occurred.[26]

Recently, in August of 2003 researchers at the University of Connecticut report the sudden death of three cloned adult pigs.[27] The reasons associated with these animal deaths remain unresolved. Nonetheless, the scientist suspect it is the result of abnormal gene regulation caused by methylation issues.

Many scientists are concerned that these subtle and not-so-subtle "imprinting errors" raise as yet unresolved safety issues concerning the food products from cloned livestock. Ian Wilmut has said that commercial production of meat and dairy products from cloned animals should not begin until large-scale, controlled trials have been conducted. Cloners now working on dairy production say they are comparing the milk from their clones with natural milk, but Wilmut told the magazine *New Scientist* that study of cloned animals should look not only at milk, but also at the animals' health profiles and life spans. Wilmut warned that even small imbalances in an animal's hormone, protein, and fat levels could compromise the quality and safety of meat and milk.[28]

While Infigen and other cloning companies have already proclaimed the safety of their food products, scientists have yet to complete necessary studies. The NAS' August 2002 report on animal biotechnology notes that scant research on the safety of meat and milk from embryo-derived clones exists. As for SCNT cloning, food safety issues are even less clear, as the NAS notes:

> The cloning of animals from somatic cells is more recent. Limited sample size, health and production data, and rapidly changing cloning protocols make it difficult to draw conclusions regarding the safety of milk, meat, or other products from individuals that are themselves somatic cell cloned individuals.[29]

Some scientists warn that abnormal gene-expression, which likely causes the health problems of clones, is likely to also affect the meat and milk of cloned livestock. The NAS notes that studies to confirm or refute this have not been done: "There are to date no published . . . comparative analytical data assessing the composition of meat and milk products of somatic cell clones, their offspring, and conventionally bred animals."[30] FDA's reliance on one study concerning milk derived from cloned an animals and the no meat studies does little to alter the NAS' finding that the science necessary to adequately assess risks does not yet exist. Similarly, FDA cannot point to studies that adequately assess whether abnormal gene-expression creates inherited traits in cloned animals' progeny.

Additional food safety concerns stem from the high failure rates of cloning pregnancies and the typical sickly nature of newborn clones. Scientists often infuse the surrogate mothers of cloned livestock with massive doses of hormones to improve the odds that the cloned embryos will implant in the surrogates' uteruses. While the clones are typically the genetic offspring of highly prized parents, the surrogate mothers hold no such intrinsic value. Many surrogate mothers are destined for slaughterhouses soon after giving birth, opening an avenue for large amounts of veterinary pharmaceuticals to enter the human food supply. The clones themselves, often born with severely compromised immune systems, frequently receive massive doses of antibiotics and other medications.[31] Commercialization of cloning would almost certainly increase levels of veterinary hormones and antibiotics in the human food supply.

Commercialization of cloned livestock for food production could also increase the incidence of food-borne illnesses, such as *E. coli* infections, resulting from slaughter of such animals. According to the NAS study:

> Because stress from [the] developmental problems [of cloned livestock] might result in shedding of pathogens in fecal material, resulting in a higher load of undesirable microbes on the carcass, the food safety of products, especially such as veal, from young somatic cell cloned animals might indirectly present a ... concern."[32]

Significantly, the FDA Risk Assessment does not address this issue in any manner.

Finally, the allowance of commercialized cloning may broadly affect the overall health of the U.S. farm animal population by further eroding genetic diversity. Modern livestock breeding techniques have already reduced the genetic diversity of many populations of farm animals. Over 90% of U.S. dairy cows are the Holstein variety. Eight of the 15 breeds of swine raised in the United States in the middle of the 20th century no longer exist. Similarly, only five breeds comprise nearly the entire U.S. poultry flock, and almost all white eggs come from white leghorns.[33] Large-scale commercial cloning of animals would further erode livestock diversity. Entire herds and flocks could share a single genome. While breeders would aim to clone animals with desirable genetic characteristics, genetic weaknesses would inevitably be passed along as well. Herds of genetically identical animals would likely be highly susceptible to communicable diseases and environmental hazards. One NAS scientist has warned that allowing cloning in livestock production could lead to "genetic bottlenecks" that dilute diversity and leave farms vulnerable to epidemic disease.[34] According to the U.K. Farm Animal Welfare Council,

> [T]he potential of introducing deleterious genes ... must not be forgotten. Furthermore, any tendency to lose genetic diversity may make it difficult or even impossible to reverse the effect of such deleterious genes once recognised. This might result in an increased risk of genetic abnormalities, susceptibility to disease and other welfare consequences. We do not believe that control of these problems should be left to the industry but rather that statutory regulation is required.[35]

Again, the FDA Risk Assessment fails to address the erosion of genetic diversity in U.S. livestock herds and its impact on herd health management that may be caused by animal cloning.

Conclusions

For consumers, commercial livestock cloning could inundate the food supply with novel products that have not been safety tested and have raised safety concerns among some of the leading scientists in the cloning field. For farm animals, the spread of cloning is likely to bring genetic defects, premature aging, and widespread suffering. Meanwhile, if the FDA Risk Assessment is any indication regulators seem poised to place the interests of a few biotech firms over those of small farmers, consumers, and farm animals.

As a result of the inadequacies described above, the FDA should immediately institute a moratorium on the commercialization and marketing of milk and other edible products derived from cloned animals or their progeny. Prior to any commercialization FDA should take the following steps:

> (1) Engage in a far more rigorous scientific review of data related to cloned animals and their edible products to address the clear data inadequacies of the current Risk Assessment.

(2) Hold several additional advisory panel meetings to analyze and discuss new data. This meeting should be the beginning of FDA's safety assessment of the animal clone issue. Pronouncements of preliminary risk assessment findings should not be made until significant further public analysis of data occurs,

(3) Hold public field hearings on the animal cloning issue similar in nature to the Year 2000 FDA meetings on agricultural biotechnology. Consumer opinion counts and the FDA will not receive such input unless it engages in a national dialogue on this issue.

(4) Fully integrated and assessed ethical and animal welfare concerns into its risk analysis. The agency must explore ways in which animal welfare issues are part of its risk assessment rubric.

(5) Propose and established an inter-agency mandatory pre-market regulatory approval process complete with mandatory labeling prior to any commercialization. The FDA must begin an inter-agency process with USDA and other federal agencies to develop a comprehensive regulatory approval process for all edible products derived from cloned animals and their progeny. This process should include solicitation and public release of legal opinions from FDA's and USDA's Office of General Counsel concerning the extent to which the New Animal Drug Application process, Animal Health Protection Act, Federal Meat Inspection Act and Poultry Products Inspection Act provide the agency with authority to regulate cloned animals.

Endnotes:

[1.] Food and Drug Administration, Animal Cloning: A Risk Assessment (Draft Executive Summary), October 21, 2003, at 7.

[2.] Id at 9-10.

[3.] United Kingdom, Agriculture and Environment Biotechnology Commission, Animals and Biotechnology, September 2002, at 36.

[4.] National Research Council of the National Academies, *Animal Biotechnology: Science-Based Concerns*, Washington, DC: National Academy Press, 2002, 66.

[5.] Sharon Begley, "Little Lamb Who Made Thee," Newsweek, March 10, 1997.

[6.] James C. Cross, "Factors Affecting the Development Potential of Cloned Mammalian Embryos," *Proceedings of the National Academy of Sciences*, 98 (May 22, 2001), 5949-5951.

[7.] Rick Weiss, "Human Cloning Bid Stirs Experts' Anger; Problems in Animal Cases Noted," Washington Post, March 7, 2001.

[8.] Two embryos were surgically removed for study after 40 days of pregnancy, so it is impossible to know for sure whether these would have survived to viability.

[9.] Jonathan R. Hill, et al., "Development Rates of Male Bovine Nuclear Transfer Embryos Derived From Adult and Fetal Cells," *Biology of Reproduction*, 62 (2000), 1135-1140.

[10.] Jose B. Cibelli, et al., "The Health Profile of Cloned Animals," *Nature Biotechnology*, 20 (January 2002), 13-14.

[11.] Audrey Cooper, "Cloned Calves Die at California University," Associated Press, April 3, 2001.

[12.] John Travis, "Dolly Was Lucky," Science News Online, Oct. 20, 2001, <www.sciencenews.org/20011020/bob15.asp>.

[13.] Jacky Turner, *The Gene and the Stable Door*, a report for the Compassion in World Farming Trust, Petersfield, Hampshire, UK: January 2002, p. 6.

[14.] John Travis, "Dolly Was Lucky," Science News Online, Oct. 20, 2001, <www.sciencenews.org/20011020/bob15.asp>.

[15.] Simon Collins, "Cloned Animals Dying at AgResearch," the New Zealand *Herald*, Nov. 14, 2002.

[16.] Jose B. Cibelli, et al., "The Health Profile of Cloned Animals," *Nature Biotechnology*, 20 (January 2002), 13-14.

[17.] See chart, Pew Initiative on Food and Biotechnology, Animal Cloning and the Production of Food Products: Perspectives From the Food Chain, 2003, at 23.

[18.] Amy Norton, "Cloned Mice Die Earlier, Study Shows," Reuters Health, Feb. 11, 2002; John Whitfield, "Double Take on Cloning," *Nature* advance online publication, Feb. 11, 2002, <www.nature.com/020204/020204-15.html>. The full paper appeared in the Feb. 11, 2002, edition of *Nature Genetics*.

[19.] "Dolly Is Arthritic," AgBiotechNet, Jan. 15, 2002, <www.agbiotechnet.com/topics/Database/newsarticle.asp?id=990&name=>.

[20.] Jane Wardell, "Dolly the Cloned Sheep Put to Death," Associated Press, Feb. 14, 2003.

[21.] Maggie Fox, "Study: Clones Have Abnormal Genes," Reuters, Feb. 3, 2003.

[22.] ; John Whitfield, "Double Take on Cloning," *Nature* advance online publication, Feb. 11, 2002, <www.nature.com/020204/020204-15.html>.

[23.] Merritt McKinney, "Flawed genetic 'marking' seen in cloned animals," Reuters Health, May 29, 2001; Kang, et. al., "Aberrant methylation of donor genome in cloned bovine embryos," Nature Genetics 2001;28:173-177, abstract at http://www.nature.com/cgi-taf/DynaPage.taf?file=/ng/journal/v28/n2/abs/ng0601_173.html&_UserReference=C0A804EF4650D90ABBCAED26142C3B519510

[24.] Helen Altonn, "Cloning Isn't Safe. UH Researchers warn," Star Bulletin, July 6, 2001.

[25.] John Travis, "Dolly Was Lucky," Science News Online, Oct. 20, 2001, <www.sciencenews.org/20011020/bob15.asp>.

[26.] "Don't Clone Humans, say animal researchers," Science, Volume 291 (5513), pp. 2552, archived summary at **http://www.gene.ch/genet/2001/Apr/msg00026.html;** Melissa Schorr, note 17.

[27.] Helen Pearson, "Adult Clones in Sudden Death Shock," Nature, August 27, 2003.

[28.] "Duplicate Dinner," New Scientist, May 19, 2001.

[29.] National Research Council of the National Academies, *Animal Biotechnology: Science-Based Concerns*, Washington, DC: National Academy Press, 2002, 66.

[30.] National Research Council of the National Academies, *Animal Biotechnology: Science-Based Concerns*, Washington, DC: National Academy Press, 2002, 66.

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[32.] National Research Council of the National Academies, *Animal Biotechnology: Science-Based Concerns*, Washington, DC: National Academy Press, 2002, 66.

[33.] Janet Raloff, "Dying Breeds: Livestock Are Developing a Largely Unrecognized Biodiversity Crisis," Science News Online, Oct. 4, 1997, <www.sciencenews.org/sn_arc97/10_4_97/bob1.htm>.

[34.] Regalado, note 5.

[35.] Colin Spedding, *Report on the Implications of Cloning on the Welfare of Livestock*, Farm Animal Welfare Council, Tolworth, Surrey: December 1998.