Comments of Consumers Union to
US Food and Drug Administration on
Docket No. 2003N-0573, Draft Animal Cloning Risk Assessment
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Summary

Consumers Union, publisher of *Consumer Reports*[1], welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) Draft Animal Cloning Risk Assessment. We believe this Risk Assessment is inadequate and should be withdrawn. The major shortcomings which would have to be addressed before it could be considered valid are:

1. Insufficient data on composition of milk and meat from cloned animals and their offspring. The conclusions of safety appear to be based on data on milk from 43 cow clones, and data on beef from 16 cow clones, and 5 pigs. There are no data at all from other species. These are insufficient data on which to base a conclusion of safety for all milk and meat from cows, pigs, and goats, all breeds, under all husbandry and management conditions. Milk and meat from clones could have altered quality and nutritional characteristics. At lease one study recommends further investigation of potential to cause allergic reactions.
2. Failure to consider effects of poor health of clones on food safety and public health. Poor clone health, documented in the Risk Assessment, could result in increased antibiotic use, increased antibiotic resistance, and wider dispersal of dangerous pathogens such as *E. coli* 01578:H7. These possibilities must be considered in deciding whether cloning is a safe technology for humans.
3. Failure to consider the possibility that sick and/or unsafe animals may not always be removed from the food supply during antemortem inspection.
4. Failure to conclude that the technology is unsafe for animals, despite extensive data presented as to very high rates of illness, death and deformities in clones. The data show that a vast majority of clones die shortly after birth. The Risk Assessment should assess the safety of the technology for animals, not just humans.

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[1] Consumers Union (CU) is an expert, independent, nonprofit organization whose mission is to work for a fair, just, and safe marketplace for all consumers. CU publishes *Consumer Reports*, which has over 4 million subscribers to the print edition and over 1.5 million subscribers to the online edition ConsumerReports.org To maintain our independence and impartiality, Consumers Union accepts no outside, no free test samples, and has no agenda other than the interests of consumers. Consumers Union supports itself through the sale of our information products and service, individual contributions, and a few noncommercial grants.

Given the paucity of data that directly address the safety of meat and milk from cloned animals, the FDA used indirect measures of food safety, primarily data on the health of the clones at different life stages. The operating hypothesis is the notion that an animal that appears healthy must be safe to eat (e.g. the Critical Biological Systems Approach). This approach is not scientific—this is reasoning by inference, not from data. Furthermore, FDA has bent over backward to interpret data from cloning companies in a way that minimizes the potential problems raised by SCNTs. Both of these problems need to be remedied in the final Risk Assessment.

We also strongly disagree with the notion FDA put forward in media materials and elsewhere that clones are simply "identical twins" born at different times and that clones (e.g. somatic cell nuclear transplants, SCNTs) show no "unique hazards" compared with other artificial reproductive technologies (ARTs). Scientifically speaking, SCNT clones are not "identical twins" and the problem of aberrant nuclear-mitochondrial interaction (due in part to the presence of mitochondria from two parents) is a "unique hazard" for SCNTs compared to other ARTs.

We believe that FDA should require safety testing of the products of cloned animals before they are placed on the market. In addition, we believe that FDA should require labeling of the meat and milk from cloned animals.

Food Safety Assessment: Insufficient Data

The data presented in the new FDA Draft Animal Cloning Risk Assessment are too scanty and are not of sufficient quality to draw valid conclusions about the safety of meat and milk from cloned animals and their offspring. FDA's Risk Assessment should assure that milk and meat is not only safe, but as nutritious as conventional.

The compositional data on milk and meat from clones and non-clone comparators on which FDA bases its conclusions ranges from poor to non-existent. In the case of cows, the FDA was able to find only seven published studies on milk parameters that collectively involved only 43 cow clones—27 Holstein, 9 Freisen, 1 Brown Swiss, 4 Jersey, and 2 HolsteinXJersey. For meat, there are only two peer-reviewed studies that collectively involved only 5 cloned Japanese Black Beef cattle. FDA also reviewed meat composition data for 11 cows supplied it by Cyagra, a company that produces cloned cattle. There are no compositional studies on milk and meat from offspring of cloned cattle.

In the case of pigs, there are no peer-reviewed data comparing meat composition of clones and non-clone comparators, nor of offspring of clones and offspring of non-clones. FDA relies on data submitted by a company, Viagen, that compares the meat composition of 5 clones as well as meat composition data from 242 offspring of clones. The meat composition data of offspring of clones and non-clones was published in the scientific literature after the FDA released their Draft Animal Cloning Risk Assessment

(Walker et al., 2007). For goats, there were no published studies or other data on compositional data on milk and meat.

Food safety assessment of cattle clones and their progeny

Milk

When it comes to cattle, the FDA-reviewed data on milk composition from clones vs non-clones come from only seven peer-reviewed studies that collectively involved 43 animals. Of these seven studies, only 2 of them involved appropriate controls. Heyman et al. (2004) found that first lactation milk yields and somatic cell counts (SCC, which are a measure of milk quality; extremely high counts indicate udder infections) for three Holstein clones were similar to those of age-matched non-clone comparators raised under similar condition. Although the mean SCC didn't differ between clones and non-clones, the variability in SCC was more than twice as large for the clones compared to the non-clone comparators, which is just the reverse of what one would expect. Tian et al. (2005) compared the milk from a single lactation cycle of only four Holstein clones to the milk from four Holsteins of the same age and parity that lived in the same facility from 2 months of age and received the same diets and management practices; such controls were designed to reduce variation and facilitate comparison. There were no significant differences in the various milk parameters looked at (total fat, total protein, total solids, lactose, non-urea nitrogen, somatic cell counts); although the differences in somatic cells counts (SCC) was not statistically significant, SCC of clones was about 10% higher than non-clone comparators.

The other five studies really did not use appropriate controls. A study involving 15 dairy cow clones of three different breeds (12 Holsteins, 1 Brown Swiss and 2 HolsteinXJersey [Holstein Jersey cross]), produced by Infigen, Inc., used comparator animals of approximately the same age and lactational stage, but the comparator cows were housed on different farms and so were fed different rations than the clones; in addition the ration for the clones changed during the course of the lactation (Walsh et al. 2003). Walsh et al. (2003) found differences in the fatty acid profiles of the milk over the course of the lactation, with the differences in palmitic acid and linolenic acid being statistically significant. In addition, there were statistically significant differences in levels of potassium, zinc, strontium, and phosphorous. However, the authors chalked up these statistically significant differences to differences in diet, concluding that there were no "obvious differences between milk from clones and non-clones" (Walsh et al., 2003: 213). Given the fact that clones and comparators were not raised on different farms and received different diets makes this a poorly designed study that makes the results very hard to interpret.

Three of the milk composition studies were carried out in Japan. Two of these studies involved comparing milk of clones to that of the donor animal from which the clone was derived (Aoki et al., 2003; Yonai et al., 2005); this makes a statistical evaluation virtually impossible. The third Japanese study is a report, "Investigations on the Attributes of Cloned Bovine Products" published by the Japan Livestock Technology

Association, of which there is only a seven-page English language summary and there are not enough details in the summary to evaluate the quality of analyses.

Two of the milk composition studies were carried out in New Zealand. Wells et al. (2004) compared milk from six Freisen clones to milk from the non-clone donor and found statistically significant differences in bovine serum albumin and levels of linolenic and linoleic acid. However, the authors concluded that the levels of these nutrients were within the normal range for the breed and so considered the differences not to be meaningful. The same lead author later published a paper a year later that included the six Freisen clones from Wells et al. (2004) and three more Freisen clones and compared the levels of various vitamins, minerals, and amino acids in the milk of these clones to five comparator animals and found no statistically significant differences (Wells, 2005). However, no information is given on the comparator animals, so we don't know how they were chosen or whether they were kept under the same husbandry conditions and fed the same diets as the clones.

Meat

For the bovine meat composition data, FDA looked at only two published studies that involved only 5 cloned (e.g. SCNT) Japanese Black beef cattle. Tian et al. (2004) did a controlled study but it involved only 2 cloned bulls. Interestingly, there were four surviving "apparently normal" cloned bulls, but only 2 of them were used for the study with no discussion as to how those two bulls were chosen. There were two sets of controls: genetically-matched comparator bulls produced using semen of the son of the donor bull and fed the same diet as the clones, and breed-matched bulls which were simply Japanese Black beef cattle of the same age as the clones. Out of the many variables measured, there were 12 where the clones and genetic comparators showed statistically significant differences. For 10 out of 12 of these significant measurements, the clones were higher than either the genetic or breed comparators. The authors considered the differences to be the result of the superior genetics of the donor animal. Takahashi and Ito (2004) looked at the caracass characteristics of a Japanese Black beef cow, but the study involved only a single SCNT clone that was sampled at 28 months of age, so no statistical analysis could be performed

In addition to the two published studies, FDA also looked at meat composition data on 11 cloned cattle and 11 comparators supplied by a private company, Cyagra. This industry study found "no biologically significant differences" in the meat composition data between clones and comparators. However, the study is poorly designed, with animals of widely differing ages being compared, which makes it virtually impossible to find statistically significant differences. Rather than compare animals of roughly the same age reared under the same conditions, Cyagra used six females clones aged 15 to 43 months and five male clones aged 12 to 17 months. The eleven comparator cattle were simple "over 12 months of age." It is not surprising that such a poorly designed study found "no biologically significant differences."

Offspring

There were no compositional data at all on milk or meat from offspring of cloned cattle.

Published Cattle Data Not Considered by FDA

After the FDA Clone Risk Assessment was published, a carefully controlled French study compared health, milk and meat parameters on 37 Holstein clones and 38 were breed, age and sex-matched contemporary control animals that were kept under the same conditions at the same experimental farm where the clones were kept (Heyman et al., 2007). In this carefully controlled experiment, the French scientists detected subtle difference between clones and the comparators. Heyman et al. (2007) noted that previous work on composition of milk or meat from SCNTs had not found "obvious differences," but pointed out that these studies either involved a very small number of animals (e.g. Takahashi and Ito, 2004; Tian et al. 2005) or were not carefully controlled as environmental conditions and herd management can contribute to the variability of the data (e.g. Walsh et al., 2003).

The larger sample sizes and more carefully controlled conditions French study make it more scientifically rigorous. For the milk quality study, Heyman et al (2007) compared the fatty acid composition of milk at days 80 and 180 of lactation of 5 cloned cows and 5 comparator cows. For the meat composition study, they sampled semitendinosus muscle at 8, 12, 18 and 24 months of age from nine cloned heifers and eight control heifers. Walsh et al. (2003) had found significant differences in fatty acid profiles of milk (particularly levels of palmitic acid and linolenic acid), but pointed out that since the comparator animals were not born on the same farms or fed the same diets, they concluded that the differences were not meaningful. Interestingly, Heyman et al. (2007) found "differences in the fatty acid composition of milk and muscle arising from two families of clones" (Heyman et al., 2007: 134). Furthermore, rats fed the milk or meat from the clones showed no difference in allergenicity of these products, no detection of IgE antibiodies nor significant differences in antibodies for IgG, IgA and IgM compared to control rats. Rather then conclude that there is no potential allergenicity problem, the French scientist instead point out the problems with their test and call for further research in this area to fully answer the question: "we cannot exclude that some allergic response could be detected using different non-consanguinus strains of rats. Moreover, allergic responses markedly differs between human and animals; *therefore, the above results, instead of being fully conclusive about the lack of allergenicity of products (milk, meat) from clones, provided strong support for the need for more comprehensive analysis of risks related to potential allergenicity"* (Heyman et al., 2007: 139). Unlike the FDA's Risk Assessment, this French study realizes the complexities involved and calls for further research.

In sum, given the paucity of data on SCNT cattle and the lack of any data at all on offspring as to milk and meat composition, the available data are not adequate to draw conclusions about safety.

Food safety assessment of pig clones and their progeny

When it comes to pigs, the FDA could not find any published studies on the meat composition data on clones or clone progeny. The FDA relied solely on data supplied by a cloning company, Viagen, Inc. that had "designed two studies to evaluate the health, growth, and meat composition of swine clones, fertility of boar clones, and health, growth and meat composition of swine clone progeny vs. age-matched, genetically related, artificial insemination (AI)-derived comparator animals" (FDA, 2006: F3). The meat composition data were collected from 4 clones and 242 offspring of clones. Data on 2 more clones were excluded from the study. The data on the excluded clones contradict the finding of no significant differences between cloned and conventional meat.

In the first study, Viagen began with seven clones—6 "Hamline" and 1 "Duroc," all females—and 15 conventional comparators, all females, that were age-matched and sired by the same Hamline nuclear donor boar in a conventional (e.g. AI) program. These 7 cloned pigs began the study at 50 days of age and all survived until the end of the study at approximately 195 days of age. However, for the comparison of carcass characteristic, Viagen only used data from 4 clones. Two Hamline clones were excluded because they were "approximately 45.45 kg [e.g. 100 pounds] lighter than any of the other animals in the experiment at the time of slaughter" while the Duroc clone was excluded because the carcass was condemned at slaughter due to a lung adhesion (FDA, 2006: F21). In spite of excluding data from 2 clones (about 30% of the total sample size) simply because they were smaller than the other animals, the data clearly showed that the comparators were still over 50% larger than the clones at birth (1.72 kg vs. 1.13 kg, respectively). And excluding data simply because the animals were too small does not seem scientifically valid. The fact that FDA elsewhere admits that these two clones "were euthanized due to chronic health problems at the end of the study" (FDA 2006: F11-F12) is more damning. Excluding clones with chronic health problems from the analysis has the effect of making the SCNT clones resemble normal pigs in the study.

Based on the data from 4 clones, the carcasses of clones tended to have less back fat and to be a slightly darker and more red in color than the non-clone comparators; given the small sample size (4 clones and 15 comparators), only difference with the thickness of back fat measured on the first rib was statistically significant (see Table F-7 in FDA, 2006). FDA suggests that the differences in backfat thickness and marbling color were due to the fact that the clones were also almost 10 pounds lighter, on average, than the non-clone comparators. As noted, two clones that were 100 pounds lighter were removed from the study.

For the meat composition data, FDA only excluded the 2 smallest clones, keeping the data from the Duroc clone that had been condemned at slaughter, so there were data from 5 clones. FDA concluded that the meat composition data "were remarkably similar,

and no biologically relevant differences were noted" (FDA, 2006: F?). However, the data show that of the 17 amino acid levels measured, 16 were slightly lower in the clones; of the 13 fatty acids and cholesterol levels measured, all but two fatty acid levels and the cholesterol level were slightly higher in the clones. The FDA does not mention nor discuss these differences; they simply state that the difference were not "biologically relevant."

The second study looked at offspring of cloned pigs. Four boar clones (3 Hamline and 1 Duroc) were bred to 49 female pigs (gilts) and three AI-derived boars (the Hamline nuclear donor and two AI sons of the Duroc nuclear donor) were bred to 40 female pigs (gilts). As a result of these breedings, there were 36 litters (402 total progeny) from the clone boars and 25 litters (300 total progeny) from the non-clone comparator boars. However, for the carcass characteristics and meat composition data, Viagen supplied data on only 242 of the 402 clone progeny and 163 of the 300 progeny of non-clone comparators. No statistically significant differences were found in the carcass characteristics, although, unlike with the clones, the back fat values were larger for all three areas measured (first rib, last rib, last lumbar) for offspring of clones compared to offspring of non-clone comparators for both breeds (e.g. Hamline, Duroc) (Table F-17, FDA, 2006).

For the meat composition data, although no clear differences in the average values for most nutrients (amino acids, fatty acids and cholesterol, minerals, and vitamins) were found, it is interesting that the variability (e.g. the standard deviation) of the data for 14 of the 15 amino acid tested for was higher for the progeny of clones compared to non-clone progeny. For the amino acids, 7 of the 15 had higher values, 4 had lower values, and 4 had the same value for progeny of clones compared to progeny of non-clone comparators (Table F-18, FDA, 2006).

In sum, the available data are not adequate to draw a conclusion about the safety of pork from clones.

Food safety assessment of goat clones and their progeny

When it comes to the safety of milk and meat from cloned goats, FDA notes that "No meat or milk composition data were identified." In addition, no milk and meat composition data are available for progeny of goat clones. Rather than conclude that more data are needed, FDA instead concludes that "products from goat clones pose no additional food consumption risks." It is contrary to the fundamental principles of scientific inquiry to come to a conclusion without any data to support it. FDA cannot validly conclude that milk and meat from goats is safe.

FDA Food safety conclusions overall

Overall, FDA had actual data on milk composition from 43 cloned cows and no data on milk from offspring of cloned cows. For meat composition, FDA had data from 16 cloned cows and no data for offspring of cloned cows. For pigs, FDA looked at data

from only 4 clones and 242 offspring of clones. For goats, FDA had data on neither milk nor meat composition of clones nor their offspring. These data—on only a few dozen animals in some categories, and no animals at all in other categories, are completely inadequate on which to base a conclusion about cloned food. The safety of millions of meat dinners and glasses of milk cannot be assessed just on the basis of 59 cloned cows and five cloned pigs.

Critical Biological Systems Approach Not Scientific

Given the paucity of data that directly address the safety of milk and meat from cloned animals (such as compositional data on meat and milk) and clone progeny compared to that of non-clone comparators and offspring of non-clone comparators, respectively, the FDA used indirect measures of food safety, primarily data on the health of the clones at different life stages.

Use of these indirect measures is justified by a highly questionable and un-scientific framework/assumption—the Critical Biological Systems Approach—which assumes healthy animals must be safe to eat. As FDA states, "the *Critical Biological Systems Approach*, (CBSA) is based on the hypothesis that a healthy animal is likely to produce safe food products" (FDA, 2006). The CBSA breaks down the life of the animals into 5 developmental stages—gestation and giving birth; perinatal period, juvenile development, reproductive development, post-puberty (e.g. adulthood)—and then looks at the health of the animals at each stage. The CBSA assumes that if an animal has health problems at a early developmental stage and survives to a later developmental stage, then those health problems will often resolve themselves.

This is not a valid approach to evaluating safety. In fact, many diseases, like cancer and diabetes, show up later in life rather than earlier. A particular concern would be if cloned animals looked healthy but carried bacteria that could make human sick, such as *Salmonella* or *E. coli* 0157:H7.

FDA Should Not Assume Unhealthy Animals Removed at Slaughter

A large percentage of clones (a majority in some studies) have such serious birth defects that they do not survive to adulthood. FDA assumes the deformed or sick animals that result from cloning will not enter the food supply because they will be discovered at antemortem inspection. The Risk Assessment therefore need only consider clones that "appear to be healthy" or that are exhibiting subtle health effects. Since the majority of health problems and/or birth defects have been seen in younger animals, the FDA just assumes these animals won't make it into the human food supply because "local, state, and federal regulations . . . exclude frankly malformed, diseased, and otherwise unhealthy animals from the human food supply" (FDA, 2006). Since FDA excludes these animals from their Risk Assessment, FDA places its emphasis on identifying "subtle health effects" that could have arisen by the process of SCNT cloning.

FDA further assumes "that if clones were to pose food consumption risks, the only mechanism by which those risks could arise would be from inappropriate epigenetic reprogramming . . . Progeny of animal clones, on the other hand, are not anticipated to pose food safety concerns, as natural mating resulting from the production of new gametes by the clones is expected to reset even those residual epigenetic reprogramming errors that could persist in healthy, reproducing clones" (FDA, 2006: ??). Thus, one needs to look for subtle health effects in the clones, as these effects are not expected to be passed to the next generation. FDA further argues that such "inappropriate epigenetic reprogramming" that may occur with SCNTs lead to results that are not different than what is seen with artificial reproductive technologies (ARTs), although their frequency might be higher in SCNTs.

There is a profound fallacy in FDA's assumption that antemortem inspection will catch all these potentially sick and deformed animals. The meat inspectors already face an overwhelming task and the USDA's Food Safety Inspection Service is moving more toward having plant employees do the inspection, while the Federal inspectors simply oversee the paperwork. Problems have already arisen with USDA inspections. For example, take enforcement of USDA's rule mandating the removal of specified risk materials (SRMs) form cattle over 30 months of age from entering the human food chain. The consumer group Public Citizen issued a report in August, 2005 that demonstrated there were 829 documented violations, from January 2004 through March 2005, of USDA's rules on ensuring removal of SRMs from animals over 30 months of age (Public Citizen, 2005). Given the lapses in USDA's inspection program when it comes to potentially very serious threat of mad cow disease, it cannot be assumed that USDA inspection will effectively ensure that all animals that are sick or unwell would be effectively removed.

Unique Risks Exist and Require Assessment

As for the notion that there are no "unique risks" posed by SCNTs clones, FDA has failed to consider the that there are quantitative differences between the risks posed by SCNT clones compared to other ARTs, with the risks being far more frequent, often by ten-fold or more, in the former compared to the latter. Thus quantitative differences are important. However, there are also qualitative differences in risks posed by SCNT compared to other ARTs. A unique risk posed by SCNTs, but not by other ARTs had to due with the potential for abnormal nuclear-mitochondrial interaction, with SCNTs often having mtDNA from both parents (e.g. donor and recipient cells), while embryos produced using other ARTs only have mtDNA from one parent (e.g. the mother). Since dysfunctional mitochondria can wreak havoc on an organism and lead to many types of health problems, this important and unique risk deserves further scrutiny before any milk and meat from SCNTs are allowed on the market.

FDA Fails to Assess Data or Draw Conclusions on Impact on Human Health of Sickly Clones Carrying Disease or Requiring Extra Drugs, Especially Antibiotics

It is clear from studies FDA reviewed on animal health that clones have higher rates of illness and death than non-clone comparators, particularly at the younger ages. This could lead to greater use of drugs on clones, which in turn could exacerbate antibiotic resistance. FDA's Risk Assessment failed to assess this risk.

In both cloned cattle and sheep, one of the biggest health problems is large offspring syndrome (LOS). As the name implies, LOS refers to offspring that are abnormally large at birth, but they also have a range of other abnormalities. FDA lists 11 clinical signs associated with LOS, including fetus weight more than 20% larger than average for the breed, deformities of limb and/or head, disproportionate or immature organ development, *increased susceptibility to infection*, and cardio vascular problems. Since cattle with LOS tend to have increased susceptibility to infection, there would be a greater need for antibiotics and other drugs to help fight the infections in those LOS cattle. Although LOS doesn't appear to happen normal reproduction or AI, it does happen with some of the ARTs, such as in-vitro fertilization (IVF), embryo culture, as well as with SCNTs.

The incidence of LOS in SCNT clones is very high. FDA has identified 13 studies that look at rate of LOS in SCNT cow clones; 12 were published studies and the other was data supplied by industry (Cyagra). Of the 13 studies, 10 only look at SCNT clones while 3 also looked at transgenic cattle produced via SCNT. In the studies, incidence of LOS in SCNT clones varied from 8% (1 in 12) (Miyashita et al. 2002) to 100% (8 of 8, 6 of 6) (Batchelder 2005, Kubota et al. 2000). If the studies are pooled together, then 54.6% (239 of 438) of clones suffer from LOS (Table V-4 in FDA 2006). Excluding the 3 studies that also included transgenic clones hardly changes the result: 51.2% (151 of 295) of these clones suffer from LOS.

Since LOS basically doesn't happen with normal reproduction or AI, having an incidence of over 50% of the animals having LOS, and thus being potentially more susceptible to diseases than regular animals is a big problem. Unfortunately none of these studies reported the actual amount of antibiotics and other drugs used in treating LOS animals. If the embryos are large enough, this can also cause problems for the dam and may require cesarean section and other medical interventions, which could include drugs and hormones.

Another important health risk associated with SCNT clones is hydrops, which refers to abnormal fluid accumulation in parts of the placenta and/or fetus itself, which can lead to complications with the pregnancy and potential health problems in the fetus. Hydrops is a very rare condition in cattle and is estimated to occur at the rate of 1 in 7,500 pregnancies in general cattle population (Hasler et al. 1995).

Producing embryos via in vitro techniques and then transplanting them to cattle dramatically increases the rate of hydrops; one large study found 1 case of hydrops in 200 IVP (in vitro production) pregnancies in cattle, or a rate of 0.5% (Hasler et al. 1995). With SCNT clones, the risk of hydrops is far larger than even the case of IVP. The FDA identified 8 studies in the scientific literature that looked at rate of hydrops in SCNT clones; 3 of these studies involved animals that were transgenic and/or SCNT (Table V-2, FDA 2006). The rate of hydrops varies in these studies from 13% (1 of 8) (Batchelder 2005) to 42% (18 of 43) (Wells et al. 2003). If we pool all the studies together, the rate of hydrops for SCNT is 21.3% (66 of 310); if we exclude the transgenic clones, the rate increases slightly to 28.9% (33 of 118). Thus, the rate of hydrops is more than 50 times higher in SCNT births compared to IVP births (28.9% and 0.5%, respectively) and more than 216,800 times higher than the rate in the general cattle populations. This is a phenomenally large increase in a problem that can cause difficult births and cause health problems to both the surrogate carrying the SCNT clone as well as the SCNT clone itself. Some of these health problems could require medical intervention that involves drugs.

In the Cyagra data set on SCNT cow clones, difficult births were quite common. Some 45% of the animals investigated (26 of 58) had umbilical surgery, usually to close enlarged umbilical vessels that don't close naturally. The surgery is done to prevent complications such as umbilical infections and bleeding. Any animals with umbilical infections and bleeding would have to be treated with antibiotics and other drugs.

For pigs, there is far less data on health. Pigs produced using SCNT do not appear to be susceptible to LOS, but they still appear to suffer from health problems associated with weakened immune system. A Korean study found that that 63% (22 of 35) of live born SCNT piglets died within the first week of life (Park et al. 2005). Health problems in these animals included inflammation of a brain membrane and sever congestion in the lungs and liver. Many of the clinical symptoms described are similar to those caused by various bacterial diseases common in the pig industry. In addition, a number of the piglets were described as being born weak.

A study carried out by scientist at the University of Connecticut found that even adult SCNT clones can die suddenly (Lee et al., 2003). In the study, 4 cloned piglets were born and one died within days. The other three pigs died unexpectedly of heart failure just before reaching 6 months of age. Dr. Jerry Yang, who led the research stated that " 'It was totally shocking,' says Yang. He has dubbed the fatalities 'adult clone sudden death syndrome' " (Pearson, 2003, available at http://www.nature.com/nsu/030825/030825-2.html). Since pigs are often sold to the markets at 5 months of age, this shows that adults can experience health problems.

There definitely is the possibility of indirect safety effects that are the result of cloning. For example, if the immune system of the clone is impaired, as a number of studies suggest, then such animals may be more susceptible to disease and/or stress which could result in the need for more medications (such as antibiotics) to treat such diseases. There have been reports in the literature that cloned calves, lambs, goats and pig have

died of bacterial infection and sudden death of unknown cause in the neonatal period (Carroll et al., 2005).

More recently, scientists at the University of Missouri evaluated the innate immune response (via measurements of cortisol and two cytokines—tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)-6) of 9 cloned pigs (from two different cell lines) compared to11 genetically similar non-cloned pigs exposed to an endotoxin (lipopolysaccharide). Before the study began, the cloned pigs had lower levels of cortisol and TNF-alpha. They found that the cloned pigs had a weaker immune response to the endotoxin, with levels of cortisol, TNF-alpha and IL-6 all lower, sometimes dramatically so, in the cloned pigs compared to the non-cloned comparators, suggesting the clones had a crippled immune system (Carroll et al., 2005). As the lead researcher, Dr. Jeff Carroll said, "I've looked at the immune response of hundreds of young pigs and I've never seen anything that low until I looked at a clone" (Anon., 2005: 20). The researchers call for "further investigation of the immune system of cloned animals" (Carroll et al. 2005: 564). Interestingly, FDA, despite their extensive review of the literature failed to mention the work of Carroll et al. (2005), even though it was funded by USDA.

In a review of cloning, New Zealand researcher notes that "any underlying frailties in cloned animals may not be fully revealed until the animals are stressed in some manner" (Wells, 2005: 2??). Such underlying frailties or weakened immune systems, as suggested by work with mice, cows and pigs, means that such animals may have to be treated with drugs. In addition, drugs, including various hormones, often have to be administered to the surrogate animals to help the surrogate carry the clone fetuses to term.

In sum, the data on cattle show that they are very susceptible to health problems that could increased the need for drugs, especially antibiotics and hormones. The LOS occurs in more than 50% of the SCNT cow clones compared to 0.00013% (1 in 7,500) in the general cattle population. LOS cattle and sheep are more susceptible to infections which means that more antibiotics could be given to them. The large size of LOS clones means that they are often delivered by cesarean section with application of exogenous corticosteroids (Wells et al., 1999). Thus, for cattle and sheep, where LOS is a problem, increased use of drugs, especially hormones, are often used on the surrogates that carry of clones. Thus could lead to increased levels of these hormones and other drugs in the carcasses of the animals.

In pigs, the data clearly show them to have weakened immune systems. Thus, the studies involving pigs and cattle clearly show them to be an increased risk of infectious diseases that would necessitate use of antibiotics and other drugs. This would probably lead to increased use of antibiotics in both cattle and pig production. At the same time, there is huge problem at present with the overuse of antibiotics in US animal production; anything that would significantly increase use of antibiotics, such as widespread use of SCNT clones should be discouraged. FDA should not allow SCNT clones on the market until the question of increased use of antibiotics and other drugs in the production of

SCNT clones has been adequately studies; at present there are no studies that directly address this question.

In addition, as the National Research Council pointed out, the "stress from these developmental problems might result in shedding of pathogens in fecal material, resulting in a higher load of undesirable microbes on the carcass, [so that] the food safety of products, such as veal, from young somatic cell cloned animals, might indirectly present a food safety concern" (NRC, 2002: 65). Thus, the stressed SCNT clones could be carrying or shedding dangerous pathogens such as *E. coli* 0157:H7, *Campylobacter*, or *Salmonella* which can all cause serious food safety problems.

Overall, FDA fails, in this Risk Assessment to assess the risk resulting form clones being more sickly and requiring drugs to stay alive. FDA risk assessment must assess whether cloned animals may be more likely to carry or shed pathogens such as *E. coli* 0157:H7, *Campylobacter*, or *Salmonella* which can all cause serious food safety problems. It must also assess the issue of increased antibiotic and other drug use, whether this will result in more risks of drug residues in milk and meat, and whether this will exacerbate the problem of antibiotic resistance.

FDA Fails to Conclude that SCNT is Unsafe for Animals

FDA requires new animal drugs to be proven safe for human, and the environment before they are allowed in the environment. Although cloning is a new reproductive technique rather than a new drug, we think FDA should hold it to the same standard.

FDA fails to draw conclusions as to whether cloning is safe for animals. The data cited show that it is not—it results in high rates of sickness, deformities and death. The Risk Assessment should be revised to assess the safety of cloning to animals.

For cattle, most clones die before they're born and a lot are born dead (stillborn) or have to be euthanized for deformities and other abnormalities. The Cyagra data set contains information on 134 clones. Some 18.6% of these clones (25 of 134) were born dead or euthanized that day. Eleven of the 25 clones that died the day they were born were stillborn; the others were euthanized for various problems such as "abnormal development," "severe contracture," and "abnormal deliver."

For survival to 6 months of age, FDA identified 25 studies, including the Cyagra data set and 6 that involved transgenic and SCNT animals (Table V-1, FDA 2006). Pooling the data from all 25 studies yield data on 718 live born clones. Of the 718 live born cow clones, some 488, or 68% are still live after 6 months. If we only include data on SCNT clones and not include animals that are transgenic as well, the survival rate to 6 months decreases slightly to 66.1% (353 of 534). Thus, approximately one-third of all the SCNT cow clones die between birth and 6 months of age. Data from USDA's own National Animal Health Monitoring Service (NAHMS) show that only 3% of beef cattle

and 2% of dairy cattle produced through natural matings or AI die between birth and 6 months of age (Table V-1, FDA 2006). Thus SCNT clones death rate from birth to 6 months of age is some 10 times to 16 times higher than that of naturally produced dairy cows and beef cows, respectively.

SCNT cloning also can produce quite a range of deformities and at a higher rate than from regular reproduction. Some of the deformities found in the various studies cattle include limb deformities, abnormal or degenerating kidneys, digestive tract problems, chronic heart failure, degenerative nephrosis, musculoskeletal abnormalities and cryptorchidism.

For pigs, there are very few data on mortalities and deformities. One Connecticut study found that of 4 pig clones born, one died within a week and the other three died unexpectedly at 6 months (Lee et al. 2003). One deformity that has been seen is anal atresia, which is lack of an anal opening. Anal atresia occurs naturally in pigs at a rate of 0.1% - 1.0% (Wiedemann et al. 2005). A New Zealand study found that 1 of 28 (or 3.6%) pig clones born had anal atresia, which is 3.6 times to 36 times higher than the rate that occurs naturally.

There are also interesting differences in the survival of progeny of clones compared to progeny of non-clone comparators between the breeds (Table F-11 in FDA, 2006). The percentage of mummified pigs (dead, dessicated fetuses) was 3.3, 2.8, 1.7, and 0 percent for the progeny of Hamline comparators, Hamline clones, Duroc comparators, and Duroc clones, respectively. In both breeds of pigs (Hamline and Duroc), the percentage of mummified pigs was larger for the non-clone pregnancies compared to the clone pregnancies and all but the Duroc clones had rates of mummified pigs greater than the national average of 0.2 percent. FDA had no explanation for these results.

More interestingly, a significant number of pigs died around the time of birth, with the rates being clearly higher for the clone offspring compared to the non-clone comparator offspring for both breeds, although the effect was stronger for Durocs than Hamlines. For Hamlines, the pre-weaning death rate was 21 percent higher for progeny of clones compared to progeny of non-clone comparators (22.5% and 18.6%, respectively). For Durocs, the pre-weaning death rate was almost 85 percent higher for progeny of clones compared to progeny of non-clone comparators (31.4% and 17.0%, respectively), with almost one-third of the progeny of Duroc clones dying shortly after birth. Although the difference in pre-weaning death rates is more pronounced for progeny of Duroc clones, FDA tries to explain away this difference by arguing for the exclusion of a litter of 13 Duroc clone progeny and their mother that died shortly after birth due to the stress from high temperature and humidity. FDA notes, however, the other female pigs were also heat-stressed, but didn't remove data from those pigs. Again, FDA interprets data in such a way to minimize the potential effect of cloning. Even if one accepts FDA's argument and removes the data on these 13 progeny of a Duroc clone, the pre-weaning death rates are still over 21% higher for the progeny of clones compared to progeny of non-clone comparators for both pig breeds (Duroc and Hamline). Yet,

FDA tries to downplay these figures, stating that although a "substantial number of pigs were lost around the time of birth . . . *these losses were slightly higher in the group comprised of progeny derived from clones*" *italic added* (FDA, 2006: F??). Increases in pre-weaning death rates of 21% and 85% for progeny of Hamline and Duroc clones, respectively, compared to progeny of non-clone comparators do not constitute "slightly higher" death rates. Again, FDA interprets data in such a way to minimize the potential effect of cloning.

The study also included data on blood clinical chemistry and hematology at three points during the pigs life: between 3 and 30 days old, between 12 and 15 weeks old, and at approximately 24 weeks old (see Tables F-12a and F-12b in FDA, 2006). Data were taken on 18 hematology parameters and 35 clinical chemistry parameters. Just after birth, more hematology values for offspring of comparators were considered outliers compared to those of offspring of clones. Thus, some 5.5% of all the hematology values for offspring of comparators were considered outliers compared to 3.9% of the hematology values for offspring of clones. By the end of the study, the rate of outliers in the hematology values had declined in offspring of comparators from 5.5% to 3.5%, while that figure increased in offspring of clones from 3.9% to 4.9%. The clinical chemistry parameters show a similar pattern. At the start of the study, the rate of outliers of clinical chemistry values for offspring of comparators vs offspring of clone was similar—3.4% and 3.2%, respectively. By the end of the study, the rate of outliers in clinical chemistry values had declined in offspring of comparators 3.4% to 2.7%, while that figure increased in offspring of clones from 3.2% to 4.3%. The finding that the percentage of outliers for both hematology and clinical chemistry parameters increases over the course of the study for offspring of clones, while it decreases for offspring of comparators, suggests that clones may have more problems later in life.

The FDA looks at the 18 different hematology variables and the 35 different clinical chemistry variables and attempts to explain away any differences as not having much biological relevance or how the values could be artifacts based on handling or when the animal was fed. It's as though the FDA is trying to interpret the data in a way to lead to the conclusion that all these blood measurements do not really differ between offspring of clones and offspring of comparators.

In sum, contrary to FDA, we feel the data on offspring of clones are disturbing—particularly the increase in preweaning death rates of offspring of clones compared to offspring of comparators and the increases in the rate blood measurements (both hematology and clinical chemistry) being considered outliers (e.g. extreme values) to increase over time with the offspring of clones while it decreases over time with offspring of comparators. The fact that any differences were seen in offspring of clones compared to offspring of comparators deserves much more scrutiny. Clones are known have much higher preweaning death rates compared to non-clones. The fact that preweaning death rate of offspring of clones was higher, depending on clone source, compared to offspring of non-clones, suggest that some of the adverse health impacts in clones are being passed on to their offspring and so should deserve much more scrutiny. Instead, FDA tries to

explain away all this troubling data so that they can conclude that offspring of clones are not that different than offspring of non-clone comparators.

Overall, cloning results in high rates of death, birth defects, and other adverse health problems. FDA's Risk Assessment should include conclusions on the safety of cloning for animals, not just humans, for both clones and their offspring.

FDA Incorrectly Asserts that Clones are Identical Twins and Pose No Unique Risks

In their press release discussing the Draft Animal Cloning Risk Assessment, the FDA concludes that "meat and milk from clones and their offspring are as safe as food we eat every day" makes two critical claims that we feel are not true. First, FDA claims that a clone is like "identical twins born at different times."[2] Second, as Dr. Sundloff, head of the FDA's Center for Veterinary Medicine, states, "Cloning poses no unique risks to animal health when compared to other assisted reproductive technologies currently in use in U.S. agriculture."[3]

Clones Are Not Identical Twins

The notion that clones are "identical twins born at different times" is scientifically wrong and very misleading. There is a fundamental distinction between identical twins produced naturally and a SCNT "clone." Identical twins normally arise by the splitting of an already fertilized egg, so that the two twins share not only the same genetic complement but also have split the cytoplasm from the egg. With SCNT clones, a very different process takes place (Campbell et al. 1996). The egg [from which the nucleus has been removed] comes from one animal, the nuclear material comes from a somatic cell from another animal. This somatic cell is usually fused with the enucleated egg, and then is stimulated electrically or biochemically, while the resulting embryo, if it starts to grow, is then transplanted into the womb of a third animals which acts as the surrogate mother. Thus, a clone of an existing animal will not share the same egg cytoplasm as the original animal, and, while it might share the genes of the original animal, the fact that a nucleus from a somatic cell has been used means that the genes in the somatic cell are subtly different that genes from a fertilized egg. As the FDA notes, the genes in somatic cells need to be reprogrammed so that they are more like fertilized cells. Indeed, research has suggested that, for proper development to occur, a donor nucleus must undergo a reversal of differentiation and a genome-wide epigenetic reprogramming (Riek et al. 2001). Difficulties in this process are believed to be the cause of the high rate of birth defects, and other health problems, in clones. While the FDA acts like a lot is known about epigenetic reprogramming, the reality is that, some ten years after Dolly, there is still a lot that is not know about epigenetic reprogramming which helps explain why the vast majority (e.g. 95%) of cloned embryos do not survive to adulthood. As Dr. Robert Lanza, the vice-president at Advanced Cell Technology (a major cloning company), recently pointed out, "When Dolly was born, we thought that in a few years we would

[2] At: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01541.html
[3] At: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01541.html

understand the magic in the egg that allows it to reprogramme a cell's DNA," Lanza says. "But cloning is still essentially a black box" (Anon. 2007: 802).

Scientific studies also confirm that genetically identical clones can differ substantially. A carefully controlled study using pigs tried to separate out the effects of cloning from environmental effects. This pig study used age-, breed-, and sex-matched clones and control animals housed under the same conditions (Archer et al., 2003). If clones were "identical twins" separated by age, one would expect there to be lower variability in virtually all the parameters looked at among the clones compared to the controls as the clones have far less genetic diversity compared to the control animals. Interestingly, there were a number of traits where the clones were just as variable, or more variable, than the control animals. For example, the weight of the cloned pigs at 27 weeks was just as variable as non-cloned pigs of the same age; indeed, one of the cloned pigs weighed about 10 kilograms less than any of the control pigs. Blood chemistry data also revealed two groups of traits: one in which cloned pigs had less variability than controls (as expected) and one in which clones had the same variability as control pigs. The authors conclude that cloning "increases the variability associated with some traits. This finding is contrary to the expectation that cloning can be used to reduce the size of groups involved in animal experimentation" (Archer et al., 2003: 430).

New Zealand scientists got similar results in a study of cloned cows that carefully controlled for outside factors—such genetic background of the fetus, age of the surrogate recipients and their reproductive—that could cause variability. If clones are simply "identical twins born at different times," then they should show less variability for the various placental and fetal measurements. The authors were surprised to discover "greater variability within the cohort of NT fetuses with the same nuclear genetics than within the cohorts of AI and IVP fetuses, given that sexual dimorphism in the growth of AI and IVP fetuses is expected to increase the variability within these two control groups. *This suggests that nuclear genetic background alone does not account for the phenotype. The cause of this variability is unknown*" (Lee et al., 2004: 9).

Viagen, a cloning company, supplied FDA with a data set on cloned pigs and offspring of cloned pigs. Interestingly, cloned pigs, when mated to non-clone pigs cause a greater variability in litter sizes—cloned boars produced many more very small litters and very large litters than normal boars. If clones were just identical twins, we'd expect there to be less variability in litter size in offspring of clones compared to offspring of non-clone comparators.

Clones Pose Unique Risks

The notion that cloning poses "no unique risks" compared with other artificial reproductive technologies is highly misleading. First, by focusing only on whether or not "unique risks" occur with cloning ignores the importance of *quantitative* differences in risks between cloning and other reproductive techniques. Over 90% of cloning attempts end in dead animals. The figures are even worse if you consider the production of healthy offspring. According to a recent article in *Nature* on the tenth anniversary of

Dolly, "Only 2-5% of cloned animal embryos grow into health offspring" (Anon, 2007: 802). There are definitely quantitative differences that are important. The problem of hydroallantois rarely occurs in natural cattle pregnancies but occurs at a rate some twenty times higher for pregnancies established with cloned embryos compared to IVF embryos (40% and 2%, respectively).(Wilmut et al., 2002) The rate of stillbirths in a study of heifer cloned cattle by Infigen was 24%; this rate is 3.5 times the rate in Canadian Holstein heifers (6.9%) (Lohuis et al., 1993, available at http://cgil.uoguelph.ca/pub/articles/stillbirth.html). A study of the frequency and occurrence of late-gestation losses from cattle cloned embryos found that the overall rate of live births from IVF embryos was more than 7 times the rate for adult somatic clones (49% vs 6.8%, respectively) (Table 1 in Heyman et al. 2002). The incidence of loss for late-gestation losses (between Day 90 of gestation and calving) was 43.7% for adult somatic clones compared to 0% in the control IVF group. Also, a review article on SCNT, found that the number of clone embryos that developed to become live young was between 0 and 4%, a figure far lower than that for other assisted reproduction technologies (Wilmut et al., 2002). In sum, quantitative differences are important.

Secondly, and more importantly, there are unique risks associated with SCNT. In the Risk Assessment, FDA claimed that the only real risk associated with SCNT is the problem of epigenetic reprogramming associated with putting the nucleus of a differentiated somatic cell into an enucleated egg (egg which has had its nucleus artificially removed); the genes in the nucleus of that somatic cell must be reprogrammed so that they can act like they come from an undifferentiated cell. This is in fact a unique risk, and contradicts FDA's claim that there are no unique risks. As the FDA argues, "incomplete or inappropriate epigenetic reprogramming appears to be one of the primary underlying causes for the relatively low success rate of cloning, and the source of potential subtle hazards for the consumption of food from animal clones." The FDA then focuses its discussion of epigenetic reprogramming on the methylation of DNA as the major component influencing epigenetic regulation of gene regulation.

However, there are two areas that the FDA ignores that represent unique risks posed by SCNTs: the effect of nuclear-mitochondrial interaction arising from a donor nucleus and epigenetic restructuring of somatic chromatin, e.g. aberrant histone acetylation. The issue of nuclear-mitochondrial interactions is an important one as the FDA has focused almost exclusively on epigenetic reprogramming problems as being a major cause of SCNT failure and has ignored the issue of mitochondrial dysfunction. Mitochondria are called the powerhouses of the cells as they are the main suppliers of energy, in the form of ATP, for cellular functions. In addition, mitochondria play critical roles in cell signaling and programmed cell death (Hiendleder et al., 2005).

Finally, mitochondria have a small genome that is separate from the nuclear genome (Lloyd et al., 2006). Mitochondrial DNA (mtDNA) codes for some of the proteins involved the electron transport chain (ETC) pathway. The mtDNA also codes for a number of transfer RNAs and ribosomal RNAs. However, all the proteins involved

in mitochondrial translation are encoded by nuclear genes, meaning that proper reproduction of the mitochondria requires interaction of the mtDNA and nuclear DNA (nDNA) (Jacobs and Turnbull, 2005); if this interaction is aberrant, many things could go wrong, such as overproduction or underproduction of mitochondria. In addition, many of the proteins involved in the ETC are coded for by nDNA, so that any aberrant interaction between mtDNA and nDNA could also adversely impact energy production in cells.

Mitochondria are located outside the nucleus in the cytoplasm of the cell. Egg cells contain a large amount of mitochondria, while sperm contain many fewer mitochondria (sperm cells consist almost solely of genetic material). During normal mating, sperm mitochondria get labeled and are eliminated from the embryo before the 8-cell stage in cattle and rhesus monkeys, so that the developing embryo only has maternal mtDNA (Sutovsky et al., 1999). However, the process of SCNT often results in the mixture of two different mtDNAs—one from the donor cell (the somatic cell), the other from the recipient cell (the enucleated egg)—because the donor cell is often fused with the enucleated egg cell. The presence of only one type of mtDNA in a cell is called homoplasy, while the presence of two types of mtDNA in a cell is called heteroplasmy. Thus, SCNT clones may be heteroplasmic (e.g. with mtDNA from both "parents"—the nuclear donor [e.g. somatic cell] and the [enucleated] egg recipient), while animals produced via normal mating or other ARTs (artificial reproductive technologies, e.g in-vitro fertilization, embryo culture and transfer) are homoplasmic.

In SCNT clones produced via the fusion of a somatic cell and an enucleated egg, in addition to the possibility of heteroplasmy, the cytoplasm from the somatic cell also contains compounds involved in the replication (e.g. polymerase γ [PolG]) and transcription (e.g. mitochondrial transcription factor A [TFAM]) of mitochondria that are encoded by nuclear genes. In embryos produced via IVF (in vitro fertilization), PolG and TFAM levels are dramatically reduced between the 2-cell and 4-cell stage, while in SCNT embryos, the PolG and TFAM levels are not reduced at the 4-cell stage. The persistence of PolG and TFAM in SCNT embryos but not in IVF embryos suggests that nuclear-mitochondrial interaction following SCNT is out of sequence as the onset of mitochondrial replication is a post-implantation even (Lloyd et al. 2006). This could lead to disruption in the number of mitochondria that are passed on to different cells and lead to a number of problems.

The FDA does discuss the issue of mtDNA but only refers to one article: "Although there has been speculation that mitochondrial dimorphism may affect development of SCNT embryos, only one study was identified that looked specifically at mitochondrial effects on embryo development (Takeda et al. 2005)" (FDA, 2006: 185). FDA ignores the fact that numerous studies have found that SCNT clones do exhibit heteroplasmy. Indeed, a review article on mtDNA and SCNT—published in 2004—has a table which lists 6 different studies, published between 1998 and 2003, that demonstrate varying levels of heteroplasmy in cattle and sheep clones; some of the studies have shown that up to 59% of the mtDNA in a clone may come from donor mtDNA (St. John et al. 2004). Other studies suggest that in some heteroplasmic embryos, particularly

bovine SCNT clones, the donor mtDNA is preferentially replicated over the recipient (e.g. enucleated egg) mtDNA (Do et al. 2002, Takeda et al. 2003). This finding is important as it's possible that in heteroplasmic embryos there is a kind of competition between the donor and recipient mtDNA, so that the net effect could be reduced numbers of mitochondria which could result in phenotypes that look like mtDNA-depletion syndromes. Other studies have also pointed out that mutations in mitochondrial genes as well as in the nuclear genes involved in mitochondrial translation can give rise to a number of diseases (often called mtDNA-depletion syndrome) in humans, some of which are very severe (Hiendleder et al. 2005, Jacobs and Turnbull 2005, St John et al 2004). Since mitochondria are the powerhouses of the cells, those cell types most in need of energy, e.g. muscles, nerve cells, liver, etc. have the largest number of mitochondria, while cells that are less energy dependent have much lower numbers of mitochondria. For example, in humans there are roughly 6,800 mtDNA copies in each cardiac muscle cell (Miller et al. 2003), compared to about 409 mtDNA copies in each peripheral blood mononuclear cell (Gahan et al. 2001) and only 2 copies of nuclear genes. Thus, cell types most in need of energy (and therefore lots of mitochondria) often are adversely affected in mtDNA-depletion syndrome leading to myopathies and neuropathies; examples include cardiac myopathy, mitochondrial myopathy, Leber's hereditary optic neuropathy, diabetes mellitus and deafness (DAD). However, since energy production is so important to the cell, if mitochondrial disease, depending on the cell type affected, can cause muscle wasting, nerve damage, seizure, strokes, blindness, deafness and more, with recent studies also implicating mitochondria in diseases such as Alzheimer's and Parkinson's (Lemonick, 2006). Indeed, there is now a field of study on "mitochondrial diseases," as "defects of mitochondrial metabolism cause a wide range of human diseases that include examples from all medical subspecialties" (Schapira 2006: 70).

A number of researchers have noticed similarities between some of the mitochondrial depletion diseases in humans and some of the abnormalities seen in SCNT and hypothesize that aberrant nuclear-mitochondrial interactions in SCNTs could be responsible for some of these abnormalities. A research team in Germany found that "A survey of perinatal clinical data from human subjects with deficient mitochondrial respiratory chain activity has revealed a plethora of phenotypes that have striking similarities with abnormalities commonly encountered in SCNT fetuses and offspring. We discuss the limited experimental data on nuclear-mitochondrial interaction effects in SCNT and explore the potential effects in the context of new findings about the biology of mitochondria" (Hiendleder et al. 2005: 69). Researchers in the United Kingdom have suggested that potential overpopulation of mitochondria could lead to the large offspring syndrome often seen in SCNT cow clones and call for more work in this area: "a cytoplasm over-populated with mitochondria would lead to cellular expansion that might be indicative of the reported large-offspring syndromes. This under-researched area of investigation could provide clear answers to some of the developmental abnormalities witnessed in NT offspring and aborted feotuses, whether mediated through failure of somatic cell reprogramming or independently" (St John et al. 2004: 638-639).

In sum, there is a unique risk posed by SCNT clones that is not posed by other ARTs (artificial reproductive technologies): the potential for aberrant nuclear-mitochondrial interactions. Embryos created via SCNT embryos differ from those created by other ARTs in two ways: they may be heteroplasmic (e.g. contain mtDNA from two sources) and nuclear-encoded mitochondrial DNA transcription and translation factors persist in SCNT, but not IVF, embryos. Given that there is a long list of diseases that are influenced by aberrant mitochondia, any aberrant nuclear-mitochondrial interaction, due to heteroplasmy and/or persistence of mitochondrial transcription and translation factors in the SCNT clones, should raise red flags that deserve more study. The area of mitochondrial diseases is an emerging field and there is a lot of information that is still unknown. Until the FDA understands more about nuclear-mitochondrial cross talk and the impact of heteroplasmy, they should refrain from approving SCNT clones.

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