



# THE CENTER FOR FOOD SAFETY

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Food and Drug Administration  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

Docket # 2003N-0573

## CFS Comments on FDA's Draft Risk Assessment on Animal Cloning Submitted on May 2, 2007

### 1. Introduction

The Center for Food Safety (CFS) hereby provides comments and supporting attachments to Docket No. 2003N-0573, on the Food and Drug Administration's (FDA) draft risk assessment on animal cloning. On December 28, 2006 the FDA released a draft risk assessment on animal cloning using somatic cell nuclear transfer (SCNT or SNT). On the basis of this flawed risk assessment, FDA has stated that it expects this year to approve milk and meat from cloned animals and their progeny, despite widespread scientific concern about the safety of cloned food, mass public opposition to cloned food and the substantial animal cruelty and other ethical concerns involved with cloning. CFS strongly opposes this premature and risky approval. The risk assessment fails to justify FDA's conclusion that food products from cloned animals and their progeny are safe and it fails to analyze potential harms involved with animal cloning. The agency has also ignored concerns regarding risks to animal welfare, and the ethical concerns held by many Americans. In 2003, FDA assured the public that the agency would take such concerns into account in its review of cloned food,<sup>1</sup> but now asserts that these concerns are not in the agency's purview.

CFS is a national non-profit public interest membership organization working to protect human health and the environment from potentially harmful food technologies and to promote sustainable agriculture. On October 12, 2006, CFS along with animal welfare, consumer protection, and reproductive rights organizations, filed a petition to the FDA seeking the regulation of cloned animals. The petition argued that animal cloning fits within the definition of "new animal drug" under relevant provisions of the Food Drug and Cosmetic Act (FDCA)<sup>2</sup> and should be regulated as such. The FDA never responded to the petition and rather than addressing

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<sup>1</sup> Randi Fabi, "FDA to Consider Ethical Concerns on Animal Cloning," Reuters, March 11, 2003

<sup>2</sup> 21 U.S.C. § 360 (b)

CFS' argument, the FDA adopted a regulatory approach with no basis in law and which fails to comply with basic standards for evaluating risks posed by biotechnology. CFS resubmits this petition and its supporting attachments and urges FDA to follow its own statute which requires treating cloning as a new animal drug pursuant to the FDCA.<sup>3</sup>

A review of the draft risk assessment reveals that FDA failed to adhere to established guidelines for conducting risk assessments regarding animal biotechnology, as articulated by the National Resource Council of the National Academy of Sciences (NAS).<sup>4</sup> This failure resulted in a limited evaluation of potential harms, i.e., FDA narrowed its research on harms from only one area of concern (epigenetic changes in clones) when the NAS 2002 report specifically requires an evaluation of all harms *regardless of likelihood*.<sup>5</sup> Furthermore FDA relies on many troubling assumptions, detailed below, and dismisses relevant data revealing significant differences in composition of milk and meat products derived from clones and their progeny. In addition, the paucity of data evaluated in the risk assessment does not support FDA's conclusion that products from animal clones and their progeny are safe for human consumption.

Moreover, with these comments CFS is submitting a report that analyzes the scientific basis for the risk assessment.<sup>6</sup> This report finds "that FDA's conclusion of safety is based upon scant data from few peer reviewed studies", that "the Agency's assessment of the data is slanted, information is selectively reported to fit predetermined conclusions, and FDA fails to consider possible side-effects of cloning that independent scientists...say should be considered in a regulatory review." The report further faults the risk assessment for relying "heavily on unpublished data from two cloning companies...who have a financial interest in FDA approval."

In light of the clear deficiencies in the FDA's risk assessment on animal cloning, CFS urges the FDA to **ban** the use of clones and their progeny in food production unless:

- FDA establishes a mandatory pre-market review process, including independent and transparent long-term testing (with the burden of proof of safety on the clone developer) to demonstrate food safety;
- FDA regulates cloning as a new animal drug and requires generational studies including investigations into potential food safety threats from unexpected metabolites potentially created by the cloning process;
- Animal cruelty issues from the frequent deformities and health problems of animal clones are technically resolved and animal cloning can meet the highest standards for animal welfare;
- The review process shows no harmful impacts from the use of cloning;
- FDA prepares an Environmental Impact Statement assessing the environmental effects of cloning;
- FDA has consulted a federal advisory committee that has addressed the many ethical issues around animal cloning, and broad public discussions have resolved the unique ethical and moral issues raised by cloning; and

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<sup>3</sup> CFS Petition Seeking Regulation of Cloned Animals, attached hereto as "Exhibit 1."

<sup>4</sup> See NAS 2002 report, *Animal Biotechnology*, p. 74-75.

<sup>5</sup> Id.

<sup>6</sup> See Not Ready for Prime Time: FDA's Flawed Approach to Assessing the Safety of Food from Animal Clones, attached hereto as "Exhibit 2"

- If the above conditions are met, FDA must require labeling of all food from clones and their offspring, to protect consumer choice.

## 2. Regulatory Authority for the Risk Assessment

The preparation of risk assessments in the evaluation of the safety of animal cloning does not appear to be mandated by any federal statute or regulation; no FDA documents mention any legal mandate to conduct any assessment in this circumstance and the statutes and regulations listed by the NAS as relevant to animal biotechnology do not appear to cover the cloning of livestock.<sup>7</sup> The draft risk assessment (RA) states as a principle assumption however that animal clones and food products derived from them would “be subject to the same laws and regulations as conventional animals and their food products”<sup>8</sup>, including the Pasteurized Milk Ordinance<sup>9</sup>, USDA inspection criteria, and absence of drug residues.<sup>10</sup>

The risk assessment procedure currently used by the FDA was first described by the NAS in its 1983 report titled “*Risk Assessment in the Federal Government*” (“1983 report”), an attempt to consolidate the risk assessment procedures practiced in the US regulatory agencies.<sup>11</sup> When it became evident to FDA that somatic cell clones were being developed for commercial breeding and food producing in the fall of 2000, the agency contacted NAS to conduct an independent scientific peer review of available safety data on cloned animals and food derived from them.<sup>12</sup> The FDA stated that one conclusion of the 2002 NAS report titled “*Animal Biotechnology: Science Based Concerns*” (“NAS report”) was that the FDA conduct a more thorough risk assessment regarding livestock cloning, “taking into account all available knowledge that exists.”<sup>13</sup> The NAS report adjusted the risk assessment process outlined in the 1983 report in order to accommodate the potential risks of animal biotechnology, as the four steps articulated in the earlier report were only appropriate for substances for which dosage can be described in discrete units and that cannot reproduce themselves.<sup>14</sup>

FDA specifically cites the 2002 NAS report for the risk assessment framework used in the RA.<sup>15</sup> The RA conveys the steps as articulated by the NAS report, with one important exception: step one, as presented in the RA omits several crucial words present in step one as articulated in the NAS report. Step one in the RA reads: “identify potential harms;”<sup>16</sup> step one of the NAS report reads: “identify the potential harms *regardless of likelihood.*”<sup>17</sup> Instead of

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<sup>7</sup> NAS 2002 report, *Animal Biotechnology*, Appendix B “Regulatory Framework for Animal Biotechnology”, pp. 163-165

<sup>8</sup> FDA RA, p. 6

<sup>9</sup> The Grade “A” Pasteurized Milk Ordinance, available at <http://www.cfsan.fda.gov/~ear/pmo03toc.html>

<sup>10</sup> FDA RA, p. 248

<sup>11</sup> FDA RA, Appendix A, p. A-3

<sup>12</sup> CVM Update on Livestock Cloning (July 13, 2001), available at [http://www.fda.gov/cvm/CVM\\_Updates/clones.htm](http://www.fda.gov/cvm/CVM_Updates/clones.htm)

<sup>13</sup> FDA, CVM and VMA Committee Meeting (November 4, 2003), available at [http://www.fda.gov/cvm/CVM\\_Updates/03VMACTrans.htm](http://www.fda.gov/cvm/CVM_Updates/03VMACTrans.htm)

<sup>14</sup> NAS report, p.75

<sup>15</sup> FDA RA, Appendix A, Table A-1

<sup>16</sup> Id.

<sup>17</sup> NAS report p. 75

conducting a thorough investigation to identify all potential harms, the RA relies heavily on a series of assumptions, detailed below, that leaves many potential harms unidentified.

### 3. The RA Fails to Recognize Important Potential Risks Identified by the NAS

The NAS and FDA seem to agree that epigenetic reprogramming is the main cause for concern relating to both animal health and food safety.<sup>18</sup> However, FDA focuses only on direct risks from epigenesis, while NAS identifies potential indirect harms associated with epigenetic reprogramming and potential animal health risks unrelated to epigenetic problems that the RA ignores. In addition to the risks to animal health and food safety detailed below, the NAS report identifies a risk to human health not addressed in the RA, namely that the reduced genetic diversity in cloned animal populations could create new reservoirs of infectious disease that could spread to humans (i.e. *Influenza*).<sup>19</sup> The RA does not address risks to human health unrelated to consumption of products from cloned animals and their progeny.

#### a. Risks to Animal Health

The NAS report identifies reduction in genetic diversity as a direct, indisputable result of animal cloning and identifies specific risks associated with it.<sup>20</sup> One risk to animal health presented in the NAS report is the potential for more rapid spread of disease amongst cloned livestock. Specifically, the NAS report states “disease could spread through susceptible populations more rapidly than through more genetically diverse populations. This...concern is well documented and several studies illustrate the susceptibility of species with low genetic diversity to infectious disease.”<sup>21</sup> The RA does not discuss this potential risk to animal health. Instead the FDA only searched for peer reviewed studies specific to cloned animals and it does not appear to have included any studies regarding problems with decreased genetic diversity if the studies themselves did not involve clones.<sup>22</sup> This omission exemplifies the narrow approach to risk assessment the FDA has undertaken in the RA.

#### b. Risks to Food Safety

The NAS report specifically identified “pathogen shedding” in veal and products from young SNT clones as a potential threat to food safety.<sup>23</sup> The NAS hypothesized that abnormal patterns of gene expression (epigenetic changes called “subtle hazards”) result in developmental problems that cause stress, potentially resulting in pathogen shedding in young SNT clones. Specifically the NAS stated the “shedding of these pathogens in fecal matter, resulting in a higher load of undesirable microbes on the carcass, the food safety of food products, such as veal, from young somatic cell cloned animals, might indirectly present a food safety concern.”<sup>24</sup> The RA discusses developmental problems associated with abnormal gene expression at length,

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<sup>18</sup> See NAS report, pp.48, 64 and FDA RA, p. 65

<sup>19</sup> NAS report, pp. 48-49

<sup>20</sup> See *Id.*, p. 48-49

<sup>21</sup> *Id.*, p. 49

<sup>22</sup> See FDA, CVM and VMA Committee Meeting (November 4, 2003), available at [http://www.fda.gov/cvm/CVM\\_Updates/03VMACTrans.htm](http://www.fda.gov/cvm/CVM_Updates/03VMACTrans.htm)

<sup>23</sup> NAS report, p. 65

<sup>24</sup> *Id.*

and research studies presented in the RA document the presence of infectious disease in cloned livestock. For example, Park et al. (2004 and 2005) reported that 22 of 35 live born SCNT cloned pigs died within one week of various infectious diseases including cerebromeningitis and possibly *E.coli*, *Salmonella*, *Streptococcus* and other bacteria.<sup>25</sup> At no point however does the RA discuss the food safety risk presented by the presence of these bacterial agents or other infectious diseases. Instead, the RA relies on the assumption that diseased animals will not enter the food supply, although the RA gives no plan for how such animals will be identified and culled. The RA also fails to address whether potentially hazardous infectious disease agents could go undetected or could enter the food supply by other means (i.e. from contact with fecal matter) and if they can, whether the use of SNT technology could increase the risk of food contamination.<sup>26</sup>

The failure on the part of the FDA to identify potential harms associated with livestock cloning, including those already identified in the NAS report on animal biotechnology, reflects a clear failure to assess the potential risks of livestock cloning in a meaningful way.

#### 4. The Studies Cited in the RA Are, at Best, Inconclusive

The FDA admits that the data available on livestock cloning is limited, and that uncertainty as to the risks associated with it persist. Specifically, the RA states: “[d]ue in large part to the novelty of the technology, the concentration of data at the earliest stages of clone development, and limited data directly addressing food safety, uncertainty will persist in any estimates of risk associated with animal cloning.”<sup>27</sup>

##### a. Studies on Animal Health

Although the risk assessment framework used by the FDA divides livestock development into five “developmental nodes,” FDA admits there are limited studies available regarding nodes 4 (Reproductive Development and Function) and 5 (Maturity and Aging).<sup>28</sup> Furthermore, the RA admits that data on the health and development of bovine clone progeny is sparse and that most studies are observational with only one study analyzing hematology and clinical chemistry of clone progeny.<sup>29</sup>

In its conclusions regarding risks to animal health, the RA states that a strict quantitative analysis of the risk SCNT poses to animals could not be performed given the small number of animals studied and the variable rates of adverse outcomes.<sup>30</sup> The RA admits that SCNT does in fact increase the frequency of animal health risk, but its focus on qualitative differences allows the FDA to discount this increased risk.<sup>31</sup> Specifically, the RA states: “SCNT results in an increased frequency of health risks to animals involving the cloning process, but these do not

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<sup>25</sup> FDA RA, p. 156

<sup>26</sup> See e.g. Id., pp. 292, 294-295

<sup>27</sup> Id., pp. 43-44

<sup>28</sup> See FDA RA, pp. 97-98, 104, 163

<sup>29</sup> Id., pp. 151-152

<sup>30</sup> Id., pp. 174-175

<sup>31</sup> Id., p. 309

differ qualitatively from those observed in other ARTs [assisted reproductive technologies] or natural breeding.”<sup>32</sup>

The substantial quantitative differences in the health of cloned animals as compared with their non-cloned counterparts, detailed in section 5 (a) below, obviate the need for quantitative analysis of risks to animal health posed by cloning.

b. Studies on Food Safety

The RA forthrightly admits that there is a dearth of studies on the safety of food products from livestock clones and their progeny, stating: “[d]espite the extensive literature search performed, and the large number of papers that were reviewed for animal health, few reports directly addressed food safety.”<sup>33</sup> The number of studies reviewed in the RA concerning the safety of food products from the progeny of cloned livestock is highly limited. Most data provided is for swine progeny only.<sup>34</sup> To support its finding that products from the progeny of clones pose no additional food consumption risks, the RA relies heavily on the underlying biological assumption that any epigenetic abnormalities resulting from abnormal gene expression in clones will disappear during the natural reproductive process such that any clone progeny will lack the abnormality. Specifically the RA states: “[t]he rationale for this [underlying biological] assumption...dominates the conclusion that edible products from any clone progeny pose no additional food consumption risk(s)...”<sup>35</sup> This assumption remains unsupported with concrete evidence and is contradicted by evidence from peer-reviewed research.

Two more troubling assumptions made in the RA further limit the thoroughness and usefulness of the RA’s food safety assessment. The first assumption is that obviously diseased or malformed animals will not enter the food supply.<sup>36</sup> The second assumption, that possible abnormal gene expression would not introduce any new, potentially toxic substances into milk or meat of otherwise healthy animals.<sup>37</sup> These assumptions form the basis of the very limited milk and meat constituent analysis, focusing on key nutrients alone instead of a more comprehensive analysis. Specifically, the RA states: “[b]ecause...there is no *a priori* reason to expect that SCNT will introduce any new, potentially toxic substances...the remaining food safety concerns addressed whether subtle changes have occurred that would alter the presence of important nutrients.”<sup>38</sup> The RA cites “impracticality” to justify its failure to conduct a comprehensive analysis: “[m]ilk from cows, sheep, and goats are...estimated to be composed of more than 100,000 molecules...Not every component in milk has been identified and characterized; thus determining whether animal clones are producing a hazardous substance in their milk although theoretically possible, is highly impractical.”<sup>39</sup>

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<sup>32</sup> Id., p. 309

<sup>33</sup> Id., pp. 43-44

<sup>34</sup> See e.g. Id., p. 296

<sup>35</sup> Id., pp. 90, 296

<sup>36</sup> Id., Appendix E, p. E-13

<sup>37</sup> FDA RA, p. 249

<sup>38</sup> Id., p. 249

<sup>39</sup> Id., p. 254

Again, instead of identifying potential harms regardless of likelihood as advised by the NAS, the FDA systematically excluded the consideration of possible harms not only by narrowing the scope of the assessment but also by basing its RA on a litany of unsubstantiated assumptions.

## 5. Studies Observe Differences Between Cloned and Conventional Livestock

Both studies on animal health and on the composition of milk from livestock clones cited in the RA reveal significant differences between cloned and non-cloned livestock; the potential effects of these differences were not explored in the RA.

### a. Studies on Animal Health

The studies on animal health showed real risks to animals involved in cloning. As mentioned above, the FDA decided not to conduct a quantitative analysis on animal health data given the small numbers studied and the variability in adverse outcomes. The adverse outcomes reported in the studies ranged from “large offspring syndrome” and other developmental abnormalities to bacterial infections and other diseases.

A chart of nine studies documenting the incidence of hydrops (fluid retention during pregnancy) reveal that the rate of this abnormality ranges from 15% to 42% in clone fetuses, and only 0.5% in non-clone fetuses.<sup>40</sup> Heyman et al. (2002) observed severe hydroallantois, a form of hydrops, in 15% to 24% of SCNT clone pregnancies as compared with 0% with *in vitro* fertilization derived pregnancies.<sup>41</sup> Although the RA acknowledges that the frequency of abnormalities is higher for SCNT clones than non-clones, it concludes within its limited qualitative assessment framework that the problems observed are not unique to cloning. Specifically, the RA states: “the adverse outcomes noted with SCNT are not unique, but are of concern due to their increased frequency.”<sup>42</sup> Given the dramatic differences in frequency revealed by the data, it is clear that qualitative analysis alone is an insufficient tool for assessing risks to animal health.

Significant concerns have been raised about the longevity of livestock clones, beginning with a study on Dolly the sheep conducted by Shields et. al. (1999) which shows a 10-20% reduction in Dolly’s telomere length as compared with non-cloned sheep of the same age.<sup>43</sup> Various studies conducted since the Dolly study, including Betts et al. (2001), have indicated that cloned animal DNA has shorter telomeres than non-cloned animals and at least two studies, Blasco et al. (1997) and Rudolph et al. (1999) have linked telomere shortening with premature aging in mice.<sup>44</sup> Although these studies alone raise significant concerns regarding clone longevity, the FDA concluded there is insufficient data to draw any conclusions.<sup>45</sup>

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<sup>40</sup> Id., p. 112

<sup>41</sup> Id., p. 113

<sup>42</sup> See Id., Appendix C, p. C-13

<sup>43</sup> FDA RA, p. 101

<sup>44</sup> See Id.

<sup>45</sup> See Id., p. 88

## b. Studies on Food Safety

Many of the studies cited in the RA for the proposition that milk from cattle clones does not pose a food safety concern, reported significant differences between the milk of cloned and non-cloned cattle. One example is the Walsh et al (2003) study, which appears to be the largest and most comprehensive study on the composition of milk from cloned cattle.<sup>46</sup> Testing of 15 dairy cow clones from 5 donor cell lines of 3 breeds of cattle revealed: 1) significant differences in the amount of palmitic acid and linolenic acid; 2) different fatty acid profiles for the cloned milk; and 3) the greatest variability observed in the mineral content of the cloned milk--differing significantly in potassium, zinc, strontium, and phosphorous levels.<sup>47</sup> Though the overall conclusion of the study was that there were “no obvious differences between the milk from clones and non-clones”, the researchers merely speculated that the differences could be attributed to diet, lactation cycle differences and seasonality<sup>48</sup>. No additional studies showing whether differences in milk composition are likely attributable to these dietary and other differences or to the cloned status of the animals were cited by the FDA in the RA.

Wells et al. (2003) reported statistically significant differences in bovine serum albumin (“BSA”) and two fatty acids in one milk sample from a cloned cow. A later study by the same group found statistically significant differences in BSA levels and two fatty acids in the milk from six cloned cows.<sup>49</sup>

The significant differences in cloned milk composition revealed by these studies raise serious concerns about whether milk from clones is safe for human consumption. Without more data, any conclusions regarding the safety of food products derived from clones and their progeny are unfounded.

## 6. Conclusion/Overall Assessment

The admittedly sparse and obviously inconclusive studies reviewed by the FDA do not provide an adequate basis for concluding that cloning livestock is even relatively safe. Furthermore the studies cited in the RA observed significant differences between cloned and conventionally bred animals and in the products derived from them. Dismissing these important differences as a function of small sample sizes and dietary differences and then determining that livestock cloning is safe enough to be used in the livestock industry without mandating further study is clearly arbitrary and capricious and irresponsible. Finally, the failure to consider important risks to both animal health and food safety specifically identified by the NAS raises serious doubts about the legitimacy of the RAs scope and hence its utility in assessing the risk posed by livestock cloning.

Because the RA did not meaningfully assess the safety of animal cloning, substantial doubts as to the safety of cloning persist. CFS therefore urges the FDA to ban all food products

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<sup>46</sup> See Id., pp. 260-261

<sup>47</sup> Id.

<sup>48</sup> Id.

<sup>49</sup> Id., pp. 267-268

from clones and their progeny until comprehensive, independent and transparent long-term testing has been conducted.

Respectfully submitted,

/s/

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