Animal Welfare for Sale:
Genetic Engineering, Animal Welfare, Ethics, and Regulation

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November 18, 2008

Executive Summary

Genetic engineering,[1] particularly of animals, raises numerous concerns and is a highly controversial topic. The ethics of genetic engineering, the implications for animal health and welfare, the consequences of a genetically engineered (GE) animal escaping into the environment, the risk to human health of using products derived from GE animals, the socioeconomic ramifications, religious concerns, and consumers' rights are all weighty and complicated questions that need to be answered before allowing this technology to infiltrate our lives.

An underlying source of discomfort is that genetic engineering is a powerful technology, but it is not predictable. Genetic engineering is associated with a tremendous amount of animal suffering, and AAVS estimates that a staggering 10-50 million animals are used in genetic engineering experiments every year in the U.S.[2] Overall, less than one percent of genetic modification attempts are successful. Errors and unintended effects are common, which is why hundreds to thousands of animals are used to make one genetically engineered animal who can go on to be commercialized. Unanticipated diseases and pathological conditions are inherent throughout the process. There is much we do not yet know about how genes work, and there is great potential, if something does go wrong, for the impact to be enormously consequential.

As such, it is essential that there be constraints on and oversight of the use of this technology to protect animals, people, and the environment. The FDA's draft guidance for industry on GE animals (Docket No. FDA-2008-D-0394) and the USDA request for information on GE animals (Docket No. APHIS-2006-0188) are encouraging signs that government is recognizing this need. However, the FDA, by regulating GE animals as containing new animal drugs, does not (and arguably cannot) address all the concerns.

First and foremost from AAVS's perspective, it is important to not focus solely on regulating GE animals, but to also be discussing *if* animals should be genetically engineered at all. The majority of people disapprove of genetically engineering animals, and given the serious threats to animal health and welfare, AAVS does not think animals should be manipulated in this way or subjected to such risks. However, if genetic engineering is allowed to proceed, there must be rigorous oversight of any and all attempts to genetically engineer animals.

The FDA's proposal, however, does not provide for rigorous oversight, as animal welfare and ethics generally fall outside of the FDA's purview. Also, the FDA is indicating that it will choose to exercise enforcement discretion such that the overwhelming majority of animals involved in genetic engineering experiments would not be required to go through the new animal drug regulatory process.

In addition, the entire new animal drug regulatory process is confidential, closed to scrutiny by independent parties. Consumers and watchdog groups would not be allowed any input into whether a genetically engineered animal should be approved for human consumption or allowed into the environment, and indeed would not even learn that such an animal was under consideration until after the approval had already been granted. Other shortcomings of the FDA's proposal is that the FDA's authority to regulate environmental risks is questionable, and the agency does not plan to require that food from GE animals be labeled if the nutritional content is not altered.

To ensure that animals are not suffering or being exploited unnecessarily, to respect the interests of the public, and to protect the environment, it is necessary to address the concerns and risks raised by genetic

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[1] The terms genetically modified, genetically engineered, and transgenic are used interchangeably in this report and are used to describe any organism whose genome has been modified through biotechnology.
[2] See pages 4-5 of this report for how this estimate was derived.

engineering in a more comprehensive and transparent manner than that provided by the FDA. The USDA has some jurisdiction over GE animals and should examine its regulatory authority beyond that provided by the Animal Health Protection Act, which is currently the focus of the agency's request for information. Ultimately, however, federal legislation is required to address the concerns associated with genetic engineering. AAVS urges the relevant federal agencies to seek such legislation from Congress and to keep GE animals off the market in the meantime.

AAVS's assessment of the FDA draft guidance is provided in greater detail in the middle of this report and highlights our concerns regarding the FDA's authority and inclination to protect animal health and welfare, lack of transparency, and lack of sufficient detail to demonstrate that risks will be appropriately addressed. Preceding these comments are our main concerns about the animal health, animal welfare, and ethical implications of genetically engineering animals, which provide the basis for our assessment of the FDA guidance. We also provide recommendations at the end regarding elements of a more comprehensive approach to addressing the concerns raised by the genetic engineering of animals, including roles for the FDA and USDA, and the need for federal legislation.

Main Points

Animal Welfare

- Extremely large numbers of animals are used to produce each line of genetically modified animals, with tens of millions of animals involved in genetic engineering experiments every year.
- Research and development of genetically modified animals often entails painful and invasive procedures.
- Unpredictable and unintended complications frequently arise from the genetic manipulation of animals, resulting in unanticipated disease syndromes, physical impairments, and other pathologies.
- Most animals involved in genetic engineering experiments do not receive protection under the Animal Welfare Act.

Ethics

- Before any genetically modified animal is allowed on the market, there must be a public discussion about whether humans *should* be creating genetically engineered animals and if there should be boundaries on what is considered permissible.
- Genetic engineering and animal patenting increases the commodification of animals, promoting the treatment of animals as objects.
- The ethical justification for genetically engineering an animal should be evaluated, particularly when the potential benefits are of questionable value or alternative approaches are possible.
- The majority of people disapprove of genetically engineering animals, particularly for food use.

FDA Oversight Problems

- FDA authority under the new animal drug rubric, as outlined in the draft guidance, is insufficient to adequately address concerns about animal health and welfare, ethics, transparency, environmental protection, and labeling.
- Ethics is not addressed at all in the guidance, and the FDA intends to exercise enforcement discretion to exclude the majority of animals involved in genetic engineering experiments from the new animal drug requirements.
- The FDA did not address whether it would withhold approval of a genetically engineered animal based on animal welfare or environmental risks.
- The new animal drug application process is confidential and closed to public participation.

- The FDA's draft guidance is insufficiently detailed to assess how comprehensively animals, people, and the environment will be protected from the risks associated with genetic engineering.

Recommendations for the FDA and USDA

AAVS recommends that the FDA and USDA impose a moratorium on the development and approval of any genetically engineered animals until the following occurs:

- An independent ethics advisory committee, at either the agency level or within the Executive Office, should be established to initiate a national dialogue and conduct a broad ethical review on whether we should be genetically modifying animals.
- If genetic modification of animals is permitted:
  - No genetic engineering of animal should be allowed to proceed until a comprehensive regulatory system is developed.
  - Boundaries should be established and a framework developed for the evaluation of genetic modification applications. Animal welfare and ethics should be explicitly considered along with questions of human and environmental safety.
  - The USDA should actively seek legislation to: (1) expand the AWA to cover mice, rats, and birds bred for use in research, cold-blooded animals including fish, and farm animals used in biotechnology experiments for any purpose; and (2) require ethical reviews at the IACUC level of proposals to genetically modify animals.
  - The USDA should develop regulations for animal care and monitoring provisions to anticipate, provide for, and reduce the likelihood of any potential adverse outcomes for genetically modified animals.
- If the commercial production of a genetically modified animal is proposed:
  - An independent animal welfare and ethics advisory committee, within HHS, USDA, or interagency and open to public participation, should be established to assess animal welfare impacts and ethical implications before commercial production is allowed.
  - If commercial production of a genetically modified animal is permitted, the USDA should address and regulate the animal welfare impacts associated with such commercial production. If the USDA does not believe it has adequate legislative authority to do so, the agency should seek this authority from Congress.
  - If the FDA is to regulate genetically engineered animals as new animal drugs, the agency must ensure, prior to granting any approval, that it can adequately address concerns regarding animal health and welfare, ethics, transparency, labeling, environmental safety, and human health through its regulatory authority or in conjunction with additional agencies.

While these steps will help address some concerns raised by genetically engineering animals, the FDA and USDA lack sufficient authority to address all concerns and should seek federal legislation from Congress.

Animal Health and Welfare

Genetic modification frequently results in animal health and welfare problems, as evidenced by a growing body of scientific literature documenting such problems.[3,4,5,6,7,8] Though the public is increasingly concerned with the health and welfare of animals, discussions regarding the use of genetically modified animals have paid relatively little attention to addressing these animal welfare issues.

Several aspects of the genetic engineering process pose risks for animal welfare. Because the technology is highly inefficient and largely unpredictable, remarkably large numbers of animals are needed both to develop and to maintain a desired line of genetically modified animals. In addition, genetic manipulation often creates unintended and unexpected effects that compromise the health and survivability of the genetically modified animal. Furthermore, the genetic engineering process is highly invasive, and the genetic modification itself is often intended to produce disease in the animal, raising further welfare concerns. Because some problems manifest only after several generations, it is virtually impossible to fully predict, anticipate, or prevent welfare problems.

Numbers of animals used

Extremely large numbers of animals are involved in the creation of each genetically modified strain.[9] Depending on the species used, the process can begin with injecting donor females with hormones to stimulate super-ovulation. If embryos are desired, breeding males are incorporated into the process. The donor females may then undergo surgery or be killed to harvest their eggs or embryos from their reproductive tract.

The genetic modification is then attempted. If a technique such as pronuclear microinjection is used to introduce the modification, then the resulting embryonic stem cells will be injected into additional embryos that have been harvested from additional females. Alternatively, somatic cell nuclear transfer (cloning) can be used to transfer the nuclear content of a genetically modified cell into an enucleated oocyte that has been harvested from additional super-ovulating females or from slaughterhouses.

Either way, the resulting modified embryos are then implanted, often surgically, into recipients. These recipients would have been injected with hormones and, depending on the species, mated with vasectomized males to create a pseudo-pregnant state.

The invasive procedures required for both cloning and genetic engineering raise obvious welfare concerns for a large number of animals.[10,11] In addition, the technologies are highly inefficient, greatly amplifying the repercussions for animal health and welfare.

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[3] Brown, M. J. & Murray, K. A. (2006). Phenotyping of genetically engineered mice: humane, ethical, environmental, and husbandry issues. *Ilar J*, 47(2), 118.
[4] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.
[5] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.
[6] Pritt, S., Cozine, K., & Warren, H. (2006). Management of unanticipated outcomes in transgenic mouse facilities. *Lab Anim (NY)*, 35(4), 27.
[7] Van Reenen, C. G., Meuwissen, T. H., Hopster, H., et al. (2001). Transgenesis may affect farm animal welfare: a case for systematic risk assessment. *J Anim Sci*, 79(7), 1763.
[8] Wells, D. J., Playle, L. C., Enser, W. E., et al. (2006). Assessing the welfare of genetically altered mice. *Lab Anim*, 40(2), 111.
[9] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.
[10] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.
[11] Van Reenen, C. G., Meuwissen, T. H., Hopster, H., et al. (2001). Transgenesis may affect farm animal welfare: a case for systematic risk assessment. *J Anim Sci*, 79(7), 1763.

In particular, few animals produced through cloning or genetic engineering survive birth, and even fewer contain and appropriately express the desired genetic modification. For example, due to the randomness of transgene uptake and insertion, it is estimated that, for farm animals, only 10% of genetically manipulated embryos will result in a birth. Of these resulting animals, only 10%, or 1% overall, will express the desired transgene. In mice, the success rate is only 3%.[12,13] Moreover, many of these resulting transgenic animals will not contain a stable transgene, be able to pass the genetic modification on to offspring, or exhibit the intended phenotype.[14,15]

The unpredictability of genetic modification means that additional animals are likely to be used to refine the experimental procedures necessary to produce the desired transgene insertion and expression, and also to assess the phenotype of the GM animals produced in the process. Thus, hundreds of animals might be subjected to pain and distress to create each desired transgenic animal (the founder).[16]

Hundreds to thousands of additional animals are then used for breeding or cloning to create a line or herd of transgenic animals from the founder.[17] Many of the animals will not inherit the genetic modification, will not survive the process, or will otherwise be wasted as surplus.[18]

It is impossible to know exactly how many animals are used in genetic engineering in the U.S. every year. According to the USDA, 1,012,713 animals were used in regulated experiments in 2006, the latest year for which data are available.[19] However, this figure does not include mice, rats, and birds bred for use in research, or fish, reptiles, or other cold-blooded animals, which are estimated to account for some 95-99% of animals used in research, and a similar percentage of animals used in genetic modification experiments.[20,21] A veterinarian has estimated that over 80 million rodents are bred for research every year in the U.S.,[22] and the USDA has further estimated that, once mice, rats, and birds were included in the count, approximately 31-156 million animals in total are used in research every year in the U.S.[23]

The USDA does not track how many of these animals are genetically modified.[24] However, it is possible to use statistics from the UK to estimate the number of genetically modified animals in the U.S. In 2007,[25] 1,149,752 procedures (36% of all procedures) used genetically modified animals, an increase of 11% from 2006. Of these procedures, 19,416 (1.7%) were for the generation of founder animals, 718,246 (62.5%) were for the maintenance of breeding colonies, and the remaining (35.8%) were for regulated scientific purposes. The vast majority of these procedures (94%) used genetically modified mice and rats. In fact, half of all

[12] Kaiser, M. (2005). Assessing ethics and animal welfare in animal biotechnology for farm production. *Rev Sci Tech*, 24(1), 75.

[13] Rutovitz, J. & Mayer, S. (2002). *Genetically Modified and Cloned Animals. All in a Good Cause?* Derbyshire: GeneWatch UK.

[14] ARENA/OLAW. (2002). *Institutional Animal Care and Use Committee Guidebook, 2nd Edition*. Washington, DC.

[15] National Research Council. (2002). *Animal Biotechnology: Science-Based Concerns*. Washington, DC: The National Academies Press.

[16] National Health and Medical Research Council & Office of the Gene Technology Regulator. (2007). *Guidelines for the generation, breeding, care and use of genetically modified and cloned animals for scientific purposes.* Australian Government.

[17] National Research Council. (2003). *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*. Washington, DC: The National Academies Press.

[18] Rutovitz, J. & Mayer, S. (2002). *Genetically Modified and Cloned Animals. All in a Good Cause?* Derbyshire: GeneWatch UK.

[19] USDA APHIS. (2006). *Annual Report of Enforcement, 2006.*

[20] Gauthier, C. (2004). Overview and analysis of animal use in North America. *Altern Lab Anim*, 32(Suppl 1), 275.

[21] In addition, according to 2007 statistics from the UK, which can be used to estimate animal use in the U.S., mice, rats, birds, and fish comprise 95% of the animals used in research each year and 99% of genetically modified animals. (Home Office. (2007). *Statistics of Scientific Procedures on Living Animals 2007*. London: The Stationary Office.)

[22] Carbone, L. (2004). *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy*. New York: Oxford University Press.

[23] Taylor, K., Gordon, N., Langley, G., et al. (2008). Estimates for worldwide laboratory animal use in 2005. *Altern Lab Anim*, 36(3), 327.

[24] The lack of accurate statistics on animal use, and genetically modified animal use in particular, underscores the difficulty of developing adequate regulations, as well as evaluating the effectiveness of those regulations in protecting animal welfare and promoting the "3Rs" – replacement, reduction, and refinement of animal use.

[25] Home Office. (2007). *Statistics of Scientific Procedures on Living Animals 2007*. London: The Stationary Office.

procedures (49%) using mice used genetically modified mice. An additional 239,263 procedures involving genetically normal animals were used in the production and breeding of genetically modified animals.[26]

Thus, if more than one-third of animals are used in genetic modification experiments every year in the UK, it can be approximated that a staggering 10-50 million genetically modified animals are used every year in the U.S. This number continues to rise, with the National Research Council (NRC) noting in 2004 that the development and use of genetically modified animals had been rapidly increasing since 1999.[27,28,29] The NRC further noted that, "In light of the potential for 150,000 distinct mouse genotypes and thousands more phenotypes, it has been estimated that 60 million animals may be needed for mouse genomics research alone."[30] While the vast majority of genetically modified animals are mice and rats, the interest in the genetic modification of farm animal species has been rising.

Unintended effects of genetic modification

Complications frequently arise from the genetic manipulation of animals that pose significant threats to animal health and welfare. The complications are often unpredictable and can vary depending on where and how the transgene inserts, the expression of the transgene, and the genetic background of the host animal. As a result, unanticipated disease syndromes or other physical manifestations, which lead to pain and distress, occur.[31]

In pronuclear microinjection, a method frequently used to generate transgenic animals, transgene insertion is random, and complications will vary for each transgenic animal produced. More than one copy of the transgene can integrate into the genome, and the precise location of insertion cannot be controlled.[32,33] As a result, insertional mutations, in which the transgene inserts into and disrupts a functional gene, occurs in 5-20% of transgenic animals produced, resulting in pre-natal mortality in approximately 75% of cases.[34,35] Targeted gene transfer, such as through homologous recombination, can provide greater predictability regarding transgene insertion, but complications are still likely.

Appropriate regulation of transgene expression can also be difficult to control. Transgene expression may be too low or too high, or the transgene may be expressed at the wrong times or in unwanted locations.[36] For example, transgenes targeted for expression in the mammary gland of lactating females have exhibited expression in inappropriate tissues (ectopic expression), and serious, often lethal, pathological conditions

[26] Fetal and embryonic life forms are not included in the UK's statistics.

[27] National Research Council. (2004). *National Need and Priorities for Veterinarians in Biomedical Research*. Washington, DC: The National Academies Press.

[28] In the UK, the use of genetically modified animals in 2007 was more than five times higher than in 1995. (Home Office. (2007). *Statistics of Scientific Procedures on Living Animals 2007*. London: The Stationary Office.)

[29] In Canada, where records on genetically modified animals are not yet regularly collected, the use of genetically modified animals increased 73% from 1997 to 1998 alone. (Gauthier, C. & Griffin, G. (2000). *The Use of Animals in Scientific Research and as Sources of Bioengineered Products*. Ottawa ON: Canadian Biotechnology Advisory Committee.) In addition, roughly two times as many mice were used in Canada in 2006 as compared to 1997, reversing a decade of steady decline, largely attributable to the increase in use of genetically engineered mice. (Canadian Council on Animal Care. (2007). *CCAC Survey of Animal Use, 2006*.)

[30] National Research Council. (2004). *National Need and Priorities for Veterinarians in Biomedical Research*. Washington, DC: The National Academies Press.

[31] See notes 1-6 above. Also, Rivera, J. & Tessarollo, L. (2008). Genetic background and the dilemma of translating mouse studies to humans. *Immunity*, 28(1), 1.

[32] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.

[33] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.

[34] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.

[35] Van Reenen, C. G., Meuwissen, T. H., Hopster, H., et al. (2001). Transgenesis may affect farm animal welfare: a case for systematic risk assessment. *J Anim Sci*, 79(7), 1763.

[36] Houdebine, L. M. (2002). The methods to generate transgenic animals and to control transgene expression. *J Biotechnol*, 98(2-3), 145.

have been caused by elevated levels of recombinant growth-promoting factors produced in many different organs.[37]

In addition, the effects of adding or deleting a gene cannot be accurately predicted, as genes often have multiple functions that are poorly understood. The transgene may interact with other genes in ways that are unknown. Changing an animal's internal environment could alter the pathogens to which it is host, or immune-deficient animals could be affected by diseases not typically seen in immune-competent animals.[38,39]

According to Pritt, et al. (2006), "…commonly encountered unanticipated outcomes include toothless mice, runting, skin problems (moist dermatitis, etc.), and malocclusions….Additional unanticipated outcomes that have been identified…, for which animal care and veterinary involvement was needed to help mitigate any potential animal welfare concerns, included stubby legs, chronic conjunctivitis (allergic reactions), underdeveloped eyes, and necrosis of the pinnae in hybrid mice."[40]

Examples of welfare issues reported in Jackson Laboratory's TBASE database for transgenic lines include weight loss, abdominal distention, intestinal obstruction and rupture, and gallbladder distention and rupture, with most animals dead by one month; retarded growth and infertility; impaired immune system; development of multiple tumors; and hind limb weakness and paralysis.[41] At the University of Washington, "the most frequently encountered unanticipated problems are infectious in nature…."[42]

In a classic case, pigs genetically modified with human or bovine growth hormone to make them grow faster and produce less fat were found to suffer numerous painful, unanticipated side effects, including crippling arthritis that left them unable to walk, liver and kidney damage, ulcers, diarrhea, protruding eyes, and reproductive difficulties and anomalies such as mammary development in males.[43] According to an NRC report, "Of the 19 pigs expressing the transgene, 17 died within the first year. Two were stillborn and four died as neonates, while the remainder died between two and twelve months of age. The main causes of death were pneumonia, pericarditis, and peptic ulcers. Several pigs died during or immediately after confinement in a restraint device (a metabolism stall), demonstrating an increased susceptibility to stress."[44]

Making it even more difficult to anticipate outcomes, different results are seen depending on the location of the transgene insertion, the number of transgene copies inserted into the genome, the age and sex of the animal, and the genetic background of the animal. Some adverse outcomes worsen or do not become apparent until the animal ages, or manifest only after several generations. The same genetic construct can also produce completely different phenotypes in different strains of the same animal.[45]

All of these complications create risks for animal health and welfare. That these risks cannot be reliably anticipated further increases the likelihood that an animal will suffer as a result of an unintended consequence of genetic modification. The inefficiency and unpredictability of genetic modification also results in a very large number of animals being used to create and assess the phenotype of a transgenic

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[37] Van Reenen, C. G., Meuwissen, T. H., Hopster, H., et al. (2001). Transgenesis may affect farm animal welfare: a case for systematic risk assessment. *J Anim Sci*, 79(7), 1763.

[38] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.

[39] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319, Pritt, S., Cozine, K., & Warren, H. (2006). Management of unanticipated outcomes in transgenic mouse facilities. *Lab Anim (NY)*, 35(4), 27.

[40] Pritt, S., Cozine, K., & Warren, H. (2006). Management of unanticipated outcomes in transgenic mouse facilities. *Lab Anim (NY)*, 35(4), 27.

[41] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.

[42] Ibid.

[43] Pursel, V. G., Pinkert, C. A., Miller, K. F., et al. (1989). Genetic engineering of livestock. *Science*, 244(4910), 1281.

[44] National Research Council. (2002). *Animal Biotechnology: Science-Based Concerns*. Washington, DC: The National Academies Press.

[45] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.

animal. In addition, attempts to refine the experimental procedures, such as the design of the transgenic construct to achieve appropriate expression, consumes even more animals.[46]

Intended effects of genetic modification

In many instances, genetically modified animals are designed to be ill, used for basic and applied research into human disease.[47] In these cases, the genetically altered animal is intended to model causes or symptoms of human disease, and often no treatments are available to alleviate the associated pain or distress. As such, genetic modification has "the potential to compromise animal health and welfare by causing or predisposing the animal to pain, suffering, distress or lasting harm…."[48]

Research protocols commonly involve creating lines that experience premature lethality, altered bodily functions, increased tumor production, decreased disease resistance, altered susceptibility to microorganisms,[49] arthritic conditions, ulcerative colitis,[50] and uniquely human conditions such as Alzheimer's disease,[51] schizophrenia,[52] and Huntington's disease.[53] Many genes are also studied for their role in development and basic physiological functioning. The creation of genetically modified mutants to study these genes will often result in health problems, and increased mortality is likely.[54]

In agriculture, the purpose of the genetic modification is often to increase production and efficiency, which often carries consequences for animal health and welfare, as evidenced by the increasing emergence of production-related diseases. As explained by one scholar, because "there are no legal or regulatory constraints on what can be done to animals in pursuit of increasing agricultural productivity," then "if the pain, suffering, and disease of the animal does not interfere with the economic productivity, the condition is ignored."[55]

Problems arising from reproductive technologies

In vitro procedures, including somatic cell nuclear transfer (cloning) and microinjection, are used in both the development and breeding of transgenic animals. Often, these procedures result in numerous health and welfare problems that are often fatal. While such problems are not unique to genetic engineering, they do comprise an integral part of the process,[56] and thus must be considered when assessing impacts to animal health and welfare.

According to Van Reenen, et al. (2001), "Reported data on actual transgenesis experiments fully substantiate the association between in vitro technologies and LOS [Large Offspring Syndrome] and have shown high perinatal mortality rates (up to more than 50%), increased birth weights, and severe pre- and post-mortem pathologies among transgenic lambs and calves generated by nuclear transfer and a high incidence of

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[46] Kind, A. & Schnieke, A. (2008). Animal pharming, two decades on. *Transgenic Res*(Online First).

[47] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.

[48] Wells, D. J., Playle, L. C., Enser, W. E., et al. (2006). Assessing the welfare of genetically altered mice. *Lab Anim*, 40(2), 111.

[49] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.

[50] Buehr, M., Hjorth, J. P., Hansen, A. K., et al. (2003). Genetically modified laboratory animals--what welfare problems do they face? *J Appl Anim Welf Sci*, 6(4), 319.

[51] Liu, L., Orozco, I. J., Planel, E., et al. (2008). A transgenic rat that develops Alzheimer's disease-like amyloid pathology, deficits in synaptic plasticity and cognitive impairment. *Neurobiol Dis*, 31(1), 46.

[52] Hikida, T., Jaaro-Peled, H., Seshadri, S., et al. (2007). Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. *Proc Natl Acad Sci U S A*, 104(36), 14501.

[53] Yang, S. H., Cheng, P. H., Banta, H., et al. (2008). Towards a transgenic model of Huntington's disease in a non-human primate. *Nature*, 453(7197), 921.

[54] Dennis, M. B., Jr. (2002). Welfare issues of genetically modified animals. *Ilar J*, 43(2), 100.

[55] Rollin, B. (2007). Ethics and Genetic Engineering. Presented at *Animals and Bioengineering: A consideration of law, ethics and science*, Duke University School of Law, November 9-10, 2007.

[56] Flint, A. P. & Woolliams, J. A. (2008). Precision animal breeding. *Philos Trans R Soc Lond B Biol Sci*, 363(1491), 573.

congenital malformations, an increased birth weight, and a high perinatal mortality rate among calves originating from in vitro-produced embryos subjected to microinjection."[57]

In particular, gene transfer through cloning has emerged as a preferred method for generating and propagating transgenic farm animals. The vast majority of the time (80-99%), however, the procedure fails, resulting in serious animal health problems that raise significant concerns for animal welfare.[58,59]

Despite more than a decade of research, cloning efficiency has not improved significantly,[60] and cloning, like genetic modification, is considered "time consuming and unpredictable."[61] The inefficiency and animal welfare concerns associated with cloning "makes the technology commercially less valuable and socially hardly acceptable."[62]

Summary

According to Flint and Woolliams (2008), "What is clear is that the difficulties of ensuring the necessary integration of the transgene into the genome…has been a challenge of questionable cost-benefit."[63] The methods used to develop and produce genetically modified animals are generally recognized to be inefficient, unpredictable, labor-intensive, time-consuming, and expensive, requiring hundreds to thousands of animals to produce a line of transgenic animals.[64,65] There is growing awareness that the unintended consequences of the genetic manipulations, the genetic modifications themselves, and the shear number of animals wasted raise serious concerns for animal health and welfare that need to be appropriately addressed.[66]

[57] Van Reenen, C. G., Meuwissen, T. H., Hopster, H., et al. (2001). Transgenesis may affect farm animal welfare: a case for systematic risk assessment. *J Anim Sci*, 79(7), 1763.

[58] Dinnyes, A., Tian, X. C., & Yang, X. (2008). Epigenetic regulation of foetal development in nuclear transfer animal models. *Reprod Domest Anim*, 43 Suppl 2, 302.

[59] Mak, N. (2008). *The American Anti-Vivisection Society's Concerns About Cloning Animals for Food: Animal welfare, ethics, and the USDA*: American Anti-Vivisection Society.

[60] Galli, C. & Lazzari, G. (2008). The manipulation of gametes and embryos in farm animals. *Reprod Domest Anim*, 43 Suppl 2, 1.

[61] Flint, A. P. & Woolliams, J. A. (2008). Precision animal breeding. *Philos Trans R Soc Lond B Biol Sci*, 363(1491), 573.

[62] Dinnyes, A., Tian, X. C., & Yang, X. (2008). Epigenetic regulation of foetal development in nuclear transfer animal models. *Reprod Domest Anim*, 43 Suppl 2, 302.

[63] Flint, A. P. & Woolliams, J. A. (2008). Precision animal breeding. *Philos Trans R Soc Lond B Biol Sci*, 363(1491), 573.

[64] Dhup, S. & Majumdar, S. S. (2008). Transgenesis via permanent integration of genes in repopulating spermatogonial cells in vivo. *Nat Methods*, 5(7), 601.

[65] Houdebine, L. M. (2002). The methods to generate transgenic animals and to control transgene expression. *J Biotechnol*, 98(2-3), 145.

[66] National Research Council. (2002). *Animal Biotechnology: Science-Based Concerns*. Washington, DC: The National Academies Press.

Ethics

Animals are not plants. Because animals are sentient, capable of feeling pain and suffering, humans have certain moral obligations and responsibilities for their humane treatment and care. Concerns about animal health and welfare raise certain moral and ethical questions about the genetic modification of animals, in addition to more deep-seated ethical questions about the technology itself. Indeed, polls by the Pew Initiative for Food and Biotechnology have repeatedly shown that moral, ethical, and religious concerns are a major source of opposition to genetically modifying animals.[67,68,69]

A fundamental ethical question is whether humans *should* be creating genetically engineered animals. This is particularly relevant given that a large number of animals are used and that animals suffer extensively as a result of the genetic modification process. Is it ever necessary to genetically modify animals? If alternative means are available, can genetic engineering be justified? Should there be restrictions regarding for what purposes a genetically modified animal can be developed? Should there be blanket prohibitions on certain uses of the technology, such as genetically modifying animals for pets or ornamental display (e.g., the GloFish)?

The patented and trademarked EnviroPig,[70] for example, has been genetically engineered to produce less phosphorous in its manure, thus making it more environmentally friendly. However, similar outcomes can be achieved through less drastic measures. Phosphorous content can be reduced, for example, by adding phytase supplement to pigs' feed instead, at a cost of only $1.14 per pig.[71] In such a case, is it justifiable to subject animals to genetic engineering when reasonable alternatives are available?

Pigs have also been genetically modified to produce higher amounts of omega-3 fatty acids, which are thought to have beneficial health effects. However, it is unclear if omega-3 fatty acids in pork have the same health benefits as in fish or flax seeds, particularly when the other unhealthful qualities of pork are considered. In addition, there is already a naturally occurring pig breed–the Spanish Ibérico–that can make omega-3 fatty acids without genetic engineering,[72] and other researchers have shown that it is possible to introduce omega-3 fatty acids in the meat of pigs by feeding them a diet supplemented with flax seeds and vitamins.[73]

As observed by noted bioethicist Autumn Fiester, "…the use of transgenic technology for this application represents the worst type of 'research waste': precious scientific resources of time, mental energy and money that could be used to tackle serious human and environmental threats are being devoted to a frivolous cause."[74] Indeed, most people would agree with Fiester, that "there is something profoundly amiss in our stampede down the biotech path for every trivial application,"[75] and a majority of people view cloning and genetic modification of animals negatively.[76,77]

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[67] The Mellman Group/Public Opinion Strategies. (2004). *U.S. Consumer Opinion Divided: Overview of 2004 Findings*. Results of a survey and focus groups conducted for the Pew Initiative on Food and Biotechnology.

[68] The Mellman Group/Public Opinion Strategies. (2005). *Public Sentiment About Genetically Modified Food (2005)*: Results of a survey conducted for the Pew Initiative on Food and Biotechnology.

[69] The Mellman Group. (2006). *Public Sentiment About Genetically Modified Food (2006)*: Results of a survey conducted for the Pew Initiative on Food and Biotechnology.

[70] Golovan, S. P., Meidinger, R. G., Ajakaiye, A., et al. (2001). Pigs expressing salivary phytase produce low-phosphorus manure. *Nat Biotechnol*, 19(8), 741.

[71] *Guelph Transgenic Pig Research Program*. Retrieved August, 2008, from http://www.uoguelph.ca/enviropig/

[72] Kolata, G. (2006). Cloning May Lead to Healthy Pork. *New York Times*, March 27, 2006.

[73] Hisey, P. (2006). Omega-3 Pork Not New in Canada. *MeatingPlace.com*, March 30, 2006.

[74] Fiester, A. (2006). Why the omega-3 piggy should not go to market. *Nat Biotechnol*, 24(12), 1472.

[75] Ibid.

[76] The Pew Initiative on Food and Biotechnology. (2005). Exploring the Moral and Ethical Aspects of Genetically Engineered Animals: Summary of a Multi Stakeholder Workshop, Rockville, MD, January 24-26, 2005.

Another example involves cows who are being genetically modified to be resistant to mastitis, a painful infection of the udder,[78] or to be resistant to bovine spongiform encephalopathy (BSE, or mad cow disease).[79] While such projects are purported as benefiting animal welfare, in truth numerous animals suffered to create these genetically engineered strains resistant to diseases that are not naturally a significant problem but rather are considered "production diseases" – a by-product of the intensive factory farming production methods used on many farms today. Mastitis occurs because cows are pushed to produce excessive quantities of milk, having been bred to produce three times more milk than normal, and could be effectively controlled using preventative measures such as good hygiene and good milking practices.[80] BSE occurs because industrial farms try to cut costs by feeding cows, who are normally herbivorous, slaughterhouse waste from other cows, chickens, and goats. Simple changes to production practices, which would reduce cruelty on the farm, would also spare countless lives from the suffering caused by the genetic modification process.

The NRC report on animal biotechnology further states that, "While reducing disease clearly is beneficial, if this also permits animals to be confined more closely, and thus decreases the opportunity for them to perform their normal behaviors, then the net effect on welfare could be negative."[81]

These examples demonstrate that, though there are many applications of genetically modified animals that are claimed to offer benefits of some kind, the ethical justification for these applications, given the costs to animal health and welfare, needs to be more closely examined.

Questions about acceptability apply equally to research using genetically modified animals and to commercialization of genetically modified animals. While the merits and usefulness of a particular "product" are often decided in the marketplace, there are real consequences to animal welfare for each genetically modified animal application allowed to go to market.

In addition, there is concern that genetic engineering substantially increases the commodification of animals, promoting the treatment of animals as mere objects for human use and benefit and disregarding their sentience.[82,83,84] Genetic engineering raises questions about the relationship between humans and animals and the place that animals have in our society, now and in the future. How much human manipulation of animals, and for what purposes, is acceptable?

Public opinion polls[85,86] show that genetic modification applications involving animals generate farm more disapproval than applications involving plants. Within animal applications, non-scientific uses, such as for food production, elicit more objections than medical uses. The greatest disapproval is for xenotransplantation.

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[77] The Mellman Group. (2006). *Public Sentiment About Genetically Modified Food (2006)*: Results of a survey conducted for the Pew Initiative on Food and Biotechnology.
[78] Wall, R. J., Powell, A. M., Paape, M. J., et al. (2005). Genetically enhanced cows resist intramammary Staphylococcus aureus infection. *Nat Biotechnol*, 23(4), 445.
[79] Richt, J. A., Kasinathan, P., Hamir, A. N., et al. (2007). Production of cattle lacking prion protein. *Nat Biotechnol*, 25(1), 132.
[80] Khamsi, R. (2005). Transgenic Cows Have Udder Success. *Nature News*, April 3, 2005.
[81] National Research Council. (2002). *Animal Biotechnology: Science-Based Concerns*. Washington, DC: The National Academies Press.
[82] de Vries, R. (2006). Ethical concepts regarding the genetic engineering of laboratory animals: A confrontation with moral beliefs from the practice of biomedical research. *Med Health Care Philos*, 9(2), 211.
[83] Rutovitz, J. & Mayer, S. (2002). *Genetically Modified and Cloned Animals. All in a Good Cause?* Derbyshire: GeneWatch UK.
[84] Kaiser, M. (2005). Assessing ethics and animal welfare in animal biotechnology for farm production. *Rev Sci Tech*, 24(1), 75.
[85] Einsiedel, E. F. (2005). Public perceptions of transgenic animals. *Rev Sci Tech*, 24(1), 149.
[86] The Mellman Group/Public Opinion Strategies. (2004). *U.S. Consumer Opinion Divided: Overview of 2004 Findings*: Results of a survey and focus groups conducted for the Pew Initiative on Food and Biotechnology.

In addition to concern for animal welfare, underlying these ethical questions is also a concern that genetic engineering is "not natural" or is "playing God." Genetic engineering takes human interference with animal reproduction to a new level, making it possible to intentionally cross species and kingdom boundaries with little knowledge or control of the consequences. Many people also view genetic engineering as "violating the integrity" of an animal.[87,88]

The likelihood that genetically modified animals would be patented raises additional concerns about the commodification of animals. In this case, animals are treated literally as "machines," "manufactures," or "compositions of matter." Indeed, 68% of people think it is unethical for governments to issue patents on animals as if they were human inventions.[89] Animal patenting also raises socioeconomic concerns, given the potential for large agribusinesses to concentrate and monopolize resources and technologies, transferring animal ownership to the hands of just a few.[90]

There are several other ethical concerns related to genetic engineering that are distinct from animal welfare issues. Many people are worried that genetic engineering in animals will lead to genetic engineering in humans since much of the science overlaps.[91] Others worry that genetic engineering technology can be co-opted for malicious purposes, such as bioterrorism, or could harm the environment.[92] A major concern for people is whether or not products from genetically modified animals would be labeled as such.[93,94]

Public acceptability of genetically modifying animals is not determined by assessments of risk and safety alone.[95,96,97] These moral and ethical issues are also weighed by the public when considering the consequences of genetic modification, and a formal ethical review process is needed to ensure their adequate deliberation during regulatory decision-making.

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[87] Kaiser, M. (2005). Assessing ethics and animal welfare in animal biotechnology for farm production. *Rev Sci Tech*, 24(1), 75.

[88] The Pew Initiative on Food and Biotechnology. (2005). Exploring the Moral and Ethical Aspects of Genetically Engineered Animals: Summary of a Multi Stakeholder Workshop, Rockville, MD, January 24-26, 2005.

[89] Opinion Reseach Corporation. (2004). *Animal Patents: Summary of survey findings*: Prepared for the American Anti-Vivisection Society.

[90] Rollin, B. (2007). Ethics and Genetic Engineering. Presented at *Animals and Bioengineering: A consideration of law, ethics and science*, Duke University School of Law, November 9-10, 2007.

[91] The Pew Initiative on Food and Biotechnology. (2005). Exploring the Moral and Ethical Aspects of Genetically Engineered Animals: Summary of a Multi Stakeholder Workshop, Rockville, MD, January 24-26, 2005.

[92] Rollin, B. (2007). Ethics and Genetic Engineering. Presented at *Animals and Bioengineering: A consideration of law, ethics and science*, Duke University School of Law, November 9-10, 2007.

[93] Kaiser, M. (2005). Assessing ethics and animal welfare in animal biotechnology for farm production. *Rev Sci Tech*, 24(1), 75.

[94] Riley, M. F. (2007). Ethics and Law in Animal Biotechnology. Presented at *Animals and Bioengineering: A consideration of law, ethics and science*, Duke University School of Law.

[95] Einsiedel, E. F. (2005). Public perceptions of transgenic animals. *Rev Sci Tech*, 24(1), 149.

[96] Rollin, B. (2007). Ethics and Genetic Engineering. Presented at *Animals and Bioengineering: A consideration of law, ethics and science*, Duke University School of Law, November 9-10, 2007.

[97] The Mellman Group. (2006). *Public Sentiment About Genetically Modified Food (2006)*: Results of a survey conducted for the Pew Initiative on Food and Biotechnology.

FDA Oversight Problems

Given that genetic engineering raises strong concern and opposition from the public and is a very complex issue with far-reaching consequences, it is critical that we have a rigorous and robust system in place to address these risks and concerns. The FDA's draft guidance on GE animals, which provides recommendations for how industry can comply with the requirements of the New Animal Drug Application (NADA) process to gain approval to market a GE animal or products from a GE animal, begins to address some of the issues, but does not address them all. As argued by the editorial board of the highly-respected *Nature* magazine, "More light on the process than the FDA's proposal allows is needed to build public trust and to ensure that all necessary steps are taken to avoid adverse events. The current law cannot do this. Congress should step in and produce one that does."[98]

Ethics. The FDA draft guidance on GE animals does not address ethical issues at all. This is somewhat understandable given that the FDA does not have authority to regulate based on ethical considerations. However, it is not acceptable that GE animals could be allowed on the market, based upon an approval granted by the FDA, without there having been broad and extensive public discussions about the ethical implications of genetically engineering animals. Other agencies and commissions need to be involved in the decision-making process to facilitate these discussions, and the FDA should not be the only barrier keeping GE animals off the market. An interagency or Presidential advisory committee should be established to address the ethical concerns with genetic engineering.

Enforcement discretion. *All* animals who end up involved in genetic engineering experiments must be covered under whatever regulatory system is established. According to the FDA's draft guidance, however, the agency intends to exercise its enforcement discretion to exempt the vast majority of animals from the NADA requirements.

In particular, the FDA mentions that it will likely exercise enforcement discretion for "GE animals of non-food species that are raised and used in contained and controlled conditions (e.g., FDA would not require an INAD or NADA for GE laboratory animals used in research institutions)."[99]

The basis for the FDA's determination to exercise enforcement discretion is unclear. The FDA seems to be considering those animals who are less likely to pose food safety or environmental risks. However, a primary aim of the NADA provisions is to evaluate the safety of the drug for the target animal. On that basis, all attempts at genetic engineering should be subjected to review.

Furthermore, it is unclear what information the FDA would require to determine if it would exercise enforcement discretion. What would need to be demonstrated, and how, before such a determination could be made? Laboratories, for example, do not always achieve 100 percent containment, so what amount of potential for accidental release is the FDA willing to tolerate? What if there is a GE animal who could pose significant risks to humans, other animals, or the environment if it accidentally escapes?

The FDA says that it can choose to reinstate its enforcement authority at any time if conditions change or concerns arise, but how will the agency be made aware of such changes? What would be the criteria for reinstating its enforcement authority? Would it be too late to mitigate risks if the FDA was exercising enforcement discretion but concerns did arise that triggered regulatory action?

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[98] Animals aren't drugs. (2008). *Nature*, 456(7218), 2.
[99] Food and Drug Administration (2008). *Guidance for Industry: Regulation of genetically engineered animals containing heritable rDNA constructs; Draft Guidance*, p. 6. Docket No. FDA-2008-D-0394.

Given the potential for serious and profound risks to the environment, animals, and/or people if activities involving a GE animal are not properly evaluated and regulated, it is irresponsible for the FDA to some GE animals to escape regulatory review under the new animal drug provisions.

Extent of FDA authority. Even for those GE animals who do end up being regulated by the FDA, the FDA's authority to address the concerns raised by genetic engineering is limited. The FDA has chosen to issue guidance only, which is non-binding. It is even unclear whether the FDA's determination that an rDNA construct falls under the definition of new animal drug is merely guidance or carries the weight of a more official decision.

It is further unclear at what point in the development of a GE animal an INAD file would need to be opened or a NADA would need to be filed and how risks would be regulated pre-filing. In addition, the FDA can assess animal health risks and it can prepare an environmental assessment, but it is unclear how the agency can make any regulatory determinations based on its findings. The FDA guidance does not state that the FDA has the authority to withhold approval of a GE animal based on animal welfare or environmental concerns.

Animal health and welfare. Animal welfare is not taken into consideration at all by the FDA, which restricts its assessments of new animal drugs to animal health safety, human health safety, and drug effectiveness.[100] Furthermore, as discussed above, it is hard to see how animal health would be protected, not just assessed, under the new animal drug provisions if the FDA cannot or will not withhold regulatory approval based on animal health or welfare concerns. Recent history has shown that the FDA will grant approval even when animal suffering is increased.

In the case of rBST (recombinant bovine somatotropin, also known as rbGH, or recombinant bovine growth hormone), an artificial hormone injected into dairy cows to increase milk production, the drug was approved even though it was associated with an increased incidence of mastitis, a painful infection of the udder, and lameness.[101,102] The FDA also chose not to regulate animal cloning, even though more than 95 percent of cloning attempts fail and cloned animals, as well as their surrogate mothers, are at greatly increased risk of early death, suffering from physiological abnormalities and physical defects seen only rarely otherwise.

In addition, as also discussed above, the FDA is proposing to exempt the majority of GE animals from regulatory oversight. Most of these animals, including mice, rats, and birds bred for use in research, fish, and some farm animals, are not afforded protection under the Animal Welfare Act, either.

For those GE animal applications the FDA does choose to regulate, however, the draft guidance does provide for some evaluation of risks to animal health. The FDA rightly proposes that animals derived from separate transformation events be considered to contain separate new animal drugs and require separate NADAs. Each transformation event has the potential to present a unique set of risks based on where and how the rDNA construct is inserted into the animal's genome, and it makes sense to consider those risks separately.

However, the FDA is proposing to only evaluate the health of those animals who are ready or almost ready to be commercialized. Hundreds to thousands of animals are used to create each progenitor GE animal, the animal from which the GE animals to enter commerce are derived. The health risks experienced by these

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[100] 21 C.F.R. §514.1(b)(8)(iv).
[101] FDA. (1993). *Freedom of Information Summary (FOI): POSILAC (sterile sometribove zinc suspension) New Animal Drug Application 140-872.*
[102] FDA. (2008). *Animal Cloning: A Risk Assessment.*

animals involved in the research and development phases are not assessed according to the FDA's guidance and would not bear on the FDA's evaluation of drug safety. Furthermore, it is not clear that animals covered under an INAD file would be protected against any of these risks. The FDA has provided guidance for shipping, labeling, disposition, investigational food use, and environmental considerations, and these do not provide for minimizing risks to animal health or welfare. Even if there were protections, it is not clear when an INAD file must be opened, meaning it is possible that FDA oversight would not take effect until late in the process.

Transparency. A significant difficulty with regulating GE animals under the new animal drug rubric is that the NADA process is confidential, meaning the public would not know about a GE animal until after it had been approved for commercial sale and would not have any opportunity to weigh in on the FDA's assessment and decision-making process. This requires the public to have a lot of faith in the FDA's ability to "get it right," but this is an untenable position, particularly given several recent controversies over recalled drugs and contaminated foods.

The public, including stakeholders in the food industry, deserves to know about GE animal applications prior to approval so that they can make informed decisions as to how they want to respond. In addition, members of the public may have valuable insight or perspectives to share that would affect the FDA's assessment of animal health, human health, and environmental risks. In the case of the GE salmon who had been engineered to grow faster than normal, it was members of the public, key stakeholders, who brought to the FDA's attention the fact that the agency should consult with the EPA, FWS, and NOAA Fisheries about serious potential environmental concerns.

To promote public confidence and ensure that all risks are addressed as fully as possible, all aspects of the INAD file and the NADA process must be open to the public, and no approval should be granted for allowing a GE animal to go to market without public participation. The public should know when an INAD has been filed and when exemptions under the INAD process have been granted to allow GE animals into the food supply or the environment, and the public should be able to comment before exemptions, decisions to exercise enforcement discretion, or NADA approvals are granted. The public should also be able to comment on environmental assessments (EA) and environmental impact statements, as well as decisions to provide categorical exclusion from EA requirements.

The FDA has made a verbal commitment to having a public hearing before the first GE animal application, or the first few applications, are approved. However, this commitment needs to be specified in writing, in a format that is binding so that the FDA can be held accountable for having these hearings (i.e., not as guidance). In addition, these hearings should be extended to all applications, not just the first few, and the FDA should describe in detail how these hearings will work (what forum will be provided, how input from the public will factor into the FDA's decision-making process, etc.).

Labeling. It is unacceptable that the FDA would not require that all products from GE animals be labeled as such. According to a 2008 Consumers Union survey, more than 60 percent of Americans would not buy food products from GE animals, and nearly all Americans (95 percent) want products from GE animals to be labeled.[103] Consumers have the right to be informed and to choose what they wish to purchase, particularly given the strong sentiments and high levels of concern that genetic engineering of animals elicits.

Level of specificity. It is difficult to comment fully on the adequacy of the FDA's proposal to regulate GE animals given that a large amount of the FDA's policy will apparently be determined in conversations with developers, is pending future guidance, or is otherwise described in a non-specific manner.

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[103] Consumer Reports National Research Center (2008). *Food-Labeling Poll 2008*. Retrieved November, 2008, from http://www.greenerchoices.org/pdf/foodpoll2008.pdf

For example, the FDA frequently advises developers to consult with the agency to figure out what their responsibilities will be. There is no way to know what the FDA will decide during such conversations or if the FDA's requirements will be sufficient, and there is no way to hold the FDA or the developers accountable.

In addition, at several points the FDA indicates that it may issue additional guidance in the future to explain how certain requirements might be met. It is impossible, therefore, to determine if the FDA's approach will be comprehensive or adequate enough to protect against the relevant risks.

The FDA's plans for working with other agencies to address various concerns raised by genetically engineering animals are also similarly vague. How will agencies be informed of the existence of new GE animals? How will the FDA determine if a consultation with another agency is necessary, and how will any consultations affect the FDA's decision-making process? Will FDA approval be contingent upon these consultations in some way? Without these details, it is impossible to have confidence in the FDA's approach.

As discussed above, the case of the GE salmon highlights that the FDA may not always initiate the consultations it should. Animal cloning also highlights how a consultation process without any formal parameters can create messy, difficult outcomes. In that case, the FDA was intent on allowing cloned animals on the market, but the USDA was concerned about consumer acceptance and market impacts. The FDA went ahead with the approval, and confusion resulted when the USDA requested that producers voluntarily keep some cloned animals off the market anyway.

It seems clear that the FDA does not know enough yet to specify more fully the details of its regulatory scheme for GE animals. The FDA should have engaged in greater dialogue and discussion with the public and stakeholders before issuing this guidance, but instead rushed to release this guidance without an appropriate amount of detail to elicit confidence that the agency can adequately address the risks associated with genetically engineering animals.

Recommendations for the FDA and USDA

Genetic modification of animals raises pressing animal welfare and ethical concerns. We have a moral obligation to protect animal welfare, even if there is no consequence to human health or safety,[104] and it is unlikely that much public acceptance of the technology will be possible without thoroughly addressing these concerns. "Indeed, a precautionary approach to the welfare issue in animal biotechnology would seem to be justified if not implied by humanity's assumed ethical responsibility for the stewardship of production animals,"[105] a sentiment which applies equally as well to all animals.

As a starting point, there needs to be a moratorium on the development and approval of GE animals until a national dialogue and broad ethical review is conducted to answer whether, given the animal suffering involved and other potential consequences, it is ever acceptable to create genetically modified animals and whether there are general classes of applications that should be prohibited. Early ethical review is essential to prevent wastage of animal life, as well as to provide companies with early guidance before investing large quantities of resources into developing a "product." *AAVS recommends that an independent ethics advisory commission be established for this purpose, at the agency or executive branch level, allowing for ample public participation and transparency.*

AAVS believes that animals should not be genetically modified. However, if after an independent ethics advisory committee review, the use of genetically modified animals is allowed to occur, at the very least boundaries should be established and a framework developed for the evaluation of genetic modification applications. The research and development phase, as well as the commercialization phase, must be covered, and animal welfare and ethics must be explicitly considered along with questions of human and environmental safety.

Straughan (2000) discusses an example of such a review, undertaken in the UK:

> In 1995…the Banner Committee in the UK produced a report for Government Ministers on the ethical implications of emerging technologies in the breeding of farm animals, which recognised that genetic modification might result in welfare problems, some of which might not be immediately apparent. This Committee produced three general principles for future practice:
> i. Harms of a certain degree and kind ought under no circumstances to be inflicted on an animal.
> ii. Any harm to an animal, even if not absolutely impermissible, nonetheless requires justification and must be outweighed by the good which is realistically sought in so treating it.
> iii. Any harm which is not absolutely prohibited by the first principle, and is considered justified in the light of the second, ought, however, to be minimized as far as is reasonably possible."[106]

In the U.S., many people incorrectly assume that the Animal Welfare Act (AWA) is sufficient to ensure that animal welfare is protected during research. However, the vast majority of animals used in research, particularly those used in genetic engineering experiments – mice and rats bred for use in research, fish, and farm animals used for agricultural purposes – are not covered by the AWA. Thus, there is no requirement for an Institutional Animal Care and Use Committee (IACUC) to review protocols involving these animals. Furthermore, IACUC review is not required to include an ethical review. IACUCs must cover issues of redundancy and the provision of anesthesia and analgesia, but an IACUC is not required to review if the experiment is ethical or justified.

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[104] The Animal Welfare Act, for example, is a manifestation of this obligation.

[105] Kaiser, M. (2005). Assessing ethics and animal welfare in animal biotechnology for farm production. *Rev Sci Tech*, 24(1), 75.

[106] Straughan, R. (2000). *Ethics, Morality and Biotechnology.* Biotechnology and Biological Sciences Research Council.

Therefore, AAVS recommends that the USDA actively seek legislation expanding the Animal Welfare Act (AWA) to cover mice, rats, and birds bred for use in research, cold-blooded animals including fish, and farm animals used in biotechnology experiments for any purpose. The USDA should also increase the data it collects through the Annual Report to provide more detailed statistics and a more realistic view of the number and species of animals used in research each year and the purposes for which they are used.

In addition, the AWA should be expanded to require ethical review at the IACUC level of proposals to genetically modify animals.[107] Applications should be required to demonstrate that they pass a sufficiently high hurdle to justify the genetic modification of animals and that alternatives would not be adequate.

USDA APHIS has an obvious role in promulgating standards for research involving genetically modified animals. In addition to the case-by-case ethical review by IACUCs, it is also necessary to develop regulations for the special care required for genetically modified animals.[108,109] In particular, every effort must be made to anticipate, provide for, and reduce the likelihood of any potential adverse outcomes, and genetically modified animals should be adequately monitored so that unanticipated health and welfare problems can be identified and addressed in a timely and humane manner.

With regard to commercialization, the FDA has some authority to regulate at least some of the risks under the new animal drug rubric. However, *the NADA rubric is a poor fit for adequately addressing all the concerns raised by genetic engineering* (see above, "FDA Oversight"). Animal health, animal welfare, ethics, public participation and transparency, environmental safety, and labeling are among the key issues that remain problematic despite the FDA draft guidance.

The USDA may be able to plug some of the gaps in terms of protecting animal health and welfare with its existing authority. *Given the USDA's obvious expertise in animal welfare, the agency should examine its authority to assess the animal welfare impacts associated with the commercial production of genetically modified animals in case the FDA chooses not to.* Such an assessment should include consideration of the impacts of the genetic modification in the context of the end-user environment (as opposed to the research environment), as well as standards for animal care and monitoring provisions to reduce these impacts. The animal safety data gathered for a NADA may help identify areas of concern for the animal welfare assessment.

In addition, because concerns about animal welfare and ethics affect consumer confidence in the food supply, consumer purchasing decisions, and agricultural trade, the USDA should examine its responsibility to evaluate these concerns as part of its mission to make "it possible for the full production of American farms to be disposed of usefully, economically, profitably, and in an orderly manner."[110]

AAVS recommends that an independent advisory committee, within USDA or interagency, be established to conduct evaluations of animal welfare and ethical concerns before commercial production is allowed. The committee's deliberations should involve public participation and transparency and be open for public comment.

If, ultimately, commercial production of a genetically modified animal is permitted, the USDA should address and regulate the animal welfare impacts associated with such commercial production. If the USDA does not believe it has adequate legislative authority to do so, the agency should seek this authority from Congress.

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[107] An ethics review should also be established at the National Institutes of Health as part of its grant-making process.

[108] Brown, M. J. & Murray, K. A. (2006). Phenotyping of genetically engineered mice: humane, ethical, environmental, and husbandry issues. *Ilar J*, 47(2), 118.

[109] National Research Council. (2003). *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*. Washington, DC: The National Academies Press.

[110] 7 U.S.C. §1621.

While these steps will help address some concerns raised by genetically engineering animals, *AAVS believes that the FDA and USDA lack sufficient authority to address all concerns and should seek federal legislation from Congress to develop a comprehensive regulatory plan.*

Without a unifying piece of federal legislation, oversight of the genetic engineering of animals will be accomplished through a variety of regulatory authorities, some of which may overlap or conflict. *All agencies with some form of regulatory authority over GE animals should coordinate the development of a clear road map indicating which regulations apply to which animals under which circumstances.* This is necessary to facilitate understanding of how these regulations apply to GE animals, and in particular where there are gaps that leave animals, people, or the environment at risk. *In the interim, no animal should be genetically engineered or allowed on the market.*

International Regulations

Passing responsible regulations such as those recommended here will not restrict science or be overly burdensome, but rather would increase harmonization with international standards. Other governments around the world, including the European Union, Canada, and Australia, are far more advanced in terms of exploring the animal welfare and ethical dimensions of biotechnology and crafting appropriate regulations.

In the European Union, for example, "animal cloning and biotechnology research is permissible only for objectives which are justified on ethical grounds and to the extent that the operations involved are performed on some ethical basis. Thus, 'non-technological concerns, such as those related to the well-being of animals, the overall ethical consequences of a certain invention, and environmental protection' are given consideration in the EU."[111]

Numerous projects have been undertaken in the EU probing public sentiment and the ethical and animal welfare implications of biotechnology,[112] including an opinion issued by the Group of Advisors on the Ethical Implications of Biotechnology concerning the Ethical Aspects of Genetic Modification of Animals.[113] The Group of Advisors concluded that, "In view of the consequences this technology may have for the health of humans and animals, for the environment and society, a policy of great prudence is required,"[114] and emphasized that animal health and welfare, ethics, and the justification of the genetic modification all need to be assessed.

In Canada, the Canadian Council on Animal Care (CCAC), recognizing that special consideration must be given to the welfare of genetically modified animals, issued guidelines on transgenic animals is 1997 "to assist Animal Care Committee (ACC) members and investigators in evaluating the ethical and technological aspects of the proposed creation, care and use of transgenic animals…."[115] ACC conduct ethics reviews of experimental protocols, evaluating the justification for the use of transgenic animals, as well as the animal welfare issues raised.[116] The guidelines provide guidance on ACC's responsibilities and what ACC should consider when reviewing protocols involving transgenic animals. CCAC also has a statement addressing "Ethics of Animal Investigation."[117]

There are also numerous units within the Canadian Food Inspection Agency (CFIA) that have responsibilities addressing animal health and ethics associated with biotechnology. For instance, the Animal Health and Production Division is responsible for the health of genetically engineered livestock and poultry.

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[111] Einsiedel, E. F. (2005). Public perceptions of transgenic animals. *Rev Sci Tech*, 24(1), 149.
[112] European Biomedical Research Association. (1996). The European politics of transgenic animals. *EBRA Bulletin*(July Issue).
[113] Group of Advisors on the Ethical Implications of Biotechnology. (1996). *Opinion 7: Ethical Aspects of Genetic Modification of Animals*.
[114] Ibid.
[115] Canadian Council on Animal Care. (1997). *CCAC Guidelines on: transgenic animals (1997)*.
[116] Canadian Council on Animal Care. (1997). Transgenic Animals, Animal Welfare and Ethics. *RESOURCE Supplement*(Spring/Summer).
[117] Canadian Council on Animal Care. (1997). *CCAC Guidelines on: transgenic animals (1997)*.

Within that division, the Animal Health Risk Analysis Unit provides guidance on risk assessments pertaining to biotechnology-derived animals. The Animal Biotechnology Unit (ABU) deals with animal health matters related to biotechnology-derived animals to determine whether or not to authorize the release of a genetically modified animal or its products. The ABU makes assessments on a case-by-case basis, since each genetically modified animal entails a unique set of circumstances and potential risks. In addition, the risk assessment covers all stages, from generation of the founder animal to production of a line of transgenic animals.[118] There is also the Canadian Biotechnology Advisory Committee, which published numerous research papers about ethics and regulation related to biotechnology.[119]

In Australia, there is a robust regulatory structure in place governing biotechnology.[120,121] The Gene Technology Act (2000), for example, established (among other things) the Gene Technology Ethics Committee (GTEC), which must include a person with expertise in animal welfare. The GTEC has published the National Framework of Ethical Principles in 2006 to serve as a "national reference point to promote an on-going dialogue on values and ethical principles relevant to gene technology,"[122] including consideration of risk to animal welfare. This Framework is observed in conjunction with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes,[123] which addresses in more detail the ethical issues related to the use of animals, establishes a framework for ethical decision-making by the Animal Ethics Committee, and sets requirements for protocols involving genetically modified animals. The Guidelines for the Generation, Breeding, Care and Use of Genetically Modified and Cloned Animals for Scientific Purposes[124] complement the Code, addressing the fact that genetically modified animals "may have specific welfare needs which will extend over their lifetime and into subsequent generations…."[125] The Guidelines discuss animal welfare and ethical issues, as well as animal care and monitoring provisions to manage impacts on animal welfare. Another federal agency, Biotechnology Australia, oversees the responsible development of biotechnology in general and monitors public concerns about biotechnology, including concerns for animal welfare.

Summary

It is clear that, though "the regulatory assessment of transgenic animals is a science-based process primarily addressing safety issues," there is "recognition among regulatory agencies that social and ethical issues will need to be considered."[126] The public, too, expects that animal welfare and ethics will be considered. Indeed, ethics will always play a role in decision-making. Providing an explicit forum for the discussion of such issues will help to strengthen the process of regulatory decision-making.

However, even with the FDA's draft guidance on GE animals, the U.S. has yet to implement a comprehensive system for the oversight of genetic engineering that requires that animal health and welfare, ethical, human safety, and environmental safety considerations are fully addressed. Congress should pass the necessary legislation before any GE animal is brought

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[118] Moreau, P. I. & Jordan, L. T. (2005). A framework for the animal health risk analysis of biotechnology-derived animals: a Canadian perspective. *Rev Sci Tech*, 24(1), 51.
[119] An archive of materials from the Canadian Biotechnology Advisory Committee can be accessed at: http://cbac-cccb.ca/epic/site/cbac-cccb.nsf/en/Home
[120] *OGTR - Legislation*. Retrieved August, 2008, from http://ogtr.gov.au/internet/ogtr/publishing.nsf/Content/legislation-2
[121] Rose, M., Grant, E., & Adams, D. (2008). Genetically modified animals in the biomedical sciences: The challenge of rapid advances & ethical demands. *Alternatives to Animal Testing and Experimentation*, 14(Special Issue), 141.
[122] Committee, G. T. E. (2006). *National Framework for the Development of Ethical Principles in Gene Technology*. Commonwealth of Australia.
[123] National Health and Medical Research Council. (2004). *Australian code of practice for the care and use of animals for scientific purposes, 7th edition*. Australian Government.
[124] National Health and Medical Research Council & Office of the Gene Technology Regulator. (2007). *Guidelines for the generation, breeding, care and use of genetically modified and cloned animals for scientific purposes*. Australian Government.
[125] Rose, M., Grant, E., & Adams, D. (2008). Genetically modified animals in the biomedical sciences: The challenge of rapid advances & ethical demands. *Alternatives to Animal Testing and Experimentation*, 14(Special Issue), 141.
[126] Einsiedel, E. F. (2005). Public perceptions of transgenic animals. *Rev Sci Tech*, 24(1), 149.