"Hybrids and Chimeras: A report on the findings of the consultation" by the Human Fertilisation and Embryology Authority in October, 2007 [1]

By: Taddeo, Sarah Robert, Jason S. Keywords: HFEA [2] Chimeras [3]


In 2006, the Human Fertilisation and Embryology Authority (HFEA), a regulatory institute of the Health and Social Services Department in the UK, began to discuss the implications of using human embryos and human derived cells in research. In the early twenty-first century, the HFEA regulated and monitored use of human embryos and medically collected genetic material, and it generated policy on the production and use of embryos in research in the UK. The HFEA's domain of subjects included human-animal chimeras [4], which are organisms comprised of distinct and independent animal and human cell populations. In late 2006, the UK government asked the HFEA to adjudicate whether or not the development of human-animal chimeras [4] should be permitted in a laboratory setting. To help make its decision, the HFEA opened a forum in April 2007 for the public to discuss those issues.

In November 2006, the HFEA received two requests to develop human-animal chimeric embryos. The research groups, led by Lyle Armstrong from Newcastle University in Newcastle upon Tyne, England, and by Stephen Minger at King's College, London, wanted to generate human stem cells [5], which are cells that can perpetually divide and have the potential to differentiate into more specialized cells, by creating cytoplasmic hybrid embryos, also called interspecies somatic cell nuclear transfer [6]-derived humanesque blastocysts. A cytoplasmic hybrid embryo results when scientists insert the nucleus [7] of a cell from an organism, in this case a human cell, into the enucleated (having the nucleus [7] removed) ovum [8] of an organism from another species, here a non-human animal. Scientists us the name somatic cell nuclear transfer [8] (SCNT) to refer to the process of transplanting the nucleus [7] of a somatic cell [9] into an enucleated ovum [8].

On 26 April 2007, the HFEA sponsored a meeting to encourage public debate and inform citizens of scientific, political, and ethical considerations of creating human–animal chimeras [4] and hybrids. The HFEA obtained data for the consultation in two phases, the first through a public document available on the HFEA's website, "Hybrids and Chimeras: A Consultation on the Ethical and Social Implications of Creating Human/Animal Embryos in Research," which informed the public of relevant scientific and political information, and it highlighted some ethical issues. The document provided instructions for citizens to submit their comments and opinions to the HFEA. The second phase to obtain data consisted of a scientific literature review and discussion to provide context for public and political debates. The HFEA held surveys and debates until 20 July 2007, after which they processed the information for a HFEA meeting in September 2007, when they planned to establish a policy for the creation of chimeras [4] and hybrids in a research context.

The HFEA announced its conclusions on 5 September 2007. The HFEA stated that they found no reason, in principle, to prohibit the development of cytoplasmic hybrid embryos for research purposes, as long as researchers strictly adhered to laws regulating the use of the embryos. Scientists would require special licenses to engage in experiments with human-animal chimeras [4], as with all types of embryo research in the UK. The Research License Committee, a department of the HFEA, would grant licenses after reviewing and approving research proposals and confirming that they followed established law. The HFEA would then review the decision of the Committee, and the HFEA had the power to revoke or recommend modifications to the research design. The HFEA would consider each application on an individual basis, and the HFEA must deem the research [4] as ethical. As of 2014, creation of a hybrid or chimeric embryo without a license from the HFEA is a federal offense in the UK, and it may result in a prison sentence for violators.

The HFEA released the final report of its policy on hybrid and chimeric embryos on 1 October 2007. "Hybrids and Chimeras: A Report on the Findings of the Consultation" has seven sections, in addition to a note from the HFEA’s chair, a glossary, and seven appendices. The document's sections are: "Introduction", "Scientific Understanding, International Perspective", "Consultation: The Approach Taken", "Themes Emerging from the Consultation", "Conclusions", and "The Authority's Decision". The HFEA report begins with a foreword from Shirley Harrison, who was the chair of the HFEA and the Human Tissue Authority in London when the HFEA published the report in 2007. In Harrison's note, she notes the importance of public engagement in
HFEA's decisions, and she states that the value that citizens place on this type of involvement was evident by their responses. Harrison writes that with caution and scrutiny, the HFEA will allow those approved for licensure to create cytoplasmic hybrid embryos. She also says that the HFEA will inform the public about current research and developments within the field. The "Introduction" section briefly describes how HFEA decided to permit cytoplasmic hybrid embryos.

The "Scientific Understanding" section has two subsections. In "A History of Animal-Human Constructs in Research", the HFEA describes previous cases where researchers mixed human and animal genetic material, such as in mapping the human genome \[10\] or testing the quality of human sperm \[11\]. Researchers always terminated the embryos after the first cell division. The HFEA also notes how scientists used animal–animal cytoplasmic hybrid embryos in research for more than a century. For example, in the 1890s, scientists transferred parts between frogs and other species to investigate the roles of the nucleus \[7\] and of cytoplasm in heredity.

The next subsection of "Scientific Understanding", called "Why Scientists Propose to Create Interspecies Cytoplasmic Hybrids," describes how scientists produce embryonic stem cells \[12\] through somatic cell nuclear transfer \[6\] (SCNT). Scientists remove the nucleus \[7\] of an ovum \[8\] and replacing it with the nucleus \[7\], which has genetic material, of an adult body cell. SCNT results in an organism that is ninety-nine percent genetically identical to the donor of the somatic cell \[9\]. The remaining one percent comes from DNA of mitochondria, subcellular cytoplasmic organelles that produce energy for nucleated cells and that do not reside in the nucleus \[7\] of the cell. An organism made via SCNT has mitochondria from the ovum \[8\].

The HFEA claims that research using human stem cells \[5\] would help to test drugs and develop therapies for human diseases and disorders by enabling scientists to design specific stem cell lines to model a particular disease or disorder. The HFEA states that some scientists argue that further research with stem cells \[5\] could lead to the ability to generate organs for individuals who need transplants or replacement, creating organs that are genetically identical to those who need them. The HFEA says that many scientists who the committee surveyed find such research promising.

The HFEA reviewed the policies of other countries on the creation of human-animal chimeras \[4\] for comparison in the next section, "International Perspective". The HFEA states that at the report's publication in 2007, most other countries had not established specific legislature relating to human-animal chimeras \[4\]. At the time of the report, many other European countries did not permit the creation of human cytoplasmic embryos for research under any circumstances, while other countries, including China, permitted their creation under strictly regulated protocols. The only three countries at the time that held relevant legislation were Australia, Canada, and the United States. In Australia, the government permitted human-animal chimeras \[4\] only for research to test human sperm \[11\] quality, after which the scientists must terminate the chimeras \[4\]. Canada prohibited the creation of human-animal chimeric embryos for research purposes. The United States permitted researchers to use federal funds only for human embryonic stem cell research \[13\] with pre-existing stem cell lines. The United States only allowed the research if researchers provided an explicit list of what permissible lines exist, and it prohibited researchers from using federal funds to develop new cell lines. The United States prohibited the creation, or attempt to create, a human chimera with the Draft Human Chimera Prohibition Act of 2005. Appendix C of the HFEA's document reviews the policies of twelve different nations, as well as a description on the different types of policy.

The HFEA describes its process of surveying scientific, social, and ethical issues surrounding cytoplasmic chimeric embryos in "Consultation: The Approach Taken". First, in April of 2007 the HFEA provided UK citizens with a pdf file on its website, "Hybrids and Chimeras: A Consultation on the Ethical and Social Implications of Creating Human/Animal Embryos in Research," to educate the public and to provide a forum for feedback. The HFEA and Opinion Leader, a non partisan research agency in London, obtained public opinion in three steps, first by eliciting and compiling various public views, motivations, and attitudes toward creating chimeric embryos. Opinion Leader hosted group workshops in the UK in 2007 to inform the public, followed by opportunities for questions and discussion.

The second phase of surveying occurred through an opinion poll of 2,060 randomly selected residents of Great Britain and Northern Ireland in June 2007. The HFEA provided information and questions contained in this poll in Appendix F, along with results and statistical data. The poll sought to describe the level of scientific understanding citizens had, as well as their opinions on the ethics of using hybrid embryos in research. Lastly, the HFEA elicited citizens' views through a public meeting in London held 26 June 2007. Here individuals, representatives of interested organizations, and scientists attended a lecture with interactive electronic voting throughout the lecture, followed by an evening of debate. Appendix G listed the topics of the debate and the results of the voting. Finally, in section four, the HFEA describes its methods for scientific literature review. The review explores the history of interspecies experiments, reasons scientist support the use of cytoplasmic hybrid embryos, and whether or not the goals of their use in research are feasible. Appendix B contains the review of scientific literature.

"Themes Emerging from the Consultation" provides the results and interpretation of the data that HFEA collected. This section has nine subsections. The report first discusses the use of human embryos in research, and the HFEA reports that many citizens support using for research spare embryos donated from patients undergoing fertility treatments. Some had mixed opinions on whether the use of animal egg \[14\] cells was preferable to the use of human egg \[14\] cells for research in general, while some worried about the health risks posed to women wishing to donate their eggs. The HFEA also found that scientists had mixed opinions whether SCNT should be performed using human cellular material in stem cell research.

In the second subsection, "Creating human-animal embryos", the HFEA states many citizens were initially repulsed by the idea
of mixing human and animal material. Despite this, some citizens reported that they would support research using cytoplasmic hybrid embryos if it would lead to a better understanding of human biology and of how disease forms. On average, public surveys reported that citizens preferred the use of cytoplasmic hybrid embryos rather than other types of human-animal embryos, such as true hybrids.

The third subsection, "Citing the benefits," explains that although the HFEA made explicit to the public that there were no guarantees that research that used stem cells derived from cytoplasmic hybrid embryos would produce any benefits, the mere potential for significant advancements influenced people’s opinions. The HFEA says that citizens wanted to know the rationale for the creation of human-animal chimeras. Some citizens in the UK said that cytoplasmic hybrid embryos provided an acceptable method of research if researchers achieved a greater understanding of human disease, while others argued that only if results were found would the use of human-animal chimeras be justified. The HFEA says that it finds the potential to improve the lives of humans to be the most important factor in how citizens value the research. Therefore, the HFEA stresses that researchers should communicate a complete, factual picture of this technology to the public, while providing empirical data alongside realistic explanations of the potential benefits.

The report continues with results of opinion surveys in the fourth subsection, "Scientific Worth: Views from the Consultation". The HFEA found that UK citizens in creating cytoplasmic hybrid embryos surrounded ethical issues, such as the meaning of personhood and purity of the human race. The fifth subsection, "Scientific Worth: Evidence from the Scientific Literature Review", addresses questions raised by citizens and other scientists. In reviewing scientific literature, the HFEA found that it would be necessary to reprogram the genome of the donated somatic cell in SCNT to express the proper genes for development, and therefore permitting the embryo to develop. According to the HFEA, many SCNT embryos struggle to develop into later stages, especially interspecies cytoplasmic hybrids because the mechanisms for reprogramming the genome vary between species. In using cellular material from two different species, scientists must ensure that the genetic material is compatible with the cytoplasm's proteins for an embryo to successfully develop.

The HFEA cites cases of successful SCNT human-animal blastocyst and embryo formulation in experiments conducted in China, the United States, and Korea. The HFEA identifies necessary factors for cytoplasmic hybrid embryos to develop and generate viable embryonic stem cell lines. First, there must be a particular number of mitochondria present in the embryo. Second, some of the mitochondria are present in the enucleated ovum, and some are absorbed with the nucleus and cytoplasmic material of the somatic cell used in SCNT. These mitochondria must replicate and express their proteins, regardless of their origins. Lastly, the proteins created from the mitochondria must interact harmoniously with the proteins produced from DNA in the nucleus for the cell to produce energy and survive. Therefore, the DNA and mitochondria of both species must work together for the cell to function properly.

The report explores alternative methods of obtaining stem cells for research purposes in the sixth subsection. "Alternatives to Using Human-Animal Embryos", which offers two possibilities for alternative methods. First, researchers may explore other sources of stem cells. Scientists can genetically reprogram adult stem cells, found in certain areas of the body such as bone marrow, to express properties desirable for research. The second potential source of stem cells is the blood from post-natal umbilical cords. After a human baby is born, researchers could extract stem cells from the blood in umbilical cords. The second option involves reprogramming somatic cells to return them to an undifferentiated state, and like embryonic stem cells, to be able to differentiate into any type of specialized cell.

The HFEA identifies limitations to the two options that could render themuviable. Adult stem cells are difficult to obtain and isolate because they exist heterogeneously throughout the body, even in bone marrow. In addition, stem cells from adults or umbilical cords are not pluripotent like embryonic stem cells; they are limited in the types of cells they form. Until scientists can control the mechanism of differentiation, these alternative types of stem cells will develop into only a select range of cell types. Therefore, stem cells may only hold the potential to treat a specific range of diseases related to the types of cells they form. The potential to treat a wide range of diseases makes embryonic stem cells more practical to use for therapy because they may differentiate into any type of cell. The sixth subsection of the report states that the scientific community argues that all avenues of research to create stem cells should be explored to describe the mechanisms of stem cells and their applications for therapy.

"Concern for the future: The boundaries to research" presented the public's concerns which they voiced through polls and discussions in 2007. The HFEA report conveys a few common apprehensions of citizens, which relate to a series of issues: what constitutes a human, the integrity of what it means to be human, allowing odd and confusing human-animal chimeras to mature to birth, and skepticism to trust scientists with the power to create such creatures. Some citizens supported these technologies, while others said that the costs or potential harm outweighed the benefits. The HFEA reports that some individuals feared that without strict legislature and governance in place, scientists may be irresponsible in their pursuit of knowledge, and the citizens cited the Nazi experimentation of World War II. Others felt that irresponsible scientists would not be an issue if officials informed the public about their research and maintained transparency.

"Regulation: Limits and controls" cites a public concern about the boundaries of research using human-animal embryos. Citizens said that such research and practices, if legalized, should be strictly regulated and monitored. The public supported the establishment of severe legal penalties to those who violate codes of practice. The last subsection of "Themes Emerging from
The consultation," "Levels of Understanding", concludes with a few demographic statistics of those who were polled and who attended the public debates. Most of the citizens polled were previously uneducated about stem cells [8], creating hybrid embryos, and their potential for therapy. There were many misconceptions among the citizens about the actual techniques involved in this research, the intentions of scientists, and existing legislation of research using embryos. Some stated that they perceived a lack of accessible information on these topics, despite the consultation document provided by the HFEA. Those who attended the debates were more informed on relevant topics than those randomly selected for polling, as the debates had a self-selected crowd. The attendees also agreed that the UK public should be kept informed on current research using embryos. The HFEA acknowledges the public's desires, and it agrees that making current and relevant information accessible to the public is important.

The HFEA summarizes its interpretation of the data with eight points in "Conclusions". First, scientists lacked incentives to produce other types of interspecies embryos, including human transgenic embryos, true hybrids, or human chimera embryos. Further, no researchers planned to allow these embryos to mature to birth. Although future developments in science might inspire incentives to do so one day, the HFEA says those slippery slope issues raised by citizens are not of legitimate concern. Second, the HFEA acknowledges a lack of time to explain to the public the importance of all types of embryo research, the different types of chimeric and hybrid organisms, and the different types of research benefits involved. The debates, consultation, and polls focused on the creation and use of cytoplasmic hybrid embryos. Third, the HFEA acknowledges the public's questions about the scientific worth of creating such embryos. Although many scientists support the technology and see it as a promising avenue of research and disease therapy, there is no guarantee of results, making it difficult for scientists to conclusively identify the benefits of this research. Next, the HFEA reiterates the potential benefits of the research as an important aspect in the public's acceptance of creating human–animal cytoplasmic hybrid embryos. The HFEA found that a utilitarian rationale for research is the most critical factor for support among UK citizens.

The fifth point of the "Conclusions" section states that all dimensions of the consultation process addressed and considered alternative methods of deriving human stem cells [8]. The report reviews how scientists could implement adult stem cells [20], umbilical cord [22] blood, the reprogramming of somatic cells, and it reviews the shortcomings of each. The next point acknowledges the interest of the public to be kept current on developments within the field. Seventh, the HFEA notes that private citizens wished to understand the regulatory controls of research involving hybrid or chimeric embryos. Finally, the HFEA concludes that there was a need to develop public understanding of the cellular and molecular mechanisms involved in stem cell research, the creation of hybrid and chimeric embryos, and their potential uses. The HFEA planned to accomplish this by providing accessible scientific information to the public.

The final section of the report, "The Authority's Decision", describes the outcomes of the consultation process. On 5 September 2007, the HFEA met to decide whether or not to license the creation and use of human–animal chimeras [8]. It found the ability to license such research was within its jurisdiction, and it found no reason to prevent the creation of cytoplasmic hybrid embryos for research purposes. The HFEA says that it would review each application individually, and scientists must adequately demonstrate to the HFEA Licensing Committee that their experiments are necessary and ethical. Finally, the HFEA says that it would make greater efforts to educate the citizens on how science and research occur within the HFEA.

The rest of the HFEA's report provides supplementary information and statistical data from their research and polling. First is a glossary of relevant scientific terms used throughout the report. Appendix A contains a timeline of historical influences leading to the creation of human–animal chimeras [46] and hybrids, influential experiments, and legal context. The findings of the scientific literature review are provided in Appendix B. Appendix C provides different views and legislation regarding embryos in other countries. Appendix D summarizes the findings of the written consultation. It provides graphs that illustrate the responses of 810 individuals to the consultation's questionnaire, and it summarizes each question. Appendix E details the public dialogues held during the three months of data surveying, including public speakers, questions raised, discussion topics, and statistics of attendees. Appendix F illustrates the results of the public polling initiative, providing specific questions that the public raised, data interpretation, and graphic representation of the results. The report describes the public meeting in London on 26 April 2007 in Appendix G, including responses participants polled in electronically, names and qualifications of those hosting the event, and an outline of topics discussed.

The HFEA's "Hybrids and Chimeras: A Report on the Findings of the Consultation" led the UK government to make policy about the use of human-animal cytoplasmic hybrid embryos for research in the UK. According to the HFEA, by developing human-animal chimeric embryos using animal egg [14] cells, scientists could have access to the quantities of human stem cells [8] necessary for research on the development of human diseases and disorders, and potentially create new therapies. The HFEA formed the deliberation from months of research and data collection on public and scientific opinion, debates, and data interpretation. Through these methods, the HFEA illustrated methods of public education and inclusion in important legislative processes, while representing the views of the public in its final decision.

Sources

1. Human Fertilization and Embryology Authority. "Hybrids and Chimeras: A Consultation on the Ethical and Social


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- The Embryo Project at Arizona State University, 1711 South Rural Road, Tempe Arizona 85287, United States


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[3] https://embryo.asu.edu/keywords/chimeras