



OPINION OF THE EUROPEAN GROUP ON ETHICS
IN SCIENCE AND NEW TECHNOLOGIES
TO THE EUROPEAN COMMISSION

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**ETHICAL ASPECTS OF RESEARCH INVOLVING THE USE OF HUMAN
EMBRYO IN THE CONTEXT OF THE 5th FRAMEWORK PROGRAMME**

Reference: Opinion requested by the European Commission on 11 September 1998

Rapporteurs: Dr. Anne McLaren
Ms Paula Martinho Da Silva
Prof. Egbert Schroten

The European Group on Ethics in Science and New Technologies (EGE),

Having regard to the request for an Opinion by the European Commission of 11 September 1998 on amendment N°36 tabled by the European Parliament which proposes to exclude from Community funding research projects that "result in the destruction of human embryos", in the context of deciding on the 5th Framework Programme,

Having regard to the Treaty on European Union as amended by the Treaty of Amsterdam to be ratified, and in particular Article 6 (formerly Article F) of the common provisions concerning the respect for fundamental rights, and the Articles 163-173 (formerly Articles 130f-130p) on research and technological development,

Having regard to the proposal for a European Parliament and Council Decision concerning the Fifth Framework Programme of the European Community for Research, Technological Development and Demonstration Activities (1998 – 2002) of 30 April 1997, and in particular Article 6 concerning compliance with fundamental ethical principles, and footnote 2 of Annex II on Scientific and Technical objectives concerning ethical requirements,

Having regard to the Common Position of the Council of Ministers of 23 March 1998 and the second reading of the European Parliament of 17 June 1998, concerning the above mentioned proposal for a Fifth Framework Programme,

Having regard to the proposal for a Council Decision concerning a specific programme for research, technological development and demonstration on "Quality of life and management of living resources" of 10 June 1998, and in particular footnote 8 on ethical requirements,

Having regard to Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions, in particular Article 6,

Having regard to the Resolutions of the European Parliament namely the Resolution on the ethical and legal problems of genetic engineering, and the Resolution on artificial insemination *'in vivo'* and *'in vitro'*", both of 16 March 1989,

Having regard to the Council of Europe Convention on Human Rights and Biomedicine signed on 4 April 1997, and the additional protocol to the Convention on the prohibition of cloning human beings signed on 12 January 1998,

Having regard to the Universal Declaration on the Human Genome and Human Rights adopted by the General Conference of UNESCO on 11 November,

Having regard to national regulations and opinions expressed by national ethical bodies within the European Union on the use of embryonic tissues,

Having regard to the report of the HER working party (Human Embryo Research) (1993) set up by the European Commission,

Having regard to the hearing held on 3 November 1998 by the EGE, with experts, representatives of the European Institutions and of interest groups (health, consumers, industry, religions),

Having heard the rapporteurs.

1. WHEREAS:

SCIENTIFIC BACKGROUND

- 1.1 The first baby to be conceived *by vitro* fertilisation (IVF) outside the mother's body was not born until 1978 in the UK, research on human gametes and embryos donated by infertile couples had been carried out for the previous 10 years. During this period there were no specific regulations concerning human embryo research.

Different objectives of human embryo research

- 1.2 Nowadays, human embryo research in which the embryo does not survive is permitted in several Member States, in particular with the applied objectives of alleviating infertility in the couple or diagnosing serious genetic or chromosomal defects in the embryo.
- 1.3 Some Member States only allow an IVF embryo to be used for research if the research is intended for the benefit of that particular embryo, and if the embryo is subsequently replaced in the uterus. If there existed the possibility that procedures might damage the embryo, this type of experimentation conducted on the embryo *in vitro*, fetus *in vivo* or the mother, is generally judged as being unethical. In practice therefore, the procedures used in this so-called "therapeutic research" are very limited. For the purposes of this Opinion, we confine the use of the term "research" to experiments on embryos which are not intended for transfer to the uterus, and which do not survive.

- 1.4 In other Member States, where research is authorised, research that is not for the benefit of the particular embryo may be permitted under licence. Most of this licensed research is aimed at either improving the success rate and the safety of IVF as treatment for infertility, and investigating the causes of infertility and miscarriage.
- 1.5 Other research projects are concerned with the diagnosis of genetic or chromosomal defects. Some Member States also allow human embryo research for the purpose of increasing knowledge of human development.

Common rules on research in Europe

- 1.6 In the Member States where embryo research is allowed, regulations normally require that any embryos used for research must not be implanted in the uterus, nor may they be cultured *in vitro* for longer than 14 days after fertilisation, a stage that in normal development would mark the end of the implantation process and the last stage at which twinning could occur. Most research projects involve culturing the embryos for a few days only.

Research on supernumerary embryos

- 1.7 In most cases, couples undergoing IVF treatment may have embryos that are in excess of the number that can safely be transferred to the woman's uterus, so-called supernumerary embryos. The couple may decide to store these for their own future use, if cryopreservation is an option, or they may donate them to other couples, or they may donate them for research, or they may decide to let them perish. These supernumerary embryos are the main source of embryos contributing to research projects.

These projects have a number of different aims.

- 1.8 One objective is to increase the "take-home baby" rate after IVF.

The possible beneficial effect of enriching the culture medium with additives (such as growth factors), or culturing them together with supporting cells from the reproductive tract, can be assessed by continuing to grow the supernumerary embryos for a few days longer *in vitro*. The normality of the cultured embryos can then be assessed by biochemical studies or chromosomal analysis.

Another objective is concerned with identifying features of the cultured embryos that might have predictive value for subsequent developmental potential.

Research on supernumerary embryos has also led to the development of safe and reliable procedures for freezing embryos (cryopreservation), so that women/couples may increase the chances of achieving a successful pregnancy by choosing to have any supernumerary embryos transferred to the uterus at a later stage. These cryopreservation methods, developed by the use of human embryo research, are now routinely used in clinical practice of most Member States, and enhance the success rate of IVF.

- 1.9 Different research projects on supernumerary embryos have been carried out to establish the safety for embryo development of removing one or more cells during embryo cleavage for the diagnosis of serious genetic or chromosomal disorders. This technique of preimplantation genetic diagnosis is now used throughout the world. New methods of using enzymes or other gene products to diagnose genetic diseases, and more efficient methods to identify aberrant chromosome constitutions, and to circumvent the problems of chromosomal mosaicism, are under investigation.
- 1.10 Other research projects on supernumerary embryos is carried out in order to produce cell lines (so-called “embryonic stem cells”) which are capable *in vitro* of forming many different cell types and tissues. Various studies along these lines have recently been reported in the US. In the future, such cell lines may be of value in the therapeutic treatment of damage due to accident or degenerative disease affecting skin, heart, kidney or nervous tissue.

Research on unfertilised eggs that are subsequently fertilised in vitro

- 1.11 Other research projects are carried out on unfertilised eggs donated for research and subsequently fertilised *in vitro*. This is an additional source of embryos for research projects, and the only source that can be used for projects involving the process of fertilisation itself, or the early stages of cleavage.

There are both clinical and ethical arguments in support of developing safe methods to cryopreserve unfertilised eggs rather than embryos, for example for their later use by women undergoing cancer treatment. After which, these women become sterile.

Different protocols for freezing and thawing may be followed by attempts to fertilise the eggs *in vitro*. Tests to see whether they develop normally after fertilisation are carried out *in vitro*, as an alternative to transfer to the uterus with the risk of abnormal development *in vivo*.

Other research projects examine the safety of removing first and/or second polar bodies as a possible alternative to embryo biopsy for the purposes of preimplantation genetic diagnosis. They also analyse the risks of using immature sperm for ICSI (Intra Cytoplasmic Spermatozoid Injection) in cases of severe male infertility.

With the aim of minimising the need for hormone stimulation of women, *in vitro* maturation of immature eggs is also being studied, combined with tests on the fertilisability of the *in vitro* matured eggs, and the normality of their subsequent development *in vitro*.

Possible future developments

- 1.12 In the past, research on human eggs and embryos, without any existing legal framework at the time, played a large role in the development of IVF as a treatment for the alleviation of infertility. Today licensed human embryo research is more closely linked to new and constantly evolving techniques of assisted reproduction.

In the near future, other objectives of human embryo research may become extremely important. Basic research in this area increases our understanding of early human development, for example the expression of “cancer genes” in human development.

LEGAL BACKGROUND

Controversies on the concept of beginning of life and "personhood"

- 1.13 Existing legislation in the Member States differs considerably from one another regarding the question of when life begins and about the definition of "personhood". As a result, no consensual definition, neither scientifically nor legally, of when life begins exists.

Two main views about the moral status of the embryo and thus regarding the legal protection afforded to them with respect to scientific research exist:

- human embryos are not considered as human beings and consequently have a relative worth of protection;
- human embryos have the same moral status as human beings and consequently are equally worthy of protection.

- 1.14 The discussion of common rules on embryo research is continuing. Recently many European countries, when discussing and signing the Council of Europe Convention on Human Rights and Biomedicine, failed to reach a consensus concerning the definition of the embryo, and, therefore, were unable to find common ground on which to place the admissibility of human embryo research within the Convention. Hence, it is up to the Member States to legislate in this area. Yet, nevertheless, Article 18.1 of the Convention stipulates “where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo”.

Initial Documentation on embryo research

- 1.15 The first important report published regarding embryo research was the Warnock Report in 1984, which studied this issue in order to examine the social, ethical and legal implications and potential developments in the field of human assisted reproduction. This report recommended important rules on embryo research.
- 1.16 The first specific legislation regarding embryo research was published in 1988 in Spain on artificial reproduction and on donation and use of human embryos and foetuses, including derived tissues, cells and organs. This permitted for the first time research on the “pre-embryo” (“pre-embryo is defined as the initial stage which starts at fertilisation and lasts until 14 days afterwards). Since then, several legislations have come into force, with different approaches regarding embryo research.

Different approaches regarding the definition of the human embryo

- 1.17 In most Member States there is presently no legal definition of the human embryo (Belgium, Denmark, Finland, France, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal and Sweden). Among those Member States which define the embryo in their legislation, the existing definitions vary considerably from one country to another (Austria, Germany, Spain, United Kingdom):
- In Austrian law, the embryo is not defined and the term “developable cells” is defined as inseminated ova and cells developed from them.
 - The German law defines the embryo as “the fertilised human egg cell capable of development, from the moment of fusion of the pronuclei”;
 - The Spanish law makes a distinction between “pre-embryo” (group of cells resulting from the fertilisation of ovum until the implantation and formation of the primitive streak – 14 days), “embryo” (process of forming organs which continues for about two and a half months) and the “fetus” (from two and a half months on);
 - The British law defines the embryo as a “live embryo where fertilisation is complete (i.e. completion is when a two cell zygote appears), including an egg in the process of fertilisation”.

Legal situation in the Member States

- 1.18 Within the EU, there are seven countries with legislation referring to embryo research, which is either treated in a law regarding specifically the embryo (Germany), or included in a law referring particularly to medically assisted reproduction (Austria, Denmark, France, Spain, Sweden and United Kingdom);

The other eight countries do not have legislation referring to embryo research (Belgium, Finland, Greece, Italy, Ireland, Luxembourg, Netherlands and Portugal); from this last group, there are countries where embryo research is implicitly prohibited by the application of constitutional rules (Ireland);

However, five of these countries are at the moment drafting legislation which specifically aims to regulate activities in the field of human embryo research (Belgium) or to insert embryo research in the framework of the medically assisted reproduction law (Italy, the Netherlands and Portugal) or, alternatively, in the domain of medical research (Finland).

Different scope of national legislation

- 1.19 Among the Member States with legal provisions on embryo research, there are many differences regarding the activities allowed and prohibited.

There are countries where embryo research is allowed only for the benefit of the particular embryo (Austria, Germany). There are Member States where embryo research is exceptionally allowed (France, Sweden,), or allowed under strict conditions (Denmark, Finland, Spain United Kingdom).

Diversity in applicable rules

- 1.20 There are some Member States where embryo research is only allowed with the approval by a national authority (Finland, Spain, Sweden, United Kingdom), and/or of a national or local ethics committee (Denmark, United Kingdom).

In other Member States where no legal provisions exist, recommendations (which are not legally binding) from national or local ethics committees or codes of practice promulgated by professional bodies apply (Belgium, Italy and Portugal).

Common rules of existing legislation in the Member States

- 1.21 Despite the different legal approaches, existing legislations in the Member States have some common principles based on similar ethical and scientific understandings which lead to common limitations and prohibitions on embryo research, such as:
- a. the time limit for the use of human embryos – including the carrying out of research activities – is generally only allowed until 14 days after fertilisation;
 - b. the prohibition of genetic modification of normal pre-implanted embryos;
 - c. the prohibition of the creation of developing human-animal hybrids;
 - d. the prohibition to replace embryos *in utero* of embryos that have been previously used for research;
 - e. the need to obtain the consent of each person whose gametes were used to bring about the creation of the embryo.

Legal provisions laid down at European level relating to Human Embryo Research

- 1.22 Some rules applicable directly or indirectly to embryo research, such as:
- The Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions, in which Article 6 (2)(c) stipulates: "...shall be considered unpatentable: ...uses of human embryos for industrial or commercial purposes ..."
 - The Council of Europe Convention on Human Rights and Biomedicine, 4 April 1997, and the additional protocol to the Convention on the prohibition of cloning human beings, 12 January 1998, which refers in Article 18.2 to "the prohibition of the creation of embryos solely for research purposes". The UK placed a reservation on this Article and therefore, the creation of embryos solely for research purposes is allowed but subject to approval by its public authority.

ETHICAL BACKGROUND

Diversity of views

- 1.23 The diversity of views regarding the question whether or not research on human embryos *in vitro* is morally acceptable, depends on differences in ethical approaches, philosophical theories and national traditions, which are deeply rooted in European culture. Two contrasting approaches exist: a deontological approach, in which duties and principles control the ends and consequences of our actions; and utilitarian or consequentialist approaches in which human actions are evaluated in terms of means and ends or consequences.
- 1.24 These views depend on how the status of the embryo is seen. Two tendencies can be distinguished. One stressing that an *in vitro* embryo must be protected as a human being from the very beginning, i.e. after an egg has been fertilised. The other stating that the status of the human embryo, and thus the degree of protection, depends on the stage and the context of development, for example, when the primitive streak appears after approximately two weeks. Also the degree of protection depends on whether an embryo transfer is intended or not.
- 1.25 The diversity in policies and regulations concerning embryo research in the Member States of the EU reflects fundamentally differing views as to the question whether research on human embryos *in vitro* is morally acceptable or not. The EC Working Group on Human Embryos and Research, set up by the European Commission, states, in its first Report [1992,3], that "(t)hese views are fundamentally different and it is difficult to see how, at these extremes, the differences can be reconciled". This is also reflected in the different discussions going on within the national ethics committees that exist in various Member States.

Common values

- 1.26 In spite of these fundamental differences in viewpoints, there are some common values and principles. These values and principles include:
- the respect for human life, from the embryonic stage;
 - the relief of human suffering;
 - the need to guarantee the quality and safety of medical treatment;
 - freedom of research;
 - free and informed consent of the women or couples concerned.

Pluralism

- 1.27 Pluralism may be seen as a characteristic of the European Union, mirroring the richness of its tradition and asking for mutual respect and tolerance.

Ethical questions related to research leading to the destruction of the embryo

- 1.28 IVF technology, as it is applied in most Member States of the EU, usually entails having spare embryos, a decision as to what should (not) be done with them is unavoidable. If other possibilities, including storage (cryopreservation) for later transfer or donation, cannot be implemented, in the end there only exist two options: research (leading to eventual destruction) or destruction.
- 1.29 In spite of the aforementioned stipulations on the Convention of the Council of Europe, the debate continues concerning the source of embryos used for research purposes: supernumerary embryos on the one hand, and unfertilised ova that is subsequently fertilised *in vitro* on the other hand.

2. THE GROUP SUBMITS THE FOLLOWING OPINION:

- 2.1 In the preamble it appeared crucial to recall that the progress of knowledge of life sciences, which in itself has an ethical value, cannot, in any case, prevail over fundamental human rights and the respect which is due to all the members of the human family.
- 2.2 The human embryo, whatever the moral or legal status conferred upon it in the different European cultures and ethical approaches, deserves legal protection. Even if taking into account the continuity of human life, this protection ought to be reinforced as the embryo and the fetus develop.
- 2.3 The Treaty on European Union, which does not foresee legislative competence in the fields of research and medicine, implies that such protection falls within the competence of national legislation (as is the case for medically assisted procreation and voluntary interruption of pregnancy). However, Community authorities should be concerned with ethical questions resulting from medical practice or research dealing with early human development.
- 2.4 However, when doing so, the said Community authorities have to address these ethical questions taking into account the moral and philosophical differences, reflected by the extreme diversity of legal rules applicable to human embryo research, in the 15 Member States. It is not only legally difficult to seek harmonisation of national laws at Community level, but because of lack of consensus, it would be inappropriate to impose one exclusive moral code.
- 2.5 The respect for different philosophical, moral or legal approaches and for diverse national culture is essential to the building of Europe.

From an ethical point of view, the multicultural character of European society requires mutual tolerance to be shown by the citizens and political figures of the European Nation States that have chosen uniquely to tie their destiny together, while at the same time ensuring mutual respect for different historical traditions which are exceedingly strong.

From a legal point of view, this multiculturalism is based upon Article 6 of the Amsterdam Treaty (ex Article F of the Treaty on European Union) which recognises fundamental rights at Union level notably based on “constitutional traditions common to the Member States”. It also declares that “the Union shall respect the national identity of its Member States”.

- 2.6 It results from the aforementioned principles, that, in the scope of European research programmes, the question of research on the human embryo has to be approached, not only with regard to the respect for fundamental ethical principles, common to all Member States, but equally taking into consideration diverse philosophical and ethical conceptions, expressed through the practices and the national regulations in force in this field.

- 2.7 As for the scope of the amendment, concerning the funding of human embryo research, on which the Group has been consulted, the Group is of the opinion that the distinction that could be made between research which implies the destruction of the embryo and research that would enable the embryo to develop to full term would be artificial. With a view to current knowledge and new techniques, it would be an unacceptable risk to implant into a woman's uterus an embryo which previously has been the subject of research and hence may have been damaged. Consequently, the amendment in question proposes not to finance research projects at European level that ultimately end in the destruction of the embryo and in doing so, covers practically all research on human embryos.
- 2.8 In the light of the aforementioned principles and specifications, the Group considers that according to the ethical dimension of the Community's Fifth Framework Programme Community funding should not a priori exclude human embryo research which is the object of different ethical choices in different countries but that this funding should, nevertheless, only be granted under the strict conditions set out in the following paragraphs.
- 2.9 The respect of pluralism does not justify *daissez-faire* attitude. Therefore, the Group repeats the recommendation given in the Opinion n° 10 of 11 December 1997 by the Group of Advisers on the Ethical Implications of Biotechnology (GAEIB) on the "Ethical aspects of the Fifth Framework Programme on Research", according to which "particular attention must be given to the ethical evaluation of research projects concerning the most sensitive fields...".

This presupposes systematic ethical evaluation, at Community level, of protocols of research on human embryos presented for Community funding. Besides, such a recommendation could be included in the Framework Programme itself.

- 2.10 However, the Group considers that amongst the fundamental ethical principles that ought to guide this ethical evaluation, priority should be given to the principle of the respect due to human life, as well as, respect regarding the consent of the woman or couple concerned.

It should also be assured that the project complies, in all circumstances, with national regulations, and that, in particular, the approval from the ethical committee(s) competent at national level has previously been sought.

- 2.11 Moreover, according to the Group, it is crucial to place human embryo research, in the countries where it is permitted, under strict public control, while ensuring maximum transparency, whether the research in question is carried out by either the public or private sector. Indeed, such transparency should be a compulsory requirement of any proposal funded by the 5th Framework Programme, since it provides the best guarantee against major risks of arbitrary experimentation.

- 2.12 However promising the medical perspectives, recent manipulations of human stem cell lines carried out in the US raise a number of ethical questions. These questions emphasise the urgency to enlarge the debate, which is just getting underway. European citizens have a right to be clearly informed about the conflicting values that research is currently facing, as well as to be put in a position to evaluate the responsibilities implied for society as a whole.
- 2.13 In order to clearly set out the most appropriate terms of this debate at European level, specific resources should be made available within the Framework Programme, to permit a global scientific and ethical evaluation of research projects carried out on the human embryo, such as are presently performed in all countries of the European Union where it is permitted. This evaluation should be made public.
- 2.14 The Group re-affirms the desire, already expressed in the aforementioned Opinion n°10, that the European Commission provides itself as rapidly as possible with a system of information, which it seriously lacks at present, regarding all ethical and legal aspects relative to life sciences, at both national and international level. Without such information, the Union would no longer be able to promote the crucial debate concerning the future of our society.

The European Group on Ethics in Science and New Technologies:

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