Deutscher Ethikrat

Human–animal mixtures in research

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PREFACE

Our conception of ourselves as members of the human species rests on the foundation of a clearly defined boundary between humans and animals. Although humans too belong in biological terms to the animal kingdom, morality and law are based on a rigid distinction, which also plays a fundamental part in religion and culture. While art often deals playfully with this difference, it consistently presupposes the existence of humans as its appreciators. The awareness of a clear distinction has never prevented people from crossing in their imagination the boundary which they themselves have drawn. Mythological tradition is replete with reports and images of mixtures of animals and humans. Figures from Babylonian, Egyptian and Greek antiquity – in particular, the Sphinx, Pegasus, the chimaerae, centaurs and mermaids – have retained their place in the visual arts and the world of fairy tales to the present day, and the aesthetic attraction of calling the boundary between species into question is manifest. However, when present-day medicine and biology seek to integrate biological material from humans and animals into a single organism, they have other objectives.

In the field of research, the breeding of mice as "model organisms" for the study of human disorders by the introduction of disease-specific human genes has been commonplace since the 1980s. Considerable advances have since been made. For example, neural precursor cells derived in the laboratory from human stem cells have been transferred into the brains of experimental animals, including primates, for the investigation and possible eventual treatment of disorders such as Alzheimer's and Parkinson's disease. Now the brain is regarded as central to the distinction between humans and animals. That being the case, what should be our attitude to a great ape that suddenly exhibits human behaviour traits? To what category do we assign a mixed entity whose embryonic development was determined by the deliberate combination of human and animal material? Is it ethically acceptable in Germany to conduct experiments such as, for example, those now permitted in the United Kingdom in which a human nucleus was inserted into an enucleated cow egg in order to obtain embryonic stem cells without the use of human eggs? In our assessment, should a distinction be made between mixtures of this kind that remain *in vitro* and ones that are implanted and may even be born?

Such research and its possible consequences compel us to reflect on the validity of the age-old presumption of a clearly defined boundary between humans and animals. What is our understanding of this distinction? What is the justification for it? What is its significance for man's[1] conception of himself, and what are its consequences for his treatment of animals? What are the ethical implications of recent developments in research that have increasingly called into question the biological boundary between humans and animals? Given the manifestly gathering pace of progress in research, it is essential to determine as of now whether binding limits must be set, and if so, where they should be drawn.

The present Opinion of the German Ethics Council is intended to help clarify the distinction between humans and animals, to facilitate the evaluation of developments with ethical implications in research involving the creation of human–animal mixtures, and to indicate where action is called for on the part of science, society or politics.[2]

The expression "human–animal mixture", or simply "mixture" or "mixed entity", is used in this Opinion as a generic

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1 The word "man" is used in this translation to denote the human species and does not imply the masculine gender. In addition, for convenience the masculine form is used where applicable throughout this translation for both sexes [translator's note].

2 Opinions on these issues have also been published by, for example, Academy of Medical Sciences (2011, United Kingdom); Bioethics Advisory Committee (2010, Singapore); Danish Council of Ethics (2008, Denmark); Human Fertilisation and Embryology Authority (2007, United Kingdom); and Scottish Council on Human Bioethics (2006, United Kingdom).

term for living organisms, even at very early stages of development, that include both human and animal components (genes, chromosomes, nuclei, cells, tissues or organs).

The document concentrates on the transfer of human material to animals. The ethical problems of xenotransplantation – i.e. the transfer of animal material to humans – on the other hand, are not considered.

1 GENERAL CONSIDERATIONS AND DEFINITION OF VARIOUS MIXED ENTITIES

1.1 Chimeras and hybrids

A chimera is defined in medicine and biology as an organism made up of genetically diverse components (cells, tissues or organs), which nevertheless constitutes a unified individual. For the purposes of this broadly based definition, it is immaterial whether the various cells come from individuals of the same species (as in an intraspecies chimera, for instance when an organ is transplanted from one human being to another) or from different species (interspecies chimeras, as in xenotransplantation). Interspecies chimeras can arise from the transplanting of cells, tissues or organs into an organism of a different species (before or after birth) or from the experimental fusion of embryos of different species (the "geep", a goat–sheep chimera, is an example). In the latter case, the result is a mixture in which cells of differing origin develop alongside each other throughout the prenatal phase. However, so far as is known today, such an entity is fully capable of development only if the species are closely related.

A mammalian organism formed from the union of egg and sperm cells so that all its subsequent cells have the same genetically mixed composition is said to be a hybrid. In the case of intraspecies hybrids, the egg and the sperm come from parents of the same species. Strictly speaking, every natural process of reproduction thus results in a kind of hybrid; however, within the discipline of biology, the term is predominantly used only when the egg and sperm cells originate from parents of different species (interspecies hybrids, such as the mule, which is a cross between a horse and a donkey).

The generic term "mixture", or "mixed entity", which covers both interspecies chimeras and interspecies hybrids, is used in this document, which, however, concentrates on human–animal mixtures. These are living organisms which include both human and animal material in different (albeit sometimes only small) proportions.

Not all human–animal mixtures can be clearly identified as chimeras or hybrids.[3] Again, experimental researchers have been using new techniques to develop mixed forms in which foreign genes or chromosomes are incorporated in embryonic cells so as to breed organisms having a unified mixed-species genetic endowment in all cells, like a hybrid – for example, a transgenic mouse with a human gene. The characteristics of the mixture depend not only on the nature of the mixed materials, but also, and crucially, on the scale and timing of mixing. A more detailed description of the techniques that may give rise to mixed entities is presented in Section 1.3. First, however, the following fundamental considerations on the boundary between species will facilitate classification of the mixed entities introduced below.

1.2 Considerations on the boundary between species

In biology, each living organism is assigned, in the discipline of taxonomy, to a given genus and species.[4] In this system, the species represents the lowest level of classification.

Throughout most of the cultural history of mankind, which is a very short period in the overall process of evolution, species were seen as fixed categories and distinguished mainly in accordance with their external features – in particular, their form and behaviour. This constitutes the typological conception of

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3 For this reason the use of the term "chimbrids" has been proposed to cover both chimeras and hybrids; see Taupitz/Weschka 2009.

4 For example, the genus of chimpanzees (*Pan*) comprises two species, the common chimpanzee (*Pan troglodytes*) and the bonobo or pygmy chimpanzee (*Pan paniscus*).

species. An example is the biblical account of the Deluge, before which the animals are taken "two and two" into the Ark and thus saved in accordance with the species to which they belong.

A conception of this kind, with unchanging categories for living things, plays an important part to this day both in man's understanding of himself and in his cultural, religious and also philosophical image of humanity and nature. It is also reflected in the scientific typology of species that originated in the eighteenth century with Linnaeus. The objectives and strategies of species protection, too, are based on the typological conception of species, concerning as they do the preservation and care by humanity of certain animal and plant species found in the wild, considered to merit protection because they are endangered, in their natural and historical diversity (hence the expression "diversity of species"). As in the past, the typological conception of species retains an essential role in all cases where external features are the best, or the only, indication of a relationship between two organisms, for instance in palaeontology. Even today, this conception remains the basis of a number of laws (on the protection of nature, animal welfare, and species preservation).

Since the nineteenth century, the concept of the variability of species has increasingly gained ground in biology. According to this approach, evolution also takes place within one and the same species in a process of differentiation that eventually leads to the emergence of new species. This is manifestly attributable partly to epigenetic environmental effects. Nevertheless, the species is seen in present-day population genetics as a reproductive community. Mating between members of different species either does not occur or results in infertile progeny; reproductive isolation, as it is known, prevails between species. However, some quite closely related species do not interbreed in nature either owing to prolonged geographical separation or because of mutual hostility. If this separation is overcome, the result is the formation of a hybrid, such as the

Italian sparrow, a mixture of the house sparrow and the Spanish sparrow. Lions and tigers in captivity, too, can interbreed.

On the level of genetics, molecular and cell biology, both close relationships and significant differences between species can be demonstrated. Humans and chimpanzees, for example, share over 98 per cent of their genetic material. Yet despite this close genetic relationship, major differences are observed in anatomy and physiology, as well as in behaviour and cognition. Analysis of the differences between species is increasingly concentrating on more complex, systemic distinctions between similar genetic material – e.g. when genes are switched on and off, what effect this has on the synthesized proteins, and how the organization of gene networks and groups of cells differs.

The species barrier can be demonstrated not only by precision genetic techniques in the laboratory. It is "defended" in mammals by the development, on the part of species, of immunological mechanisms of recognition by which foreign proteins can be identified and then eliminated. If protein from another species is injected into the blood of an adult organism, a powerful immune reaction results. Transplants of foreign cells and tissues are likewise rejected and eliminated from the body's tissue complex.

The notions outlined here are not all equally applicable to determination of the species to which each life form belongs. Our analysis of human–animal mixtures is based on the following definition of a *species*:

A biological species is an empirically determined, self-contained reproductive community of shared descent that forms a genetic, ecological and evolutionary unity. As a rule it exhibits common features (anatomy, physiology, immunology, behaviour and cognition) which distinguish its members from those of other species.

1.3 Experimental techniques giving rise to mixed entities

In the last few decades, experimental biology has developed procedures that allow genes, cells or tissues ("materials") from two species to be mixed. The following table lists the various biotechnological procedures and shows the fields in which they are already, or could be, used in humans too.[5] It should be borne in mind that all these procedures are equally applicable to the mixing of materials from two individuals of the same species. However, only interspecies mixtures are considered here.

1.3.1 Transplantation

The transplantation of cells, tissues or organs from one species into a receiving organism of another species gives rise to *chimeras*. A distinction must be made according to whether the transplant into an organism was effected after the differentiation of rudimentary organs ("transplantation chimera") or the materials of the two organisms were united prior to organ development ("embryonic chimera") so that they shared in this development.

In the former case, the influence of the donor material is usually limited, as transplanted materials must find their way into an already fully functioning organism constructed in accordance with the blueprint of the receiving species. An example of a transplantation chimera is the transfer of human cancer cells into a mouse. In the case of an embryonic chimera, entire organs or organ systems may consist exclusively or predominantly of cells from either one or the other species or develop into composite forms to which cells of both species contribute. The germ cells of the sexually mature organism, too, may then stem from one of the species or even from both.

5 See also the tabulation in Taupitz/Weschka 2009, 439 f.

Techniques that may give rise to human–animal mixtures

Procedure	**Initial material**	**Recipient**	**Result**	**Examples of application/ research interests**
Transplantation	Cells, tissues or organs	From early embryo to postnatal organism	Chimera	Animal → human: therapeutic xenotransplantation Human → animal: study of the development of human cells, tissues and organs; preclinical studies for stem cell therapy
Somatic cell nuclear transfer	Somatic cell nucleus	Enucleated egg	Cytoplasmic hybrid (cybrid); the DNA in the nucleus comes from one organism and the mitochondrial DNA from another	Human → animal: derivation of specific human embryonic stem cells without the use of human eggs
Gene transfer	DNA segments	Fertilized egg, embryonic stem cell	Transgenic organism	Human → animal: production of human proteins in animals; genetic tests and drug trials
Chromosome transfer	Chromosome(s) from somatic cells	Embryonic stem cell	Transgenic organism with foreign chromosomes	Human → animal: study of the regulation and function of human chromosomes
Embryo fusion	Embryo	Embryo	Chimera	No manifest scientific interest at present
Gamete fusion	Sperm from one species	Egg from other species	Hybrid or activated egg	Human → animal: clinical fertility test (human sperm, hamster egg); historical: human–ape hybridization

An organism having the external appearance of one species may then produce eggs or sperm of another species.

Chimeric mixtures of humans and animals are created in fundamental research in order to study the functioning of human cells, tissues or organs in animals.

In therapeutic research, human cells and tissues are transplanted into experimental animals in order to conduct invasive observations, measurements and interventions that would not be ethically acceptable in man. The aim of such studies is to investigate scientific and medical problems *in vivo* – that is, within a living organism – with all the relevant influences.

Preclinical studies are explicitly concerned with the effects of transplantation on the (usually already fully mature) receiving body, in the hope that therapeutic effects will be obtained from the human cells or tissues thus transplanted. If the results are promising, the next step is the transplantation of human materials into human recipients.

In the field of treatment, research is also conducted on transplants in the opposite direction – i.e. of animal materials into humans. The aim in this case is to overcome the scarcity of donated organs and tissues for the therapy of human disorders or organ damage by the use of animal materials. The current scientific focus is on transplants of pig tissues and organs, which are seen as particularly suitable by virtue of their physiological and biochemical characteristics. The research concerns genetic manipulation for the breeding of "humanized" pigs in order to avoid rejection, blood clotting in the transplanted organ and risks due to retroviruses integrated within the pig genome. Initial clinical studies are now in progress on the transplantation of porcine islet cells into the pancreas of diabetics. The transfer of animal cells into the brains of patients suffering from Parkinson's disease, on the other hand, has not met with the hoped-for therapeutic success.[6]

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6 According to oral communication from Guido Nikkhah at an expert meeting of the German Ethics Council held in Berlin on 26 August 2009 (unpublished).

1.3.2 Somatic cell nuclear transfer

Cloning by the "Dolly method" (somatic cell nuclear transfer) can be used to produce a particular form of hybrid, a *cytoplasmic hybrid*, or cybrid. Here, a cell nucleus from an individual of one species is transferred to an enucleated egg taken from an individual of another species. The resulting embryo has the nuclear genome of one species, but also includes a few genes of the other species in the mitochondria[7] of the egg's cytoplasm. The nuclear genome in man has some 25 000 genes, but the mitochondrial genome possesses only 37, these, however, being essential to the formation of the organism. If such an entity develops as an embryo, the result is a cybrid, with a human nuclear genome and animal mitochondrial genes.

Research on human–animal cybrids is being conducted in several countries using cow or rabbit eggs with a view to the derivation of stem cells. It is unknown whether a viable organism could arise from them, although the results of animal experiments suggest that this would be possible only in exceptional cases with very closely related species. Live births have taken place to date only in mouflon–domestic-sheep[8] and African-wildcat–domestic-cat cybrids.[9] Cytoplasmic hybrids of distantly related species, such as primates and bovines or cats and rabbits, on the other hand, have always died in experiments so far at the embryonic or fetal stage of development.[10] In this situation, it therefore seems unlikely that a viable organism could arise from human–animal cybrids in which the donor egg is obtained from a cow or rabbit. Authorities disagree on whether this artificial procedure might lead to therapeutically useful human embryonic stem cells (see Section 2.2.1).

7 The mitochondria are the cell's "power plant", supplying it with energy. They are thought to possess a genome of their own because they were originally bacteria which fused in the course of evolution with the precursors of today's eukaryotes (cells with nuclei).
8 See Loi et al. 2001.
9 See Gómez et al. 2004.
10 See Wen et al. 2003; Beyhan/Iager/Cibelli 2007; Lorthongpanich et al. 2008.

1.3.3 Gene transfer

Even if only isolated genes of a foreign species are present in all cells of the receiving organism, the *transgenic animals* concerned are hybrids in accordance with the above definition. The animal model with a human gene is used to study the functioning of this gene. Research projects are already in hand with the aim of thereby breeding animals to produce medically useful human proteins, for example in their milk.[11]

1.3.4 Chromosome transfer

The transfer of complete chromosomes between species is possible and has been demonstrated by, for instance, the introduction of human chromosome 21 into mice.[12] The resulting mice are "transchromosomal" and must be classified as hybrids since all their cells have the same genetic endowment. Humans whose cells have three copies of chromosome 21 suffer from Down's syndrome (trisomy 21). The mice resulting from the transfer of the human chromosome are studied as an animal model for Down's syndrome, as they exhibit many similar symptoms.

1.3.5 Embryo fusion

The fusion of two embryos of different species at a very early stage of development gives rise to a chimera that carries the cells of two species in approximately equal proportions. In this case, there are therefore no unequivocal donor and recipient species, so that the resulting organism can no longer be assigned predominantly to one or the other species. A now

11 See Drohan/Lubon/Velander 1997.
12 See O'Doherty et al. 2005.

classical example of such a chimera is the "geep" mentioned earlier, born in 1984 from the fusion of a sheep embryo with a goat embryo.[13] However, there is no evidence that the fusion of animal and human embryos is currently being studied, or indeed even proposed.

1.3.6 Gamete fusion

Sperm of one species can be injected into eggs of another, or otherwise made to fuse with them. The penetration of human spermatozoa into a hamster egg is used as a diagnostic test of the penetration capacity of human sperm cells. However, this "hamster test" does not give rise to hybrid embryos capable of development, since a functional nucleus cannot form. In the 1920s, the Russian biologist Ivanov attempted to create human–great-ape hybrids by cross-species insemination.[14] These experiments were unsuccessful and have not been repeated since.

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13 See Fehilly/Willadsen/Tucker 1984.
14 See Rossiianov 2002.

2 THREE CURRENT FIELDS OF RESEARCH AS EXAMPLES FOR THE ETHICAL EVALUATION OF THE FORMATION OF MIXED ENTITIES

2.1 Introduction

As the above overview shows, many procedures are available for the creation of mixtures composed of material from humans and animals. However, the ethical issues arising from these possibilities are relevant irrespective of the specific aspects of each procedure. The German Ethics Council considers it appropriate to undertake an ethical appraisal of human–animal mixtures in three fields which particularly lend themselves to consideration as examples. One example of each of these fields will be examined in detail below in order to provide an objective foundation for a differentiated ethical assessment for the purposes of the legal and ethical considerations developed in Sections 3 to 5 (see Section 6):

- *In vitro* creation of human–animal mixtures for research without transfer into a uterus, considered by the example of cytoplasmic hybrids (cybrids);
- Experimental creation of human–animal chimeras or human–animal hybrids carried to full term, considered by the example of transgenic animals;
- Chimerization by the transplanting of cells or tissues after the development of organ primordia in the receiving animal (in the fetus or postnatally), considered by the example of brain chimeras (the transplantation of human cells into the central nervous system of experimental animals).

These fields of research have recently given rise to substantial ethical controversy. Our selection permits the discussion of prominent aspects of the issue of human–animal mixtures

– namely, the formation of chimeras and hybrids as such; the mixing of prenatal and adult cell components, cells and tissues; and the possibility of transmission of features foreign to the relevant species via the germline. On the basis of its ethical examination, the German Ethics Council wishes to develop an evaluation paradigm that can be applied analogously to other forms of human–animal mixtures, with the focus on the transfer of human material to animals.

Experiments with human–animal mixtures are also conducted using non-human primates.[15] Owing to their close relationship to man, particular research issues arise, as well as appreciable ethical problems.

Primate experiments have been crucial to a number of medical breakthroughs. They permitted the development of vaccines to combat the microbial and/or viral pathogens responsible for communicable diseases such as poliomyelitis, AIDS, malaria, tuberculosis, viral hepatitis and severe acute respiratory syndrome. The same applies to therapies for the treatment of neurological disorders such as multiple sclerosis and Parkinson's disease.[16] In addition, most of our knowledge of the functions of individual brain structures, which is a cornerstone of present-day clinical neurology, is based on animal experiments with non-human primates. This knowledge is particularly relevant to interpretation of the results of imaging techniques.[17]

However, by far the highest proportion of the non-human primates currently used for scientific purposes is accounted for not by fundamental research, but by statutory toxicity and safety assessments, in particular for pharmaceutical products. This predominantly concerns the evaluation, testing and

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15 The term "primates" denotes an order of mammals comprising all prosimians, monkeys, lesser and great apes, as well as, in biological terms, man. "Non-human primates" thus signifies all primate species except humans.

16 See Scientific Committee on Health and Environmental Risks 2009; Weatherall 2006.

17 See Straumann 2007.

production of vaccines before they are used in humans.[18] Some 10 000 primates are used annually within the European Union[19] (over 100 000 worldwide), 67 per cent of them for toxicological tests and safety assessments in pharmaceutical research.[20] Overall, primates account for less than 0.1 per cent of the experimental animals used in the EU.[21] In Germany, about 167 primates are employed in fundamental research each year.[22] Great apes[23] have not been used in Germany since 1991.[24]

2.2 General description of current research activities

2.2.1 Cytoplasmic hybrids (cybrids)

A cytoplasmic hybrid, or cybrid, is defined as a living cell created by the fusion (hybridization) of an enucleated egg with the nucleus of an individual of a different species. This involves a cloning process using cell nuclear transfer, as the genetic information of the donor nucleus is copied during cybrid development (see Section 1.3). In the context of human–animal mixtures, the situation to be considered here will be that of a human nucleus and an enucleated animal egg.

There is to date no record of research involving the transfer of animal nuclei into human eggs. However, human nuclei have been transplanted into animal eggs with a view to the derivation of stem cell lines as research tools. A possible aim would be, for example, to produce cell lines from genetic variants of patients with inadequately investigated widespread severe disorders such as Alzheimer's or Parkinson's. These cell

18 See Animal Welfare Report 2007 (*Deutscher Bundestag* 2007a, 27).
19 See Scientific Committee on Health and Environmental Risks 2009, 9.
20 See Scientific Committee on Health and Environmental Risks 2009, 10.
21 See Scientific Committee on Health and Environmental Risks 2009, 11.
22 See Animal Welfare Report 2011 (*Deutscher Bundestag* 2011, 52).
23 The great apes comprise the gorilla, the orang-utan and the chimpanzee.
24 See Animal Welfare Report 2011 (*Deutscher Bundestag* 2011, 27).

lines would be used for laboratory experimentation – i.e. in cell culture – for detailed research on the variations and with a view to finding ways of correcting the defect. The use of animal eggs is intended to replace the ethically questionable application of human eggs, the harvesting of which also presents a health risk.

In the long term, it is hoped that cytoplasmic hybrids will permit the creation of patient-specific pluripotent stem cells, from which cells that are to all intents and purposes genetically identical to those of the patient can be cultured for therapeutic use. A cybrid consisting of a human–animal germ cell possesses the complete genetic information of the human nucleus. However, the cytoplasm still includes a very small proportion (less than 0.1 per cent) of animal DNA capable of independent multiplication in the mitochondria, the cell's power plant. This small proportion performs an important function during early embryo development.[25]

In 2003, a Chinese group led by Hui Zhen Sheng published details of research claiming that embryonic stem cells had been derived from cytoplasmic hybrids using rabbit eggs.[26] However, it has not so far been possible to replicate these results. Current studies paint an appreciably more critical picture of the development potential of cytoplasmic hybrids. Although Hui Zhen Sheng's team reported in 2008 on human–bovine cytoplasmic hybrids that survived to the blastocyst stage and successfully activated the stem cell genes,[27] the study by Robert Lanza's group published in 2009 showed that human–bovine cytoplasmic hybrids failed to activate three of the genes essential to stem cell development (NANOG, Oct4 and Sox2) and died after reaching the 16-cell stage.[28] Increasing doubts have since been expressed as to the prospects of success. For instance, although cybrid research was declared permissible

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25 See Facucho-Oliveira/St. John 2009.
26 See Chen et al. 2003.
27 See Li et al. 2008.
28 See Chung et al. 2009.

in the United Kingdom only in 2008, it has now ceased again for the time being as funding applications have been turned down.

To sum up, therefore, research on cytoplasmic hybrids has so far not lived up to expectations. However, owing to the dearth of data available, a final assessment of the technique's potential would be premature.

2.2.2 Transgenic animals with human genetic material

Transgenic organisms are defined as living entities whose genetic material has been modified by technical manipulation in such a way as to integrate either foreign or synthetically produced genetic material into the cell nucleus. The genes are transferred by various methods at a very early stage of individual development. As an alternative to, or in combination with, the transfer of foreign genes, individual genes can be deactivated, thus giving rise to "knockout" animals. All the cells of the transgenic animal always carry the genetic modification, which is also inherited via the germline. However, expression of the genetic modification may be confined to specific tissues (e.g. brain or blood cells).

A pioneering project in 1997 involved the creation of mice into whose genome a human chromosome was introduced by microcell-mediated transfer.[29] Recent techniques in the field of synthetic biology seek to produce artificial chromosomes or parts of chromosomes from human genetic material and to add them to the animal genome.[30]

The creation of transgenic animals with human genetic material is widespread both in fundamental research and in

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29 See Tomizuka et al. 1997; Rigos 1997.
30 See for example German patent application DE 10 2007 043 131 A1, disclosed on 12 March 2009.

applied medical research. The study of human genes in experimental animals is relevant, for example, wherever their functioning and regulation at molecular level is to be explored or experimentally modified in the living organism. Such experiments are either impossible or undesirable in humans. For instance, the effect of medicinal products or environmental contaminants is investigated in mice which carry human metabolic genes.[31] By means of the transfer of human genes, animal models of specific human disorders are created and can be used for more detailed examination of the pathological interactions at molecular level. Transgenic models of this kind exist for such disorders as Alzheimer's[32] and certain mental illnesses.[33] However, the transposability of the results to man varies substantially.[34]

In the course of scientific research to date, human transgenes have been introduced mainly to specific experimental animal species – in particular, mice, rats, fruit flies and zebra fish, as well as primates.[35] A primate model of Huntington's disease was developed for the first time in 2008, the relevant human gene being integrated into the genome of a macaque;[36] and in 2009 transgenes were stably introduced into the germline of marmosets.[37] These primates showed clinical manifestations of Huntington's disease.[38] Recent studies report stem cell lines obtained from the tissue of transgenic primates, suitable for use as a model to investigate the pathogenesis of this disorder.[39]

Initial attempts have been made to use transgenic domestic animals for the production of medically useful proteins. One

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31 See Cheung/Gonzalez 2008.
32 See Games et al. 1995.
33 See Otte et al. 2009.
34 See Lynch 2009; Morrissette et al. 2009.
35 In 2009, 591 459 transgenic mice, 8380 transgenic rats, 353 transgenic rabbits, 181 transgenic pigs and 7271 transgenic fish were used in Germany for scientific purposes (see Animal Welfare Report 2011 [*Deutscher Bundestag* 2011, 62]).
36 See Yang et al. 2008.
37 See Schatten/Mitalipov 2009; Sasaki et al. 2009.
38 See Yang et al. 2008; Chan et al. 2010; Laowtammathron et al. 2010.
39 See Chan et al. 2010; Laowtammathron et al. 2010.

of the first commercial applications concerns goats whose milk contains the anticoagulant antithrombin.[40]

A particular ethical issue is whether the transfer of individual human genes might sometimes alter important characteristics of the receiving species in such a way as possibly to affect the animal's moral status. Drastic modifications of this kind are at least conceivable at biological level. For example, a recent study in which the FoxP2 gene, which is involved in the development of human speech, was transferred to mice can be seen as an initial step in this direction.[41] The vocalizations of the mice subsequently showed changes. Alterations in brain structure were also observed, possibly indicative of improvements in certain aspects of learning behaviour.[42] In the last few years, genome research has shown that the genetic material of animals that differ greatly in appearance sometimes has a great deal in common, so that their species-specific features are attributable only to differences in the timing and location of gene activity. It is therefore not improbable that, as more and more of the genes responsible for this control of timing and location are identified, more ways will be found of manipulating them so as to modify complex characteristics on a cross-species basis in transgenic animals.

2.2.3 Transfer of human cells to fetal or adult animals (brain chimeras)

Human cells are transplanted into animals in preclinical studies in order to investigate the relevant therapeutic effects. The long-term aim of such experiments is the development of therapies involving the transplant of human cells into the human

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40 See Edmunds et al. 1998. The transgenically produced antithrombin has been marketed as ATryn since 2008 by GTC Biotherapeutics (see http://www.gtc-bio.com/products/atryn.html [2011-06-20]).
41 See Newbury/Monaco 2010.
42 See Enard et al. 2009.

body to treat accident- or disease-related destruction of cells and tissues as, for example, in dementia, stroke or Parkinson's disease.

Animal-model investigation of stem cells isolated from patients is also a promising concept. The purpose of such work is to demonstrate a possible functional defect in the patient's endogenous stem cells. Such studies may concern, for example, patient-derived induced pluripotent stem cells[43] which exhibit a genetic mutation.[44] In addition, age and various pathologies are known to have the potential effect of restricting the endogenous functioning of stem cells.[45] Hence there are certainly good reasons for animal-model investigation of these congenital or acquired functional defects in cells isolated from human subjects.

Particular ethical issues are raised by the possibility that the transplant of human nerve cells or their precursors into the brains of animals – in particular, primates – might give rise to human capabilities in the animal that could in certain circumstances alter its moral status.

The most recent discussion of this controversial question dates from 2005.[46] Researchers led by Ahmed Mansouri at the *Max-Planck-Institut für Biophysikalische Chemie* (Max Planck Institute for Biophysical Chemistry), Göttingen, and a team under Eugene Redmond jr. at Yale University had transplanted human stem cells into primate brains. Whereas the German experiments were soon aborted, those of Redmond and his group, as well as similar experiments, are ongoing.[47]

It is at present difficult to determine whether, over and above the repair of neuronal and cognitive deficiencies due to injury or disease, an animal's cognitive capabilities could be enhanced,

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43 Induced pluripotent stem cells are derived by the reprogramming of somatic cells.
44 See Ye et al. 2010.
45 See Dimmeler/Leri 2008.
46 See Traufetter 2005; Shreeve 2005.
47 See Redmond jr. et al. 2007; Redmond jr. et al. 2010.

or the animal otherwise humanized, by the transplanting of human cells. There are indications that the neuronal network structure of the donor material may be preserved when entire pieces of brain tissue are transplanted.[48] However, research to date indicates that only a small proportion of individual nerve cells transplanted into a mature brain is integrated into local neuronal networks. Again, their behaviour is dominated by their environment in the recipient's brain rather than by their genetic endowment.[49] The therapeutic effect of such transplants may sometimes be due not to functional integration of the cells into the brain's network, but to the pharmacological action of messenger substances released by the donor cells.[50]

Even where human nerve cells are successfully integrated into an animal, doubts persist as to whether functioning networks with human characteristics could arise at all in the limited space of, say, a rodent brain, as the human brain is particularly large and features complex three-dimensional structures.[51] So even if it proved feasible to create a mouse with a brain consisting entirely of human nerve cells – something hitherto confined to the realm of a thought experiment – it is very unlikely that the result would be a mouse possessing a brain with a human structure and human cognitive capabilities.[52]

On the other hand, animal experiments show that transplants of different, as yet immature animal neural tissues between closely related species can indeed give rise to mixed entities with chimeric brains that display behaviours characteristic of the donor species. This was the case with chicks that produced quail-like vocalizations after the transplant of quail brain tissue.[53]

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48 See Madrazo et al. 1988.
49 According to oral information from Guido Nikkhah and Henning Scheich at an expert meeting of the German Ethics Council held in Berlin on 26 August 2009 (unpublished).
50 See Joyce et al. 2010; Shimada/Spees 2011.
51 See Greely et al. 2007.
52 See Greely et al. 2007.
53 See Balaban/Teillet/Le Douarin 1988.

As in all forms of interspecies mixtures, the rule is that integration with functional consequences is more likely in closely related species and at immature stages in the development of the donor materials or those of the recipient.

Interest in the transplanting of human cells into animal brains – in particular, those of primates – is likely to increase further in the future, partly on account of the great advances being made in the field of induced pluripotent stem cells. This also raises the issue of the need for primate experiments as a necessary basis for clinical studies on the human brain. However, there is at present still a dearth of appropriate ethological analyses of the possible occurrence of qualitative changes in the behaviour of animals with human cells in their brains.

3 THE CURRENT LEGAL SITUATION IN GERMANY

Apart from the *Grundgesetz* (Basic Law), Germany has two laws of particular relevance to the subject of human–animal mixtures – namely, the *Embryonenschutzgesetz* (Embryo Protection Act) and the *Tierschutzgesetz* (Animal Welfare Act). The *Gentechnikgesetz* (Genetic Engineering Act) or the *Arzneimittelgesetz* (Medicinal Products Act) may also be applicable in certain circumstances. The *Transplantationsgesetz* (Transplant Act), on the other hand, is not relevant, because it concerns only the removal of *human* organs and tissues and their transfer to a *human* recipient.

3.1 Constitutional framework

The Basic Law (GG) does not contain any specific provisions on human–animal mixtures. Instead, it includes, on the one hand, requirements that concern human beings – both as the target group of legislation and as subjects of protection – and, on the other, provisions on animal welfare.

3.1.1 Target and subject of protection of fundamental rights

Only humans are covered by the field of application of the fundamental rights, such as the right to life or to physical integrity (Article 2(1) GG).[54] An animal cannot enjoy fundamental rights.

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54 Sachs, in Sachs 2009, Article 19 para. 10; the limited applicability of fundamental rights to legal entities pursuant to Article 19(3) GG need not be considered here.

However, the Constitution has nothing to say about the possible fundamental rights of a human–animal mixture. An "intermediate rights situation" between humans and animals is at any rate foreign to it. In order to determine whether an entity is entitled to the protection of fundamental rights or instead benefits from the provisions on animal welfare, that entity must therefore be assigned to either the "human" or the "animal" category. The Constitution offers no indication of the criteria for this classification.

However, the creation of human–animal mixtures could infringe the human dignity of the human subjects who might thereby be affected.[55] Again, the guarantee of human dignity is a constitutional principle of "all-embracing universality"[56] and the fundamental "orienting decision on values"[57] of our Constitution. This may perfectly well lead to a situation in which the creation and/or use of human–animal mixtures infringes human dignity in the sense of the dignity of the human species.[58] These considerations are addressed in Section 4.

With regard to *in vitro* research, the divergent views on the moral and constitutional status of an embryo *in vitro* are relevant; however, it is not necessary to discuss these again here, as they are not specific to the subject of human–animal mixtures.[59]

3.1.2 Animal welfare

Although animals or human–animal mixtures not assigned to the "human" category do not enjoy fundamental rights, they are nevertheless protected by the Constitution. Under Article 20a GG, the state, mindful also of its responsibility to future

55 Herdegen, in: Maunz/Dürig 2011, Article 1(1) para. 107.
56 Höfling, in: Sachs 2009, Article 1 para. 9.
57 Dreier, in: Dreier 2004, Article 1 I para. 42.
58 Höfling, in: Sachs 2009, Article 1 para. 27.
59 On this point, see, for example, German Ethics Council 2012, 32 ff.

generations, protects the natural foundations of life and animals in the framework of the constitutional order. Hence animal welfare is firmly embodied in the Constitution as a principle of law.[60]

All animals benefit from the protection of Article 20a GG. The mention of animal protection in that article, while providing for particular responsibility, does not mean that animals are equated with man in ethical, let alone legal, terms.[61] The state's duty of protection relates primarily to more highly developed animals, whose capacity for suffering and feeling demands that they be treated in a morally responsible manner.[62] With regard to animal welfare, the state aims at the graduated level of protection provided for in the Animal Welfare Act, under which, for example, vertebrate animals enjoy more protection than invertebrates. The distinction is ultimately based on differences in the animals' degree of "similarity to humans".[63] The more a creature resembles man, the more extensive the protection it enjoys.

3.1.3 Freedom of research

Article 5(3) GG guarantees the freedom of research. Unlike other fundamental rights (such as the right to life provided for in Article 2(2) GG), there is no requirement of a specific statutory provision; that is to say, this freedom does not depend on the existence of relevant statute law. Instead, only conflicting fundamental rights of third parties and other rights-related values endowed with constitutional status, such as animal welfare, can restrict the freedom of research in individual

60 Jarass, in: Jarass/Pieroth 2011, Article 20a para. 1.
61 Murswiek, in: Sachs 2009, Article 20a para. 31b.
62 Murswiek, in: Sachs 2009, Article 20a para. 31b; see also *Deutscher Bundestag* 2002, 3.
63 Kloepfer/Rossi 1998, 369 f.; Lübbe 1994.

situations.[64] For this reason, any provision restricting research with mixed entities encroaches on the freedom of research. Where research has implications for the rights of third parties or the interests of animal welfare, balancing of the relevant considerations is therefore necessary.

With regard to *in vitro* research in which the birth of a human being or human–animal mixture is prevented, the general dispute as to the constitutional status of an embryo, mentioned earlier, becomes relevant. After all, for those who ascribe the full protection of human dignity and/or life to the embryo only after implantation or even later, the fundamental right of freedom of research legitimizes such research, which is in their view not opposed by a constitutional requirement of equal rank. Conversely, for those who consider that an embryo enjoys the full protection of human dignity and/or life, or at least a protection graduated according to its level of development, as soon as that embryo comes into being, the freedom of research must be balanced against this position on the protection of the embryo. This being the case, research with human embryos *in vitro* is prohibited under the Embryo Protection Act (see Section 2(1) ESchG).

Unborn animals too are protected, as they are covered by the state's objective of animal welfare pursuant to Article 20a GG.[65] However, the Basic Law contains no provisions on the extent of protection. Again, the Animal Welfare Act currently in force regulates experiments involving animals only in connection with their life after birth.[66]

64 BVerfGE 28, 243 (261) on the conflict between compulsory military service and the freedom of conscience, for which freedom a specific statutory provision is likewise not required.
65 Kloepfer, in: Dolzer/Vogel/Grasshof 2005, Article 20a para. 66.
66 See Section 3.3.1.

3.2 The Embryo Protection Act

3.2.1 Prohibition of interpretation by analogy

The Embryo Protection Act (ESchG) was conceived as an ancillary criminal-law statute.[67] For this reason, the prohibition of interpretation by analogy implied by Article 103(2) GG is relevant to its interpretation. This means that the wording of the Act determines the limits of possible interpretation; a more extensive interpretation as a basis for punishability, derived, for example, from the aim and purpose of the Act, is impermissible. Particular importance attaches to the prohibition of interpretation by analogy in the rapidly developing fields of reproductive medicine and human genetics, since newly developed techniques and/or new medical and biological discoveries are often not covered explicitly by the sometimes highly casuistic provisions of the Embryo Protection Act. Gaps in the Act could be filled only by actual legislation, and not by those who apply the law.

It must in addition be emphasized that the *Stammzellgesetz* (Stem Cell Act), a later statute than the Embryo Protection Act, cannot be invoked for interpretation of the Embryo Protection Act. This applies in particular where the Stem Cell Act departs from the Embryo Protection Act, as, for example, in the case of the definition of an embryo.[68]

3.2.2 Explicit provisions in the Embryo Protection Act

The Embryo Protection Act contains specific provisions on the formation of chimeras and hybrids only in Section 7: Section 7(1)

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67 With regard to the following considerations, see Taupitz, in: Günther/Taupitz/Kaiser 2008, Introduction B para. 18.

68 Whereas the Stem Cell Act defines any totipotent cell as an embryo, the Embryo Protection Act additionally requires that the totipotent cell must have been derived from an (other) embryo in order to be deemed to be an embryo.

prohibits the creation of a number of entities, while Section 7(2) provides for a ban on certain transfers.[69]

Under Section 7(1) the following, and hence also attempts at the following, are punishable offences:

1. Uniting embryos with differing genetic information to form a group of cells using at least one human embryo;
2. Combining a human embryo with a cell that contains different genetic information from that of the embryo's cells and is capable of further differentiation with that embryo; or
3. Creating an embryo capable of differentiation by fertilization of a human egg with the sperm of an animal or by the fertilization of an animal egg with human sperm.

Section 7(2) provides that the following are punishable offences:

1. Transferring an embryo derived from an act pursuant to Section 7(1) to
   a) a woman, or
   b) an animal
   or
2. Transferring a human embryo to an animal.

The prohibitions set out in Section 7(1) No. 1 and No. 2 are distinguished by the fact that at least one human embryo must be involved. In No. 1, a human embryo is fused with another human embryo (intraspecies chimera) or with an animal embryo (interspecies chimera). On the other hand, according to the description of the relevant offence, the transfer of already differentiated cells or foreign genes to a human embryo is not prohibited. The situation of "different genetic information"

69 With regard to the following, see Günther, in: Günther/Taupitz/Kaiser 2008, Section 7.

does not apply if the perpetrator unites, or reunites, previously separated totipotent cells from one and the same embryo or otherwise cloned genetically identical embryos – something prohibited under the Embryo Protection Act currently in force.

The offence described in No. 2 differs from that of No. 1 only in the *form* of chimera formation. It presupposes the combination of the human embryo with a cell differing in its genetic information, where this cell is capable of further differentiation with the embryo. This cell may in turn be either one taken from a human embryo with different genetic information (intraspecies chimera) or an animal embryo (interspecies chimera). Over and above the provisions of No. 1, combination with non-totipotent cells is also prohibited by this provision. Section 7(1) No. 2 covers already differentiated embryonic cells or only ones that are no longer capable of development – specifically, embryonic carcinoma cells of human or animal origin that can be united with a human embryo and share in that embryo's process of differentiation.

A human embryo whose use is prohibited under Section 7 is defined in Section 8 ESchG: for the purposes of the Embryo Protection Act, an embryo is deemed to be already the fertilized egg, capable of development, from the time of nuclear fusion on, as well as any totipotent cell taken from an embryo where that cell is capable, subject to the satisfaction of the necessary further conditions, of dividing and developing into an individual.[70] Section 8 ESchG does not explicitly address the problems of human–animal mixtures. The legal authorities seem at present to be in substantial agreement that a "human" embryo for the purposes of the Embryo Protection Act exists only if all "raw materials" are of human origin.[71] The actual wording admittedly does not preclude a different interpretation, because the Embryo Protection Act distinguishes conceptually between

70 On this point, see Taupitz 2008.

71 Limbeck 2006, 82; Günther, in: Keller/Günther/Kaiser 1992, Section 2 para. 16; Taupitz, in: Günther/Taupitz/Kaiser 2008, Section 8 para. 59; Trips-Hebert 2009 with further references.

"human" embryos on the one hand (Section 7(1) No. 1 ESchG) and embryos not specified as such; Section 7(1) No. 3 ESchG, for example, prohibits the production of "an embryo capable of differentiation" by the fertilization of an animal egg with human sperm. According to this interpretation, the definition of an embryo pursuant to Section 8 ESchG could include not only "purely" human but also human–animal mixed embryos.[72] However, a more probable assumption is that the specific subject of human–animal mixtures is addressed in the Act only in Section 7 ESchG, which therefore constitutes a conclusive provision.[73] Accordingly, the Federal Government's "cloning report" dating from as long ago as 1998 called for the creation of a living organism by cell nuclear transplant using animal and human genetic material to be added to the acts prohibited under Section 7 ESchG.[74]

Section 7(1) No. 3 ESchG provides that the formation of interspecies hybrids – i.e. living organisms created with human and animal germ cells – is a punishable offence. However, the provision covers the creation of human–animal mixtures only by means of the *fertilization* of an egg by a sperm cell. The technique of producing hybrid embryos by cell nuclear transplant is not envisaged by Section 7 owing to the absence of fertilization. Nor does fertilization take place in the phase of pronucleus formation. Section 7(1) No. 3 ESchG does not therefore prohibit the production of impregnated eggs with pronuclei of human and animal origin. Other acts that are not covered are attempts to breed transgenic animals with human genes or the incorporation of human DNA sequences that deactivate the immune system into animal organs with the aim

72 Brewe 2006, 30, considers the genetic information of the relevant species contained in the cell nucleus to be the deciding factor. This, however, would raise the further question of the correct interpretation of the concept "capable of development" (on this point, see Taupitz, in: Günther/Taupitz/Kaiser 2008, Section 8 para. 20 ff.), and whether the corresponding capability of development is also present in the mixed entity produced.

73 See also Huwe 2006, 96; Trips-Hebert 2009.

74 *Deutscher Bundestag* 1998, 21.

of transplanting these organs into humans, as well as the introduction of human genetic material into the DNA of bacteria. Another restriction in relation to the offence described in Section 7(1) No. 3 ESchG is that the hybrid embryo produced by fertilization must be capable of differentiation. According to the preparatory material pertaining to the Act, this restriction was included in the legislation in order to legitimize the hamster test (see Section 1.3.6).[75]

Section 7(2) No. 1 ESchG prohibits the transfer of human or hybrid embryos created in one of the forms described in Section 7(1) to a woman or an animal. Section 7 thus denies them a right to life owing to the form of their creation and indirectly requires such embryos to be destroyed. In the case of human intraspecies chimeras, this is criticized in the literature.[76] Conversely, the prohibitions on the transfer of a human embryo to an animal (Section 7(2) No. 1(b) and No. 2) are justified on the grounds that irresponsible human experiments with human embryos are thereby banned.[77]

For the purposes of the transfer prohibitions set out in Section 7(2) ESchG, it is immaterial whether the embryo is actually implanted into the uterus of a woman or female animal. Even in circumstances that definitely preclude possible implantation and pregnancy in a woman or animal, any transfer of embryos prohibited under Section 7 ESchG therefore still remains a punishable offence.

3.2.3 Relevance of the Embryo Protection Act in other respects

Section 1(1) No. 1 ESchG prohibits the transfer of a foreign unfertilized egg to a woman. The Act admittedly does not explicitly

75 *Deutscher Bundestag* 1990, 16.
76 Günther, in: Günther/Taupitz/Kaiser 2008, Section 7 para. 32; Müller-Terpitz, in: Spickhoff 2011, Section 7 ESchG para. 1.
77 Günther, in: Günther/Taupitz/Kaiser 2008, Section 7 para. 32.

specify here (whereas it does in other sections[78]) that a human egg is meant. However, the problem of chimera and hybrid formation is, as stated, covered in Section 7 ESchG by a separate provision, since that section also includes independent transfer prohibitions. It must therefore be assumed that Section 1(1) No. 1 ESchG covers only human eggs.[79] Furthermore, a human egg can only be a cell formed from both a human nucleus and a human zona pellucida, even if both parts do not originate from the same woman.[80] It is already clear from the wording of the provision that an animal zona pellucida into which a human nucleus has been inserted cannot be deemed to constitute a human egg.[81] The inverse result of a manipulation can also not be assumed to be a human cell for the purposes of Section 1(1) No. 1 ESchG, even if the wording itself does not *a priori* preclude a different interpretation. After all, Section 1(1) No. 1 ESchG is intended merely to prevent a situation of "split" maternity,[82] which is not the case when the mixed form described is transferred, and furthermore the transfer of human–animal mixtures to a woman is covered by a specific provision in Section 7 ESchG.

Section 2(1) ESchG provides that it is a punishable offence to dispose of a human embryo produced outside the body or removed from a woman prior to completion of its implantation in the uterus, or to relinquish, acquire or use such an embryo for a purpose other than its preservation. This provision is intended to prevent any misuse of a human embryo. The term "use" is to be understood in broad terms. It covers any action which actively influences the embryo's fate, affects the embryo or acts together with it.[83] The consequence is a ban on

78 For example, in Sections 3, 8 and 9 ESchG.
79 Taupitz, in: Günther/Taupitz/Kaiser 2008, Section 1(1) No. 1 para. 15.
80 Taupitz, in: Günther/Taupitz/Kaiser 2008, Section 1(1) No. 1 para. 16.
81 Taupitz 2001, 3434 f.; Hetz 2005, 75; Middel 2006, 210 with further references.
82 *Deutscher Bundestag* 1989, 7.
83 However, the *Bundesgerichtshof* (Federal Court of Justice) does not consider certain cases involving blastocyst cells in preimplantation genetic diagnosis to constitute a prohibited "use" (see BGH, NJW 2010, 2672 [2675]); on the other hand, this does not concern research, which is the subject of this Opinion.

research with embryos, including the combination of an embryo with cells, tissue or organs from another living organism except with the intention of preserving the relevant embryo.

Section 5(1) ESchG prohibits the artificial modification of the genetic information of a human germline cell. Section 5(2) ESchG bans the use of a human germ cell with artificially modified genetic information for the purposes of fertilization. In addition, Section 5(1) ESchG prohibits the artificial modification of human germline cells; however, the prohibition does not apply if there is no possibility that the germ cell will be used for fertilization or, as the case may be, that the artificially modified non-human germline cell will be transferred to an embryo, fetus or human being or that a germ cell can arise from it.

Section 6 ESchG bans the cloning of human beings – that is, artificially bringing about the genesis of a human embryo with the same genetic information as another living or dead embryo, fetus or human being. The generally accepted view is that this prohibition also applies to cloning by cell nuclear transfer.[84] However, a combination of a human nucleus and an animal zona pellucida (and vice versa) is not covered by this prohibition, because, as stated above, an embryo is deemed to be human only if all the materials of which it is formed are of human origin. One reason for this interpretation is again that the problem of chimera formation is covered by a specific (limited) provision in Section 7 ESchG, so that it may be deduced *a contrario* that the provision set out in Section 7, applied to the creation of chimeras, is conclusive.

If it is assumed that a mixed human–animal embryo has been formed without infringement of the ban on cloning set out in Section 6(1) ESchG, its transfer to a woman will also not be prohibited under Section 6(2) ESchG.

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84 For references, see Kersten 2004, 36, who, however, does not share this view.

3.2.4 Summary

Hence the provisions of the Embryo Protection Act can be interpreted as follows in relation to the mixed entities forming the subject of this Opinion (see table in Section 1.3):

(a) The transplanting of cells to an embryo contravenes Section 2(1) ESchG unless the transplant is effected for the purpose of preserving the relevant embryo. Measures in the context of fundamental research conducted on or with the embryo, for example, thus constitute a punishable offence. It is immaterial whether the material transferred is human or animal.

(b) No one disputes that somatic cell nuclear transfer, in which a human somatic cell nucleus is transferred to an enucleated animal zona pellucida, is not prohibited under Section 7 ESchG. The predominant view, too, is that it is also not covered by another provision (e.g. Section 6 ESchG). Hence the transfer of a human somatic nucleus into an enucleated animal zona pellucida (as well as, conversely, that of an animal nucleus into a human zona pellucida), as well as the transfer of the corresponding entity to a woman, is not addressed by the Embryo Protection Act.

(c) Gene transfer, in which foreign DNA segments are transferred into a fertilized human egg capable of development, is a punishable offence under Section 2(1) ESchG because the "recipient" of the DNA in this situation is an embryo. If the human egg has not yet been (finally) fertilized – i.e., if "nuclear fusion" has not yet taken place – the act is punishable if the human egg is used for fertilization with artificially modified genetic information (Section 5(2) ESchG). This situation may also arise if the deliberately initiated fertilization process is not interrupted.

(d) The same considerations as in (c) apply to the transfer of chromosomes into a human egg.

(e) Where the "recipient" of the DNA or chromosomes (see (c) and (d)) is an embryonic stem cell, the relevant statute is not the Embryo Protection Act but only the Stem Cell Act. Like any use of human embryonic stem cells, such an action must be approved by the competent authority.

(f) Fusion of embryos is prohibited by Section 7(1) No. 1 ESchG.

(g) Gamete fusion by fertilization of an animal egg with human sperm or, conversely, of a human egg with animal sperm is prohibited by Section 7(1) No. 3 ESchG where the aim is to produce an embryo capable of differentiation.

(h) According to the predominant view, the transfer of a mixed entity to a woman is covered by the Embryo Protection Act only if a mixed entity has been created contrary to the prohibitions of Section 7(1) ESchG.

3.3 The Animal Welfare Act

All animals are protected by the Animal Welfare Act (TierSchG). Human–animal mixtures assigned to the category of animals are also covered by the Act.

No one may cause pain, suffering or harm to an animal without reasonable grounds (Section 1 TierSchG). However, the Animal Welfare Act does provide for different degrees of protection, in that most of its individual provisions apply only to vertebrates.

3.3.1 Animal experiments (Sections 7–9a TierSchG)

To protect the live animals concerned, the Animal Welfare Act includes rules for the conduct of animal experiments. The distinguishing criterion of an animal experiment, as opposed to other measures, is that the procedure concerned shall not yet have been developed to the level of standard practice and that its experimental character shall be predominant. For this reason, the development of a transgenic animal line is deemed to constitute an animal experiment as far as the second progeny generation; all animals required up to this point for the development of a transgenic line enjoy the protection provided for in the Animal Welfare Act.

All animal experiments are subject to official approval. In the case of experiments required by law, for instance for the purposes of medicinal product licensing, notification only is necessary. Approval is granted by an authority; an interdisciplinary commission (often called an "ethics commission" along the lines of the corresponding medical commissions) must first have issued its opinion on the relevant animal experiment.

Section 7 TierSchG defines an animal experiment as a measure or treatment for experimental purposes carried out

1. on animals, if potentially involving pain, suffering or harm to these animals; or
2. on the genetic material of animals, if potentially involving pain, suffering or harm to the animals whose genetic material is modified or to the animals that carry them to full term.

According to Section 7(1) No. 1 TierSchG, the protected experimental subject can only be a live born animal. Section 7(1) No. 2 TierSchG, on the other hand, protects the animal's genetic material, this protection being in the interests of the affected (subsequently) born animal.[85] Unlike No. 1, therefore, this provision also covers the manipulation of eggs and embryos. However, the possible consequences of the experiment must threaten the animal whose genetic material has been modified or which is used to carry that animal to term.[86]

Section 7(2) TierSchG provides that animal experiments may be conducted only if they are essential for a purpose specified in detail in a statute. Particular examples of permissible

85 Lorz/Metzger 2008, Introduction A para. 1.
86 Lorz/Metzger 2008, Section 7 para. 12.

experimental purposes are the prevention, identification or treatment of diseases, suffering, bodily harm or bodily complaints or the identification or modification of physiological states or functions in human beings or animals, the identification of threats to the environment, the testing of substances or products for harmlessness to the health of humans or animals, or fundamental research. In the case of experiments on vertebrates, a further restriction is imposed by Section 7(3) TierSchG. Experiments on vertebrates may be conducted only if the expected pain, suffering or harm to the experimental animals is ethically acceptable in terms of the purpose of the experiment. Experiments on vertebrates that result in prolonged or repeated significant pain or suffering may be conducted only if the intended results suggest that they will be of overriding importance to essential needs of humans or animals, including the solution of scientific problems. The consequences of the experiment must therefore be weighed against its purpose, the purpose being measured against its importance to the community. The less important the purpose of the experiment, the more weight is attached to the animal's welfare.[87]

3.3.2 Prohibition of organ or tissue removal (Section 6(1) TierSchG)

Section 6(1) TierSchG prohibits the complete or partial removal or destruction of organs or tissues of a vertebrate animal. However, Section 6(1) No. 4 TierSchG provides for an explicit exception to this prohibition if the removal is necessary for the purpose of transplantation or for the starting of cultures or for isolated study. Since the necessary measure must in addition be essential in pursuance of sentence 5 of Section 6(1) and sentence 1 of Section 9(2) TierSchG, the relevant objective must

87 Lorz/Metzger 2008, Section 7 para. 58.

not be attainable by other methods according to the current state of the scientific art.[88]

Pursuant to Section 6a TierSchG, the provisions applicable to animal experiments are more specific, so that the prohibition provided for in Section 6 TierSchG applies only to standardized procedures no longer classifiable as animal experiments.

3.3.3 Biotechnological measures (Section 10a TierSchG)

Section 10a TierSchG governs biotechnological measures. The first sentence of Section 10a TierSchG provides that measures or treatments conducted on vertebrate animals for the production, derivation, storage or propagation of substances, products or organisms, where such measures or treatments potentially involve pain, suffering or harm, may be carried out only if the conditions set out in Section 7(2) and (3) TierSchG are satisfied – that is, if the measure is essential and ethically acceptable. In pursuance of sentence 4 of Section 10a TierSchG, the requirements concerning the conduct of the animal experiment specified in Sections 8b, 9 and 9a TierSchG must also be substantially observed. Unlike an animal experiment, however, a biotechnological measure is subject not to approval but to notification.

It should be noted that Section 10a TierSchG too becomes applicable only once a standardized technique has developed from the experiment.[89]

88 See Section 7(2) sentence 2, Section 9(2) sentences 2 and 3 Nos. 2 and 3 TierSchG; Lorz/Metzger 2008, Section 6 para. 27.

89 Lorz/Metzger 2008, Section 10a para. 4 f.; however, these authors are considering Section 10a TierSchG in relation to, for example, the standardized cloning of animals and the widespread technique of embryo splitting for livestock; Hirt/Maisack/Moritz 2007, Section 10a para. 2.

3.3.4 Animal breeding (Sections 11 and 11b TierSchG)

The breeding of animals is subject in all cases to the granting of permission by the relevant authority (Section 11 TierSchG). Section 11b TierSchG qualifies the human interest in a specific genetic design of an animal with concern for the relevant animal's interests.[90] Section 11b TierSchG prohibits the practice of cruel breeding and equivalent biotechnological or genetic-engineering measures. The breeding of vertebrate animals and their modification by biotechnology or genetic engineering are accordingly prohibited if the transformation or manipulation is likely to give rise to pain, suffering or harm to the modified animals or their progeny. However, under Section 11b(4) TierSchG an exception again applies to scientific projects – although a project is deemed no longer to fall within the field of research if the use of the animal does not serve the purpose of acquiring new knowledge, but constitutes a medical measures with the aim of therapy for humans.[91]

3.3.5 Summary

The Animal Welfare Act can thus be interpreted as follows in relation to the mixed entities forming the subject of this Opinion (see table in Section 1.3):

Animal experiments

Where the experimental character of a given measure predominates, all the procedures examined in this Opinion constitute animal experiments for the purposes of Section 7(1) No. 1 or No. 2 TierSchG. However, this is disputed in the case of somatic cell nuclear transfer (see Sections 1.3.2 and 2.2.1). It is argued

90 Lorz/Metzger 2008, Section 11b para. 1.
91 Lorz/Metzger 2008, Section 11b para. 11, Section 4 para. 9.

that Section 7(1) No. 2 TierSchG does not apply because cell nuclear transplantation does not represent a manipulation of the genetic material: since the wording of Section 7(1) No. 2 TierSchG stipulates modifications of the genetic material, an animal experiment for the purposes of Section 7(1) No. 2 TierSchG exists only if genetic material of the animal itself is present and is then modified. However, according to this argument, animal genetic material is *not* modified in the case of cell nuclear transfer.[92] With a human–animal mixture too, it is possible to claim that the Animal Welfare Act *a priori* covers living organisms only if they belong unequivocally to the zoological kingdom of the animals.[93] This, however, is not the case with artificially created human–animal mixtures. Others, on the other hand, hold that such a narrow interpretation is incompatible with the purpose of the Animal Welfare Act: in view of the novelty of the procedure, it is in fact very much more likely that pain, suffering or harm will be inflicted on the animals.[94]

In the event of doubt as to whether a procedure is still experimental in nature or must already be deemed standardized, the basis, in accordance with the precept of pro-animal-welfare interpretation, must be that it is an animal experiment, since Sections 7 ff. TierSchG afford the most comprehensive protection for the animal.

Falling as they do within the purview of fundamental research, the procedures examined in the present Opinion are as a rule regarded as "essential" for the purposes of Section 7(2) TierSchG. However, it is sometimes argued that the creation of transgenic animals is ethically unacceptable because, in the balancing of harm against benefit in accordance with Section 7(3) TierSchG, account must be taken of the fact that, given the non-transposability of the results, the medical benefit to humanity is

92 This the view of Vesting/Simon 1998, 263, who conclude that Section 7(1) No. 2 TierSchG does not apply.
93 Lorz/Metzger 2008, Introduction A para. 1.
94 This is the conclusion of Hillmer 2000, 52.

questionable or at least highly uncertain.[95] Yet this by no means signifies that such procedures must always be deemed unethical. Uncertainty as to the medical benefit of a procedure is inherent in all medical research and cannot as such already justify the condemnation of that procedure as unethical; instead, ethical acceptability must be assessed in each individual case.

Prohibition of organ or tissue removal (Section 6(1) TierSchG)
The prohibition on removal set out in Section 6(1) TierSchG does not relate already to material at the level of cells or genes, but only to the stage of organs or tissues.[96] It therefore covers only the form of transplantation (see Section 1.3.1) in which tissues or entire organs are removed from an animal in the course of a standardized procedure that is no longer deemed to be an animal experiment, in particular with the aim of transplantation to man.

The removal of animal organs for transplanting to man has hitherto been more in the nature of an animal experiment for the purposes of Section 7 TierSchG, so that the practice is not banned. However, an exception to the prohibition pursuant to Section 6(1) No. 4 TierSchG would be appropriate even in the event of standardization, since organs must then be removed for the transplant.

Biotechnological measures (Section 10a TierSchG)
Section 10a TierSchG ultimately covers all the situations addressed in the present Opinion (see table Section 1.3) that are no longer classifiable as animal experiments and do not constitute removal of tissues or organs. In particular, the transgenic animals resulting from the transfer of human genes into the animal organism (see Sections 1.3.3 and 2.2.2) may fall foul of Section 10a TierSchG if produced on a very large scale as standard practice by standardized genetic-engineering measures.

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95 Hirt/Maisack/Moritz 2007, Section 7 para. 69 f. with further references.
96 Lorz/Metzger 2008, Section 6 para. 6 f.

Animal breeding (Sections 11 and 11b TierSchG)

The prohibition of cruel breeding provided for in Section 11b TierSchG applies where animals are bred or produced by biotechnological measures equivalent to breeding (where such measures no longer constitute animal experiments).

It follows from Section 11b(1) TierSchG that neither the modification of existing animals by biotechnological or genetic-engineering measures, nor the creation of an animal by biotechnology or genetic engineering, is deemed to constitute breeding. Consequently, the procedures examined in this Opinion can be deemed to constitute breeding at most if the organisms arising in a given procedure are viable and are then bred on. In particular, the breeding of transgenic animals is possible (see Sections 1.3.3 and 2.2.2). Although the development of a new transgenic animal line always constitutes an animal experiment pursuant to Section 7 TierSchG,[97] where transgenic animals are mated the situation from the third generation on constitutes continued breeding,[98] so that the requirements of Section 11b TierSchG must be observed.

3.4 The European directive on the protection of animals

Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes was published in the Official Journal of the European Union on 20 October 2010.[99] It superseded the previous Directive on the protection of experimental animals dating from 1986, on which much of the German Animal Welfare Act is based. Since the

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97 Hirt/Maisack/Moritz 2007, Section 10a para. 2; see Animal Welfare Report 1997 (*Deutscher Bundestag* 1997, 110).

98 Hirt/Maisack/Moritz 2007, Section 7 para. 2; see Animal Welfare Report 1997 (*Deutscher Bundestag* 1997, 110).

99 OJ EU L 276/33 of 20 October 2010.

new Directive must be transposed into national law by 10 November 2012, parts of the German Animal Welfare Act must be amended.

The final goal of the Directive is stated to be the complete abolition of procedures involving living animals used for scientific and educational purposes.[100] As soon as this is scientifically possible, live animals should no longer be used. However, the Directive also emphasizes the continued need, for the time being, for live animals to be used. The aim of the Directive is therefore to combine the further development of alternative approaches to animal experiments with a guarantee of the highest possible level of protection for the animals that for the time being continue to be used.

Some provisions of the German Animal Welfare Act must be amended. For instance, under Article 1(3) of the Directive, protection must be extended to fetal forms of mammals as from the last third of their normal development. In particular, however, the Directive imposes appreciably stricter requirements on research with non-human primates (Article 8). The result of an experiment must, in particular, not be achievable by experiments with other animal species. Even stricter requirements apply to certain species of non-human primates – in particular, great apes. Article 8(3) of the Directive prohibits the use of great apes for research purposes. The only, highly restrictive, exception concerns the situation of an "outbreak of a life-threatening or debilitating condition in human beings", laid down in Article 55 of the Directive as a possible provisional measure, on which the Commission and a central committee must rule. Fundamental research must not be carried out on great apes. Article 58 provides for a review of the Directive by 10 November 2017 and for periodic thematic reviews.

On the level of organization, Article 49 of the Directive calls upon each Member State to appoint a national committee for the protection of animals used for scientific purposes. This

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100 Recital 10 of the Directive.

committee is required to advise the competent authorities and animal welfare bodies on matters dealing with the acquisition, breeding, accommodation, care and use of animals in procedures and to ensure the sharing of best practice. A "procedure" here "means any use, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome, or educational purposes, which may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice" (Article 3 of the Directive). In Germany, the animal welfare commission established by the Federal Ministry of Food, Agriculture and Consumer Protection to assist it in matters of animal welfare in pursuance of Section 16b TierSchG could perhaps be charged with the functions of the national committee.

The provisions of the European animal protection directive are in fact not entirely consistent with the conclusions of some important international biomedical documents to the effect that research on human beings is permissible only if there is no alternative of comparable efficacy.[101] These have hitherto been interpreted as signifying priority for animal experiments. Another point that must be clarified is whether the implementation of the Directive might result in a disproportionate restriction of the freedom of research and an infringement of the state's obligation to protect citizens' physical integrity and health. Some, on the other hand, hold that the statutory provisions are not yet sufficiently concrete to prevent unnecessary suffering in research animals.

101 See, for instance, Article 16 of the Council of Europe's Convention on Human Rights and Biomedicine; Article 5 of the Additional Protocol concerning Biomedical Research; and principle B no. 12 of the World Medical Association's Declaration of Helsinki.

4 MORAL STATUS OF HUMANS, ANIMALS AND MIXED ENTITIES

For the ethical assessment of human–animal mixtures, their moral status is of the essence. The intrinsic moral value of the newly created entities determines whether their generation can be deemed permissible and how they should be treated. The moral status of a living organism may vary in accordance with appropriately graduated requirements of consideration, respect, rights and protection. Unconditional intrinsic moral value is expressed in the dignity of man, the central importance of which as a constitutional principle of the German Basic Law is undisputed, notwithstanding uncertainties as to its scope.

Animals are generally considered to possess a lower moral status than humans, this status increasing with their cognitive and aesthesiophysiological capabilities, which imply correspondingly increasing levels of obligatory protection. Where it is clear that a human–animal mixture will be unequivocally classifiable as human or animal, the consequent moral status indicates whether the creation of a mixture of this kind is permissible and how the mixture should be treated should its existence become a fact. On the other hand, uncertainty surrounds the moral status of a mixed entity that cannot clearly be assigned to a given species, as well as the permissibility of creating such an entity in cases where unequivocal assignment to a given species is not foreseeable from the beginning.

4.1 Moral status and human dignity

4.1.1 General considerations on human dignity

According to the universal conception on which the German Constitution is based, human dignity is an attribute of all human beings (the dignity of the species) as well as of each individual (individual dignity). The precept of respect for human dignity reminds us of the limits and the restrictive condition to which all individual and state action is subject in a democratic society: every human being must be respected for his own sake, and no one may be used exclusively as a means to others' ends. For this reason, the Basic Law invokes the inviolability of human dignity.

The foundation of human dignity lies in man's conception of himself, according to which he is seen as an end in himself and must therefore never be treated as a mere means. It is a fundamental conviction shared by Jews, Christians and Muslims, adherents of other world views and religions, as well as in the tradition of human rights and many schools of philosophy, that human dignity does not depend on a specific physical or mental condition, on any particular capacity, or indeed on social characteristics. Human dignity is therefore an essential attribute of a human being, which is not based on the consent of others, but to which every individual is entitled irrespective of his particular situation, geographical location or other circumstances.

Different conclusions can be drawn from this conception of human dignity. Whereas universalists hold that any practical relativization of human dignity is impermissible because human dignity is deemed inviolable, according to other interpretations it can perfectly well be balanced against the human dignity of other individuals. Still others make a distinction in accordance with the stage of development of a human being, so that, for example, in the view of some advocates of this position, embryos prior to implantation are not yet regarded as possessing human dignity. It is universally agreed that an infringement of human dignity must be established in concrete terms. Opinions differ on the circumstances which justify such a finding. Some invoke the different stages of development of human organisms for this purpose too, so that acts affecting embryos may be assessed differently from acts affecting born human beings, whereas, according to the universalist conception of human dignity, all human organisms must be treated equally.

Another issue is whether the construction of a human mixed entity by other individuals already constitutes a complete instrumentalization of a human being. A similar debate on the inviolability of human dignity is already taking place in the field of reproductive medicine and human genetics, in connection with the ethical justifiability or otherwise of the creation of human beings who irreversibly owe their biological make-up and hence their characteristics and features to the organization and planning of another. The addition of animal material to a human embryo that is carried to full term could accordingly be regarded as a violation of human dignity in so far as it infringes the self-determination of the human mixed entity because that entity owes parts of its genetic endowment and hence of its nature to manipulation by third parties. Others, on the other hand, argue that the eventual self-determination of an individual does not depend on whether that individual owes his existence to the planning of third parties.

4.1.2 Status of the extracorporeal human embryo

The question whether fertilized eggs already enjoy "complete" protection of human dignity, or whether this is true only of embryos or fetuses at later stages of development, or indeed only born human beings, is a central aspect of the debates on preimplantation genetic diagnosis and consumptive research on embryos. The issue of the status of the human embryo was addressed in detail by the German Ethics Council in its Opinion on preimplantation genetic diagnosis, published in March 2011, and the reader is referred to the arguments presented in that document.[102] For the purposes of the present Opinion, it

102 See German Ethics Council 2012.

is sufficient to note the absence of a consensus on the attribution of human dignity to human embryos in terms of ethics and/or fundamental rights. For this reason, different views are expressed on acts affecting human embryos.

The same basic positions are also encountered in the – even more complex – debate on the dignity and status of human–animal mixtures at the embryonic stage (on this point, see also Section 6.1). Anyone who regards fertilized eggs as enjoying individual human dignity will be unable to accept any treatment of these eggs that places their individual prospect of healthy development at risk. From this point of view, all chimerizations and hybridizations of human embryos are categorically impermissible where the aim from the beginning is to use them for research instead of allowing them to be carried to full term. Conversely, those who do not regard embryos as subjects of individual human dignity may in certain circumstances accept experiments involving mixed entities if the purpose of the research is of overriding importance. This is at any rate the case if there is no question of the entities concerned developing to the stage of birth and beyond.

4.1.3 Dignity of the species

The ban on chimera and hybrid formation laid down in the Embryo Protection Act can also be ethically justified by the notion that the dignity of man, which is likewise enshrined in the Basic Law, includes not only the perspective of the individual human subject but also a supra-individual component that relates to humanity as a whole. The *Bundesverfassungsgericht* (Federal Constitutional Court) has explicitly ruled as follows: "Human dignity [...] is not only the individual dignity of the person concerned, but also the dignity of man as a species. Everyone possesses it, irrespective of his characteristics, achievements and social status. It is also enjoyed by those who are unable to act in the full possession of their faculties owing to their physical or mental condition."[103]

Although impairment of the dignity of the species is a weaker argument than a direct infringement of individual human dignity, it may be involved if the identity and unequivocal nature of the species as such are threatened. This may be the case in particular if born mixed entities cannot be clearly assigned to a given species and therefore cause society to question whether they should be regarded as members of the human community in possession of equal rights. This risk is not presented in the same way by experiments conducted purely *in vitro*.

In addition, the formation of human–animal mixtures could affect the dignity of the species and the individual dignity of born mixed entities in so far as a knowledge of a born individual's descent and history is of vital importance to his conception of himself, his identity and his social identification. However, the descent and history of a human mixed entity is intimately bound up with both those of humanity and those of the animal involved. Should such a mixed entity be born and grow to maturity, this circumstance could impede both the formation of its identity and its social identification. The individual might see itself as belonging completely neither to the group of human beings nor to that of animals. This not only represents a problem for the individual but also has repercussions for society as a whole. On the one hand, this situation makes it difficult for society to know how to treat the mixed entity, because it cannot ascribe a clear identity to it. On the other, the deliberate creation of such an entity affects the value placed on, and the social significance of, descent and history. Their value is consciously diminished by the creation of an entity assumed to feel allegiance to neither of its families of origin (animal or human). For these reasons too, these risks do

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103 BVerfGE 87, 209 (228); see also BVerfGE 109, 133 (150).

not arise in the same way in the case of experiments conducted purely *in vitro*.

4.2 Status and welfare of animals

4.2.1 Fundamental considerations

The term *animal* covers a wide range of species, extending from low to high levels of development. Since antiquity, it has been used to justify a definition of man as a “non-animal”. This anthropocentric view places human beings, and human beings alone, at the centre of moral consideration. It presupposes a fundamental difference between animals and humans, based for example on man’s possession of reason or the faculty of speech. According to this approach, it is permissible to eat, kill and possess animals – that is, to use them as a means to an end, for example the generation of new knowledge for the benefit of humanity.

In the nineteenth century, the moral philosopher Jeremy Bentham expressed the view that all organisms susceptible to pain and suffering, including not only man but also many animals – in particular, vertebrates – were entitled to moral consideration. This “pathocentric” view is based, first, on the vital importance of suffering to our own conception of quality of life and, secondly, on our sympathy with animals. The perception (or even the mere knowledge) of animal suffering can be very unpleasant to us. Albert Schweitzer offered a different foundation for the notion of animal welfare in his “ethics of reverence for life”, according to which every living organism is worthy of protection for its own sake (the “biocentric” approach). From this point of view, life may be destroyed only where absolutely necessary. Any deviation from this principle calls for justification. Man’s intrinsic moral capacity is the basis of a comprehensive ethics of responsibility – a kind of trusteeship for everything living, for the preservation of Creation.

The aim of the German Animal Welfare Act (TierSchG) is, “on the basis of man’s responsibility for animals as fellow-creatures, to protect their life and welfare. No one may without reasonable grounds inflict pain, suffering or harm on an animal” (Section 1 TierSchG). The Animal Welfare Act thus includes extensive provisions on measures involving animals, animal husbandry and the trade in animals, breeding and animal experiments (see Section 3.3). These provisions are in general based on consideration for animals’ sensitivity to pain. For this reason, where animal experiments are conducted, it is necessary to ensure that animals do not subsequently have to continue to live in pain or suffering. However, in addition to an animal’s particular susceptibility to suffering, social proximity to man may be a relevant factor. For this reason, the Animal Welfare Act provides that in the case of specific animals – in particular, primates and domestic animals – a veterinarian must decide whether the animal must be painlessly sacrificed after an experiment (Section 9(2) sentence 2 No. 8 TierSchG).

4.2.2 The particular status of primates and great apes

Clearly identifiable graduations can be discerned in the extent of protection afforded by animal welfare legislation: most of the individual provisions relate only to vertebrates. In view of our growing knowledge of man’s nearest relatives, based particularly on ethological and genetic primate research, an increasingly vigorous debate is being conducted on whether, and if so to what extent, animal welfare legislation should be extended in relation to primates, and in particular great apes (i.e. gorillas, orang-utans and chimpanzees). The reason given is their close relationship to man, which is not only revealed in their anatomical similarity and substantial sharing of genetic material.[104] The point, in fact, is "that they share with man certain emotional and cognitive capabilities, including that of self-awareness. Ethology […] and other biological disciplines such as neurobiology offer unequivocal and convincing indications of these highly developed capabilities."[105] For this reason, great apes must be assumed to possess a more highly developed sensitivity to suffering than other animal species.

Furthermore, primates have an extensive social organization. It is pointed out in the debate that great apes have a conception of self,[106] can empathize with other beings[107] and are capable of reciprocal altruism.[108] In addition, some hold that great apes have a capacity for culture[109] and teamwork,[110] can plan for the future[111] and have a rudimentary conception of morality.[112] Some authors conclude from these arguments that great apes have the same moral status as human beings and are therefore a part of the moral community or the "community of equals".

Protagonists of the classical ethical approaches of European philosophy, on the other hand, consider that humanity occupies a special position. This is based on man's capacity for conceptualization by virtue of abstraction from individual sensory perceptions, and for generalization of moral judgements through allowance for the external perspective of others, as well as on his capacity to develop far-reaching plans for the future. The universal standpoint of knowledge and volition that man can assume differs substantially from the perceptual capabilities of an animal organism – including those of great

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104 Human beings share 98.7 per cent of their DNA with chimpanzees (see Chimpanzee Sequencing and Analysis Consortium 2005).
105 Engels, in: Hüsing et al. 2001, 230 f.
106 See Gallup jr. 1970; Gallup jr. 1977; Gallup jr. 1982. For a more critical view, see Tomasello/Herrmann 2010; Heyes 1998.
107 See de Waal 1997.
108 See Warneken/Tomasello 2009.
109 See Boesch 2003.
110 See Gomes/Boesch 2009.
111 See Mulcahy/Call 2006; Osvath 2009.
112 See de Waal 1997.

apes – in a qualitatively new capacity for reflection, which is expressed in the formation of moral judgements that can be reviewed on the basis of universal principles of reason.

Man's moral capacity and his particular dignity as a rational being make it incumbent on him to take account, in pursuing his own ends, of other organisms' susceptibility to suffering and sensitivity to pain. The closer an animal is to man in regard to the characteristics relevant to morality, the greater the obligation of consideration. Man would violate his dignity as a rational being and the resulting self-respect were he to disregard the particular vulnerability of great apes and other primates. Even if man is the only being with a moral capacity in the sense that he alone is the subject of his acts, primates, and in particular great apes, nevertheless belong to the moral community in other respects – not as subjects capable of assuming responsibility (moral agents), but as the targets of human moral obligations of protection (moral patients).

Animal experiments on great apes are prohibited in New Zealand, the Netherlands, Sweden and Austria.[113] Although the Swiss *Eidgenössische Kommission für Tierversuche* (Federal Commission on Animal Experiments) and the *Eidgenössische Ethikkommission für die Biotechnologie im Ausserhumanbereich* (Federal Ethics Committee on Non-Human Biotechnology) argued in 2006 against a ban on experiments on primates, they insisted that more restraint was appropriate in the approval of such experiments.

However, precisely because the structure and functioning of the primate brain are so similar to those of man, primates have become important experimental animals for neuroscientific research. Workers in the field of brain research emphasize that, in addition to imaging techniques, invasive experiments on primates constitute a vital source of new discoveries in the disciplines of neurology and psychiatry. Hence particular conflicts arise between the use of primates to achieve advances in

113 See *Deutscher Bundestag* 2007b, 1.

scientific knowledge for the benefit of man, on the one hand, and the protection to which primates are entitled, on the other.

4.3 Status of human–animal mixtures of indeterminate species

Human–animal mixtures are living entities which have been created artificially by the methods of experimental biology during the last few decades, and therefore constitute real organisms, whereas in earlier times they were at most the subject of myth. Ethical analysis of the creation and use of these entities is difficult because it is not always possible to assign them to one of the established categories, "human" or "animal", on which moral arguments have traditionally been grounded. The tendency appears to be for the distinction between the two concepts to become blurred.[114]

The dilemma can be resolved by an argument "enforcing" a dichotomous classification involving a careful ontological analysis as a basis for determining whether a specific mixed entity should be conceptually assigned to the human or animal category, so that the rules of human or animal ethics respectively would apply.

However, in some cases at least, the result of this analysis might be that a dichotomous assignment of this kind is unconvincing, and that the entity concerned is therefore a "true" mixture of human and animal. The issue to be decided is whether the mixing, or "blending", of traditional categories infringes traditional appraisals and how this situation should be addressed. After all, if the chimera clearly appears as "neither one nor the other", as a new entity between the human and the animal, all traditional ontological distinguishing features are mingled or abolished. A "special ethics" that takes account of this situation has hitherto existed only speculatively in the

114 For a detailed ethical consideration of the subject, see Beck 2009.

philosophical tradition. In myths and literary texts, mixed entities are sometimes presented as godlike and sometimes as creatures suffering from their nature and therefore to be pitied. However, were it to be decided that mixed entities must never come into being at all in the "phenomenal realm" – this would have to be ensured by means of statutory prohibitions – one would no longer be faced with the problem of whether a particular ethics needed to be developed for mixed entities of indeterminate species.

To facilitate ethical assessment of human–animal mixtures whose moral status might potentially have been modified by the mixing process, the next section of this Opinion develops an initial approach to the classification of these entities on the basis of ontological and scientific aspects and having regard to the qualitative and quantitative degree of manipulation involved. This is followed by a more detailed consideration of the capabilities whose modification might have implications for the moral status of a human–animal mixture.

5 ETHICAL ASSESSMENT OF HUMAN–ANIMAL MIXTURES: FOUNDATIONS AND CRITERIA

5.1 Introduction

Given that it is now, or soon will be, possible to create human–animal mixtures, the question arises as to whether, and if so within what limits, their production can be justified. One justification might be that their creation is appropriate in the context of important biological and medical research projects. However, a counter-argument might be that the dignity of the resulting organisms is violated by their instrumentalization for such purposes, or that suffering is inflicted on these organisms. In addition, the crossing of the biological species boundary between human and animal by technical means gives rise to social and cultural conflicts which extend beyond the individual living organism and the specific research project, and which must likewise be taken into account in the evaluation.

5.2 Deliberate crossing of natural species boundaries

The moral evaluation of the creation of human–animal mixtures may depend on the ethical importance assigned to respect for "natural" species boundaries. In the course of biological evolution, reproductive communities and communities of descent, each constituting a genetic, ecological and evolutionary unity, have developed. Species are distinguished on this basis. Some consider any deliberate transgression of the natural species boundaries to raise ethical problems in itself. In their view, gene transfers that permanently influence the inheritance of the receiving organism represent an illegitimate manipulation of the "order of nature", whose consequences, moreover, are unforeseeable. Man must indeed justify his actions by ethical criteria, by taking responsibility for his objectives, reviewing the means chosen for the purpose, and taking account of the likely consequences. However, there are no grounds for assuming an unconditional obligation to leave the biological boundaries between individual species as such inviolate. Although it is widely held that nature possesses an intrinsic value over and above its functional utility to man, this intrinsic value must be qualitatively distinguished from that of man, of the "end in itself", which alone constitutes the basis of an unconditional entitlement to protection.

If an intrinsic value of nature is invoked, it is also necessary to consider whether it is possessed by each individual species as an intrinsic value-related quality or whether it concerns the natural diversity of species as a whole. From this point of view, some attribute an intrinsic value to the heterogeneity of species as such, and derive from it a human obligation to protect the integrity, stability and beauty of the biological community, an obligation that is also expressed in the aim of preserving species diversity. However, a moral obligation to preserve species diversity as a whole does not imply an unconditional requirement not to cross the boundaries between individual species. From the moral perspective, the creation of human–animal mixtures cannot be prohibited simply because natural species boundaries are thereby crossed.

Nor is the argument of mere "unnaturalness" in itself a valid objection. Transplanting a pig's heart valve to save a human life can surely be deemed unnatural; it may, however, perfectly well be morally permissible if concerns such as, in particular, the risks to human health presented by the introduction of animal pathogens can be overcome.

5.3 Cultural perception of human–animal mixtures

A clear-cut separation between humans and animals predominates in the cultural tradition of civilized societies. Human beings have always been treated differently from animals. For example, humans are required to act in accordance with rules based on moral reflection and imparted principally through language, whereas conditioning and training are used in order to secure desired behaviour in animals. In certain highly developed civilizations (for instance, ancient Egypt), certain animals were regarded as sacred or even as divinities – that is, as of higher rank than humans – and this is still the case today in, for example, India. European antiquity and the Jewish, Christian and Muslim religions, however, have always drawn a clear and fundamental distinction between animals and man, who is deemed to occupy a special position.

Mixed human–animal entities have traditionally featured in mythology, their origins in our culture being mainly in ancient Egypt and Greece. Powerful emotions are often associated with the idea of such mixtures, which have also entered our fantasy world through science fiction. Depending on the particular capabilities and relationship to humanity ascribed to these creatures in the relevant tales, the predominant reaction is either fascination (as, for instance, in the case of the Egyptian Sphinx or the figures appearing in the film *Avatar*) or horror (as with the untameable centaurs of Greek mythology or the Beast Folk of Dr Moreau). With regard to mixed entities that might actually come into being through science, there are indications that the main reaction, at least initially, might frequently be one of intuitive repulsion (the "yuck factor").[115] Such spontaneous emotional scepticism concerning hitherto

115 Such a feeling has been expressed, for example, in responses to public surveys on the formation of hybrids and chimeras in the United Kingdom; see for instance Human Fertilisation and Embryology Authority 2007; People Science and Policy 2006, 69.

unknown organisms that are not readily classifiable and are therefore seen as "uncanny" may be due principally to their alien appearance and the unfamiliarity or unpredictability of their feelings and behaviour. However, it is also associated with the concern that such a manipulation of the natural order might contravene deep-seated taboos, lead to moral confusion or – in religious terms – constitute a presumption vis-à-vis God.[116]

Whenever an intuitive sense of repulsion arises, it is appropriate to examine its underlying causes. After all, it is always possible that consideration of the causes might reveal that the feeling is a reaction to a threat of infringement of the interests or rights of other people or animals. That said, the mere fact that something "arouses fear and loathing" does not suffice for its rejection as morally impermissible. Conversely, a sense of fascination is insufficient for moral endorsement.

5.4 Ontological analysis as a basis for argument

The fundamental, determining characteristics of living organisms and other entities are the subject matter of the branch of philosophy known as ontology (the science of being). From the ontological point of view, criteria based on fundamental aspects of the specific being of a living organism can be described at phenomenological level. Although ontological considerations do not necessarily make for the ethical assignment of human–animal mixtures to one or the other category, they may render this classification more transparent in the relevant context of justification. Unlike the situation with many other bioethical issues, the visual impression gained from sensory perception – as a phenomenological intuition – is more important than abstract conceptual representation where assessment

116 See Academy of Medical Sciences 2007.

of the moral status of human–animal mixtures is concerned. It is perfectly relevant to our decision whether an entity's phenotype is experienced unequivocally as human, unequivocally as animal or, alternatively, as a mixed entity of indeterminate species.

On the basis of Aristotelian natural philosophy, in which concepts such as matter, form, ontogenesis, and capability are used for the apprehension of things and living organisms, it seems appropriate, for the classification of a living organism as *human*, *animal* or a *mixture* too, to establish and take account of ontologically relevant features. Ethically relevant distinctions that do not anticipate one's eventual moral judgement can be based on a specific ontological classification of this kind. These distinctions offer, at least in part, an initial basis for empirically measurable biological features helpful for the classification of definitively proposed or already existing human–animal mixtures.

5.4.1 Substance: matter and form

Intuitive consideration, which is also the essential foundation of the taxonomic classification of living organisms, suggests that this classification should be undertaken on the basis of differences in their substance. In his ontology, Aristotle distinguishes, when discussing substance, between the as yet formless matter of which something is composed, on the one hand, and form, into which this matter is shaped, on the other. An attempt to apply this idea to living organisms while taking account of our present-day scientific knowledge requires us to determine what constitutes their matter and what represents their form. Living organisms are composed predominantly of the same organic materials, which differ significantly from the components of inanimate matter. These organic materials include, for example, the nucleotides in the DNA of cell nuclei, as well as amino acids, fatty acids and sugars, which form the biological matrix of all living organisms. Significant differences between the building blocks of *different* organisms are observed only on the level of more complex biomolecules, for instance between species-specific proteins, whose structure depends on the genetic information encoded in the DNA. Not least owing to the complex biological shaping processes involved in the genesis of these formations in the interior of a cell (DNA replication; protein biosynthesis), the level of biological macromolecules is assignable to the concept of form rather than that of matter. From this point of view, a distinction between humans, animals and human–animal mixtures cannot be made on the level of matter only, as the basic organic substances are common to all living organisms. On the other hand, on the level of form, which then extends from the sphere of molecular biology via the shape and functions of cells, tissues and organs to the specific form of the whole organism and its parts, ontological distinctions can certainly be drawn.

The form assumed by living matter is highly elaborate. Specific formal attributes crucially influence our moral intuition. This is evident, for example, from a comparison of an (actually existing) mouse endowed with a human immune system[117] with a (hypothetical) mouse whose face has been "humanized" by widening and rounding (as in some cartoon films). The immunologically "human" mouse in the laboratory does not particularly disconcert our moral intuition. If, on the other hand, one were to encounter a mouse with a human-like face, the experience might well be shocking. The same would apply in the case of an actual human being with feathers and at least the approximation of an animal form. These fictitious examples show that aspects of the visible form of a living organism considered, in particular, to be relevant to identity may strongly influence their intuitive ontological classification.

A particular manifestation of the form of living matter is biological "information" – in ontological terms, "form as yet

117 See Becker et al. 2010.

without matter". After all, the genetic information that crucially determines the species-specific embodiment and hence the shape of a living organism is transmitted in the form of the biochemically encoded sequence of DNA building blocks. The species-specific nature of the DNA, furthermore, not only is determined by the sequence of building blocks in the three-dimensional structure, but also itself determines which genes are active in what way and in what circumstances, as well as other factors. From this point of view, the genetic information constitutes the form-imparting blueprint of a living organism, whereby that organism is already unequivocally characterized even before it has assumed concrete morphological form.

With regard to the problem of mixed entities, the concept of form can be used to determine whether unequivocal assignment is possible on the basis of the material or genetic nature of the entity under consideration. As will be discussed in more detail later (see Section 5.5), ontological assessment of the form of a mixed entity also depends crucially on the quantitative and qualitative aspects of the mixture. The empirically verifiable classification of the form of a mixed entity by a taxonomic approach could constitute the basis for such considerations.

A biological species is traditionally defined as a type characterized by a set of relevant bodily features. Taxonomy in this way classifies and orders all organisms in a system comprising all life. It takes account of anatomical and/or physiological features which, considered individually or together, are intended to permit clear assignment of a living, or indeed fossil, organism to a particular group. An organism is assigned to a given taxonomic unit if its features predominantly suggest that it belongs to the category concerned. However, such assignment may be impossible if the organism exhibits typical features of two species and neither predominates (as in the case of a mule, whose anatomical features are intermediate between those of the two species concerned, horses and donkeys).

Molecular genetic classification plays an increasingly important part in modern taxonomy. Analysis of DNA marker sequences can be used to identify the species to which each cell of a chimeric – but not a hybrid – mammalian organism belongs. The assignment for the organism as a whole can then be based, for example, on a count or estimate of the number of cells of each species.

5.4.2 Process of generation; ontogenesis

As a complement to the approach of distinguishing living organisms by their form, another possible criterion is their process of generation and ontogenesis (by analogy with the Aristotelian "efficient cause"). Each living organism comes into being and develops by a sequence of processes characteristic of its species, this sequence being controlled by genetic and epigenetic information. The timing and spatial unfolding of the overall process is described and investigated by developmental biology as formal and causal morphogenesis. In the case of organisms that reproduce sexually, this process of development commences immediately after the joining of the female egg with a male sperm. Where an egg that has been fertilized in this way and is capable of development is present, the eventually resulting organism's membership of the relevant species is unequivocal at biological level too.

With regard to mixed entities, an empirically based decision on the species to which an organism belongs can usually be made according to the origin of the germ cells from which the original organism arose by fertilization. This may be helpful, for example, where cells or tissues are transferred for the purposes of chimerization into an organism that is already in the process of species-specific development.

However, there are also cases in which clear assignment on the basis of the parental germ cells is not possible. For instance, the result of natural hybridization is a mixture that cannot be conclusively assigned to one or the other species. After manipulative creation of mixed entities by embryo fusion, it is as a rule likewise impossible to assign it to one or other of the two species. Lastly, with a chimeric parent animal, the germ cells may perfectly well belong to a different species from that suggested by the form of the animal.

In many cases, the formal features of the later stages of development may also assist with the distinction (see the previous section, on form). This is because an organism's embryonic and fetal growth and shaping processes conform to the chronological and spatial schema typical of its species. In the case of chimeras, however, the earlier the cells of two species are mixed, the less likely species-typical embryonic development will be. Again, the criterion of the developmental process is a relatively unhelpful distinguishing feature for the earliest ontogenetic phase of an organism, as species-specific morphogenesis is clearly evident only after the blastocyst stage.

5.4.3 Striving for ends; capabilities

According to the notion of the "final cause", the crowning principle in Aristotle's hierarchy, every living organism strives to attain an end that corresponds to its species. In modern biology, this idea was reflected first of all in developmental biology. A chicken's egg can give rise only to a chick – or else to nothing at all. The principle at work here is "virtual preformation", a determinism resulting from processes of interaction between the genetic material and the environment.

Right from birth, every living organism is endowed with a group of species-typical capabilities that enable it to establish a set of species-specific skills during the course of its life, which it can then apply or exercise in accordance with its individual potential.[118] Depending on species, these capabilities are bound up to a greater or lesser extent with genetically or epigenetically determined patterns. Certain skills that can usually be fully

118 On capabilities relevant to status, see Section 5.6.

developed only after several years of training in childhood and adolescence attain their full flowering only in man. They are addressed in detail in Section 5.6 owing to their particular relevance to moral status.

Capabilities cannot be assigned to a specific species during the early ontogenetic phase for unborn organisms. They can be observed only in the born individual, in some cases only after a degree of maturity has been gained, and serve as features that distinguish humans from other mammals. Where certain capabilities are determined at least in part by genetic factors, they nevertheless develop only during the course of prenatal and postnatal maturation, often in interaction with environmental factors.

5.5 Ontological relevance of the degree of manipulation in the formation of mixed entities

The three ontological classes discussed above – substance, ontogenesis and capabilities – together form a coherent set of interlinked elements. However, differing emphasis may be placed on each of these elements, thus potentially leading to differences in the appraisal of normative status.

A problem with mixed entities is that features with particular ethical implications (especially those relating to brain performance) develop only after birth. Wide-ranging experiments and breeding would therefore be necessary to permit *ex post* ethical investigation of their permissibility. A complex of features that can be established *ex ante*, prior to the initiation of a project, is the *degree of manipulation* involved in the projected procedure. This has three distinct aspects:

- the quantitative ratio of the human and animal contributions to the mixed entity;

- the level of the organism on which the mixing takes effect; and
- the stage of development at which mixing is undertaken.

Quantitative data as a measure of the degree of manipulation, such as the relative proportion of foreign material integrated, are often introduced in ethical arguments. As discussed in Section 5.4.1, this is meaningless on the purely material level; on the level of form, on the other hand, a quantitative relationship can be established between the contributions of the different species, starting with the information-bearing molecules (genes, proteins, RNA and DNA).

In quantitative terms, a transgenic organism has the genetic endowment of the relevant species (about 30 000 genes in the mouse), as against one or very few newly integrated foreign genes. The transgenic contribution is thus well below 0.1 per cent. However, if a foreign chromosome is integrated, the mixing ratio increases by an order of magnitude. In the case of chimeras, the basis could be the relative number of cells of one species in the organism of the other. For instance, neuronal suspensions (e.g. a few thousand cells) could be transplanted into the brain of a mouse embryo (approximately 100 billion neurons per gram of brain tissue), and in this way the degree of manipulation could be estimated as a numerical quantity. In assessment of a chimerically "humanized" embryonic mouse brain, it was argued that this small proportion was indicative of a low level of manipulation.[119]

However, quantitative data of this kind alone are not as a rule convincing, because they must be supplemented by qualitative attributes. In this connection, different categorial aspects become relevant to assessment of the degree of manipulation: the second important aspect is the level of the organism on which the manipulation takes place (subcellular, cellular, intercellular, tissue, organ or organ system) and its repercussions

119 See Greene et al. 2005.

on the various levels up to and including the organism as a whole and the manifestations of its life. In a transgenic animal, the foreign gene or genes are present in every cell, but it is the functioning of these transgenes that determines whether the organism as a whole is fundamentally altered. Certain transgenes modify only immunological types – that is, only the immune system as an organ – while the animal remains otherwise completely unchanged.

The third aspect too is important – namely, the stage of development attained by the receiving organism when the foreign material is introduced. A qualitative leap in embryogenesis occurs with the development of organ primordia. Prior to this stage, the transplant (irrespective of whether it is a gene, a chromosome or a stem cell) can "mix in" with the establishment of the species-specific blueprint and influence or even dominate the shaping of all subsequent organs, including the germline and brain. Once rudimentary organs have formed, on the other hand, the transferred cell or tissue must take its place in a differentiated, even if not necessarily mature, organism and is subject, if the experiment is successful, to that organism's "regulatory sovereignty".

Overall, the more the situation touches on ethical spheres of particular sensitivity, the greater the degree of manipulation must be deemed to be. On the basis of the analysis so far, this will apply especially to substantial manipulation of the germline, and also to manipulation with repercussions on capabilities relevant to an organism's moral status – as well as on drastic changes in external appearance that affect the visual foundation of intuitive distinctions.

5.6 Specific capabilities with implications for status: the special position of the species *Homo sapiens*

5.6.1 Introduction

Man's special position in the animal kingdom is often justified on the grounds of the typically human development of certain capabilities. These include in particular the faculty of speech, self-awareness, the capacity for culture and – of especial ethical relevance – the capacity for morally motivated action. Capabilities and particularities of human life and society (culture, laws and morality) are based on these factors. Present-day ethology is investigating whether certain animals may exhibit at least the rudiments of such capabilities.

5.6.2 Faculty of speech

Observation of the communication of a large number of non-human primate species, as well as that of whales, dolphins and elephants, has now revealed that they possess a repertoire of different vocalizations and in some cases gestures to describe, for instance, different kinds of food or predators.[120] Over many years of association with humans, individual primates and parrots have even learned a relatively large number of words and – although this is disputed – grammatical elements of human language.[121] Some linguists, however, counter that the basis of the faculty of speech is the synthesis of symbolization with the grammatical combination of the relevant symbols. The faculty of speech proper can be said to exist only if the words become sufficiently abstract to represent things that are absent, and

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120 See Seyfarth/Cheney 2010.

121 See Savage-Rumbaugh et al. 1993; Pepperberg 2002; Kaminski/Call/Fischer 2004.

only if they can be incorporated in hierarchical syntactic structures and can be used and flexibly recombined in a variety of fields. Again, human speech can also express past and future. In this complex, efficient form, speech is proper to humanity only. It permits the accumulation of knowledge that is transmitted from generation to generation and guides action in all spheres of life. In this way, man's cultural dynamism ultimately outstripped the process of biological evolution and led to the formation of spoken and written language and the language of art and science. Speech and language became the engine of technology, science, art and religion.

5.6.3 Self-awareness

Self-awareness, in philosophy, relates to man's capacity to enter into an observing and reflective relationship with himself. Self-awareness can be seen, at least on the level of phenomenological description, as a meta-state of awareness "proper" that comprises the possession and experiencing of mental states such as perceptions, emotions, memories and thoughts. Self-awareness, in other words, involves thoughts which are in turn directed towards thoughts. It allows us to see ourselves as acting subjects, to reflect about ourselves and our own thinking, as well as to modify that thinking. In this way, we not only can see ourselves as self-determined in our actions, but, by virtue of our capacity for self-awareness, are capable also of seeing our thinking as self-determined. Again, the ability to reflect about ourselves and our thoughts in this way enables us to specify reasons for our actions and to reflect on and correct these. Accordingly, self-awareness must be conceived as an essential condition of the moral capacity typical of mankind.

The existence of a fully developed self-awareness of this kind is virtually impossible to prove without the capacity for reflective communication, a factor that impedes empirical investigation of the possibility that self-awareness might exist in non-human organisms that lack the faculty of speech. However, ethological studies indicate that many animals do indeed possess the rudiments of a self-awareness and are capable of a "meta-cognition" that enables them to reflect on their own thought processes and those of other individuals.[122] For instance, some members of the corvid family recache their food if their first caching was observed by a member of the same species – but only if they themselves are experienced plunderers. Ethologists explain such observations by claiming that the birds firstly can understand the intention of stealing food in other members of their species, and secondly are able to undertake "time travel in thought" and to establish (or re-establish) caches in such a way that they will be particularly well protected from thieves in the future as imagined on the basis of current information. In so doing, they employ sophisticated deceptive manoeuvres that also take account of potential thieves' opportunities for watching and obtaining prior information.[123] Great apes exhibit similar capabilities. However, methodological reservations persist as to the validity of such observations.

Although such conceptions of an animal's self-awareness cannot be equated with fully fledged reflective development of this capacity, they can perfectly well be used for the assessment of ethically appropriate treatment of human–animal mixtures even without evidence of fully developed self-awareness. In the case of an ethical approach based on preference utilitarianism,[124] such rudiments of an animal's self-awareness, as well as rudiments of the faculty of speech, are applied as morally relevant criteria to justify the personhood of animals, such as great apes, and consequently to declare them to merit protection on the same level as human beings.

122 See Smith 2009.
123 See Dally/Emery/Clayton 2006; Clayton/Dally/Emery 2007; Stulp et al. 2009.
124 Unlike classical utilitarianism, preference utilitarianism seeks to maximize not the sum of happiness, but the fulfilment of subjective preferences (wishes).

5.6.4 Capacity for culture

In broad terms, culture is everything that man himself brings forth and shapes creatively – all the capabilities and customs he develops – as opposed to nature which is neither created nor modified by him. Samuel von Pufendorf described "culture" as the source of human happiness, since it raised life above the necessity that was the lot of animals. He defined culture as the "totality of activities whereby individuals shape their lives in specifically human, as opposed to merely animal, form".[125]

Immanuel Kant's definition of man as a culture-producing being is expressed in relation to nature. Kant defines culture as control over nature by technical means and science and by the renunciation of instinct (i.e. by discipline and self-control). For him, man and culture are the ultimate end of nature, with which man's capacity for moral action in accordance with the categorical imperative is associated: "Act only on that maxim whereby you can at the same time will that it become a universal law."[126] A man is cultivated if he consciously directs his actions to ends that are "good in themselves".

The British anthropologist Edwin Burnett Tylor laid the foundations of modern cultural anthropology and ethnology with his comprehensive definition of culture: "Culture or civilization, taken in its wide ethnographic sense, is that complex whole which includes knowledge, belief, art, morals, law, custom, and any other capabilities and habits acquired by man as a member of society."[127] Tylor's conception of culture eliminates the distinction between culture and civilization and incorporates the observable aspects of life (habits and custom), as well as their preconditions in terms of ideas and norms (knowledge, belief and morals) and their products and artefacts (art and law).

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125 Pufendorf, quoted in Welsch 1999, 46.
126 Kant 2005.
127 Tylor 1871, 1.

From this perspective, man is thus a culture-producing being. This definition is associated, in cultural anthropology, in different ways with a set of characteristics, which include the creation and use of tools, curiosity about fire, the faculty of speech and non-verbal communication, writing, literature, learning, education, the formation of shared values, the establishment of institutions, human action in the form of work, technology, science, art and the development of theories (logic, philosophy, ideology, world views and religion), as well as tradition, without which these manifestations could not be transmitted. Man has the capacity to ascribe meaning to his existence and to render account for the task of conferring meaning.

The genesis of the attributes of man's capacity for culture is partly accounted for by certain anatomical preconditions resulting from biological evolution. The enlargement and development of the brain facilitated the assimilation of large quantities of information, flexibility and the associated capacity for conceptual abstraction, which permits problem-solving behaviour guided by general criteria. The precision motor skills involved in tool use were rendered possible by a thumb opposable to the other four fingers and by the resulting pinch grip; while a modified larynx and the development of vocal cords specifically suited to the production of speech contributed to faster and more effective communication.

For some decades now, ethology has closely investigated the significance of biological factors for human behaviour and repeatedly drawn attention to the problem of the comparability of animal and human forms of behaviour, which are commonly associated with the capacity for culture. The findings confirm that the appearance, feeling, thinking and behaviour of human beings are moulded by their biological nature, while animal studies are deemed to constitute empirical evidence of a capacity for culture in animals. For instance, primates certainly have a complex social life, use tools and employ sophisticated hunting strategies.

More than a dozen different definitions are encountered. Does the capacity for culture signify the use of tools and the faculty of speech, or the invention of writing? Is it the working of objects, their aesthetic modification and use for novel purposes, or is it the act of contemplation? Or, again, is it the capacity to acquire knowledge and ways of behaving by social learning and cognitive observation? According to this last definition, chimpanzees, other primates, dolphins, whales and some birds would be deemed to possess a capacity for culture. Hubert Markl has rightly pointed out that all animals learn and make decisions, and that some – for instance, birds and mammals – also transmit what they have learnt to other members of their species; in this sense, they exhibit culture, albeit merely on a rudimentary level compared with human, "real" culture.[128] In Markl's view, such rudiments and preliminary stages cannot be equated with fully developed achievements. Preliminary forms or elements of a capacity for culture can be observed in a number of animal species – in particular, great apes – but in quantitative terms alone these lag so far behind the more complex culture of humanity that a fundamental qualitative distinction must still be deemed to exist.

Another open question concerns the extent to which man's biological evolution has increased in complexity by virtue of an evolution on the cultural level. A cultural process of evolution, whose mechanisms must be clearly distinguished from those of biological evolution, can proceed much faster than biological evolution. It can in addition take place in the form of a goal-directed process of optimization. The theory of cultural evolution does not rest content with investigation of the development of the state, changing forms of society, and the refinement of table manners. It is always also concerned with the fate of the living organism that modifies itself in the process of modifying its world, a process which it has itself initiated: in the process of human development, which took place

128 See Markl 2009.

in a mere instant on a geological time scale, cultural evolution has assumed increasing importance. For this reason, man can be seen as the organism which, by virtue of its increasingly conscious achievements, supported by culture and frequently also facilitated by institutions, has played a part in its own evolution.

5.6.5 Moral capacity

Traditional philosophy describes mankind's moral capacity as a capability that allows an unequivocal distinction to be drawn between man and all animals. An essential attribute of a human being is that he must justify his actions and choose freely between alternative courses of action. In this sense, human dignity – in the view of, say, Immanuel Kant – is bound up with the criterion of rational self-determination, which, for its part, cannot be separated from the moral capacity. From this point of view, the dignity of man is based on the capacity, which he alone possesses, to recognize what he as a member of the human race ought to do. However, this capacity need not be translated into reality in every case and at every time in the life of an individual.[129] Instead, the moral capacity, considered in these terms, is an essential characteristic of man, even in cases where he is prevented from perceiving the normative demands of morality and subordinating his actions to them.

According to recent sociobiology and the evolutionary ethics based on it, however, the moral capacity is not a capability that distinguishes humans as a category from animals. These disciplines point out that the human moral capacity arose in accordance with the same evolutionary principles as the human figure or human physiological functions.[130] Charles Darwin already believed that natural selection also retained and

129 See Kant 2005.
130 See Schmitz 2000.

constantly propagated variants in instinct where this proved useful for survival. In *The Descent of Man* (1871), he advanced this idea primarily in connection with human social and moral behaviour.[131]

Ethologists distinguish between, on the one hand, genetically determined programmes of behaviour which underlie, for example, the seemingly altruistic actions observed between closely related social insects such as ants or bees and do not presuppose any moral considerations on the part of a given individual, and, on the other, possible rudiments of moral sensitivity studied in more highly developed animals with a capacity for flexible and complex behaviour and higher social intelligence. If animals with such capabilities exhibit forms of behaviour which, in man, presuppose moral concepts of fairness, empathy or altruism, it may be wondered to what extent at least rudiments of such concepts also influence the actions of animals. For instance, dogs react negatively to unfair situations, such as when another dog receives a better reward for the same work in an experiment,[132] while chimpanzees are seen to help others spontaneously even if effort is involved and there is no prospect of reward.[133]

Yet it remains questionable whether a moral capacity in the traditional philosophical sense can be established empirically in animals at all, given the absence of any means of communication on the level of human speech. After all, while animals studies may hint at a certain moral behaviour shared by humans and animals and at its presumed evolutionary roots, they are hard put to it to estimate what kind of process of intellectual reflection might underlie such behaviour.

The decisive criterion of human moral capacity is, precisely, not just a given "moral" manner of action that can be empirically observed, but instead the process of intellectual

131 See Darwin 1871.
132 See Range et al. 2009.
133 See Warneken et al. 2007; Warneken/Tomasello 2009.

reflection that precedes this action (or the failure to undertake this action) – that is to say, consideration guided by reason and able to invoke reasons.

5.6.6 Conclusion

Even if the capabilities discussed here are not the prerogative of humanity alone, in man they are developed to a much higher level of complexity and based on conscious reflection. This has placed them on a new qualitative level. Gradual biological steps in evolution, coupled with cultural developments, have manifestly led to the attribution of a special role to man.

It is seldom seriously claimed that the ethically significant difference between humans and animals is based on biological membership of the species as such. Biological membership of a species is relevant in so far as it indicates the essential natural precondition for the species-specific capabilities (the faculty of speech, the capacity for culture, self-awareness and moral capacity) that constitute the basis of man's special position. In this sense, membership of the species is a component of the concept of human dignity (see Section 4.1), although not its foundation. The creation of human–animal mixtures exhibiting an approximation to the typically human capabilities to a much greater extent than existing animals would call into question this culturally based and species-related foundation of our understanding of human dignity.

A vital determinant of man's special position is the intellectual and moral competence permitted by his capabilities, which enables him to see himself in the context of his nature and, in so doing, also to recognize the conditions that he needs for the preservation and unfolding of his life. Man is the only being that is aware of its dependence on other living organisms, and is also likely to remain for the foreseeable future the only organism that can, in the context of the culture which it has created for itself, take responsibility not only for itself but also for the natural, historical and cultural foundations of its life. This capability has long become an obligation. Humanity's "special position", which continues to be upheld by modern biology,[134] is demonstrated essentially in the obligation assumed by man, by virtue of his existence, for the preservation and unfolding of his conditions of life.[135]

The special position of man in the above sense does not result in a fundamental, absolute priority of his interest in the avoidance of suffering as compared with comparable needs on the part of animals. The specific nature of the general implications of man's special position in terms of animal ethics are disputed. It is beyond the scope of this Opinion to specify them in concrete form. At any rate, any approximation established by ethology to the human development of these capabilities has implications for appraisal of the moral status of the animals that possess them and the extent of protection to which they are entitled (see Section 4.2).

5.7 The precautionary principle as a basis for addressing developments in research on human–animal mixtures

The precautionary principle nowadays guides social attitudes towards new developments in the field of science as elsewhere. Hans Jonas drew attention in 1979 to the new ethical challenges presented by our technological civilization to science and society – namely, the vulnerability of nature, of the planet's entire biosphere and of the human species due to the novel quality of man's technical interventions with their irreversible consequences.[136] According to this author, man is ill-prepared for this development: "that the predictive knowledge falls behind

134 See Neuweiler 2008.
135 See Gerhardt 2007, 432 ff.
136 See Jonas 1985; concerning the following, see also Werner 2003.

the technical knowledge that nourishes our power to act, itself assumes ethical importance."[137] An ethics of responsibility directed towards the future is therefore in his view necessary: we assume responsibility for nature "because of our power over it".[138] The discrepancy between our scientific and technological capabilities and the capacity to assume responsibility must be overcome. Jonas advocates an ethics for the future based on the principles of caution and self-limitation: "Act so that the effects of your action are compatible with the permanence of genuine human life."[139] For Jonas, the increasing blurring of the boundary between fundamental research and the application of its results raises questions concerning the limits of the freedom of research. In his view, the first duty of a science that espouses an ethics of the future is the acquisition of ideas and information on the short- and long-term effects of developing technologies. Jonas is certainly in favour of self-limitation by the research community on the basis of its own responsibility, in accordance with the paradigm of the Asilomar conference on safety issues in genetic engineering held in 1975. However, he also considers external monitoring of scientific activity to be justified.[140]

Some of Jonas's ideas fed into the concept of the precautionary principle that has been an essential foundation of environmental policy and environmental law since the end of the 1980s. It was incorporated in the Treaty on European Union (Maastricht 1992), the Rio Declaration of 1993 and Article 20a of the German Basic Law. Its significance extends far beyond the environmental field, as it is also applied to the treatment of technical innovations. Expressed in simple terms, the precautionary principle is applicable in all situations where the potential consequences and corresponding probabilities of occurrence cannot be unequivocally specified.[141]

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137 Jonas 1985, 8.
138 Jonas 1985, 7.
139 Jonas 1985, 11.
140 See Werner 2003.
141 See Rath 2008, 119.

However, the precautionary principle is in fact interpreted in different ways. A narrow interpretation permits preventive measures even in situations "where it is not completely certain from the scientific perspective that harm will arise. In extreme cases, this may even mean that an innovation must be abandoned 'in the event of doubt'. In addition, it follows from this narrow interpretation of the precautionary principle that the onus of proof is reversed. It is not government that must adduce evidence that a product or technology is hazardous; instead, the manufacturer must prove that his technology or product is not hazardous."[142]

The treatment of research, which is protected by the fundamental right of the freedom of science, on the other hand, should be based on a broad interpretation of the precautionary principle, a culture of precaution.[143] A reversal of the onus of proof in research – projects being impermissible as long as uncertainty persists as to their consequences – can result in violation of the principle of the freedom of research. Precisely here, priority must be given, in the application of the precautionary principle, to openness and flexibility in relation to subsequent potential courses of action. Three possible conclusions may be adduced as examples:

1. Adoption of appropriate measures to broaden the basis of information for a scientific appraisal of risks and consequences.
2. Inclusion in an interdisciplinary scientific discourse, as well as a social discourse, with a view to laying the foundations of a responsible approach to research involving mixed entities.
3. Provisional agreement – by consensus within the scientific community or society, or as dictated by society – not to engage in certain research projects until there are sufficient

142 Rippe 2006.
143 On the following, see Randegger 2006.

indications that a given level of safety and security for society, compatibility with its norms, and protection of humanity and the environment can be guaranteed.

6 ETHICAL ANALYSIS AND EVALUATION OF EXAMPLES

6.1 Cytoplasmic hybrids (cybrids)

6.1.1 Aims of human–animal cybrid creation

As already stated in Section 2, medical research has an interest in obtaining readily reproducible stem cell lines specific to individuals and genetically identical to the donor's cells. Should a disorder be due to genetic variations or defects, these ought also to be detectable in the genes of the cell lines derived from the relevant patients. Advances in understanding of the causes of disease are expected from the acquisition of information on the functional pattern concerned.

Another important objective of medical research may in certain circumstances also directly benefit the patients concerned. In the last twenty years, partly through comparison of complete human gene sequences, researchers have identified a large number of genetically determined differences that are responsible not only for diseases but also for differences in response to specific drugs. This means that it may be possible to optimize a planned course of drug treatment by preliminary cell culture studies. The most suitable combinations of active substances for a given individual could then be assembled so as to permit "personalized medicine".

A third objective has to do with the high regenerative potential of embryonic stem cells: they are pluripotent, meaning that different types of tissue can be developed from them.

Yet the use of human eggs required for the derivation of embryonic stem cell lines presents both medical and ethical problems owing to the health risks associated with the harvesting of these eggs. The principal advantage of cybrid technology would be, precisely, avoidance of the need for human eggs, since animal eggs, for example from cows or rabbits, could be used instead. The availability of a robust method of deriving pluripotent human cell lines for disease research, individual testing of therapeutic procedures and the development of new cell and tissue therapies would certainly offer considerable medical benefits. To date, however, the human–animal cybrid approach has not been widely pursued. For this reason, insufficient data are so far available for an adequate appraisal of the technique from the medical perspective. Again, it should be borne in mind that the first experiments in this field involved the combining of material from relatively distantly related species (cow eggs and human nuclei); the prospects of success might be better if eggs from animals with a closer biological relationship to man were used. This, though, would considerably exacerbate the ethical problems.

Another possible reason for the dearth of cybrid research so far may be the development of a fundamentally new technique in 2007 – namely, the derivation of induced pluripotent stem cells (iPS cells) by the reprogramming of somatic cells. The technique involves the reprogramming of adult somatic cells by means of specific molecular signals, yielding stem cells that behave in many respects like embryonic stem cells.[144] The medical objectives mentioned above could be achieved by means of this technique without the use of human or animal eggs. The next few years will show whether the promise of iPS cells will be fulfilled, particularly in view of doubts about the future feasibility of solving certain current problems with these cells.[145] These problems concern the possibility of incomplete reprogramming, the occurrence of mutations after reprogramming, the activation of retroelements in the genome and the current need to use retroviruses or adenoviruses, which present a risk of cancer; alternatives have not yet been developed to a sufficiently mature stage.[146] Cybrid research may well

144 See Okita/Ichisaka/Yamanaka 2007; Wernig et al. 2007.
145 See Pera 2011.
146 See Blasco/Serrano/Fernandez-Capetillo 2011.

assume greater importance again in the future. In view of the associated fundamental ethical issues, criteria for its appraisal must be established on a precautionary basis.

6.1.2 Ontologically relevant aspects of human–animal cybrids

An ethical evaluation of human–animal cybrids can be undertaken on the basis of ontologically relevant aspects (substance, ontogenesis and capabilities).

A cybrid comprises a combination of a human somatic cell nucleus and an enucleated animal egg. The mass of the egg's outer envelope (the zona pellucida) and plasma is appreciably greater than that of the injected nucleus: at least 95 per cent of the mass of the initial material is of animal origin and no more than 5 per cent human. However, this fact in itself is immaterial to an ethical evaluation, as all living organisms are predominantly composed of the same basic organic materials (see Section 5.4).

In terms of form, a cybrid comprising a human somatic cell nucleus and an enucleated animal egg would, within a few days at most, presumably resemble a corresponding construct of a human nucleus and an enucleated human egg. This is because the cybrid divides like an early human embryo after the initial reprogramming steps. With regard to its intended application – the derivation, after a few days of development, of fully functioning embryonic stem cells for further experiments, including experiments on humans – the morphological resemblance to a human embryo is in fact desired by scientists wishing to create a cybrid. Although morphogenesis in the first few days of development is still crucially determined by epigenetic signals from the animal egg (cytosolic RNA, control proteins and hormonal signals), this relationship is reversed when control is subsequently assumed by the human nuclear genome.

From the point of view of cell-biology information, the clone developing after reprogramming of the nucleus would be an entity assignable to the species *Homo sapiens*, since only about 37 of the approximately 25 000 genes – namely, the mitochondrial genes – would be of animal origin and hence contain the corresponding genetic information. On the basis of its genetically encoded information, the cybrid would accordingly be some 99.85 per cent human. This characteristic too correlates with its explicit purpose – namely, the use of human–animal cybrids in preclinical experiments as a biologically equivalent substitute for purely human embryonic stem cells.

With regard to a cytoplasmic hybrid's process of generation and ontogenesis, on the other hand, assignment to either the human or the animal category is unclear. This is because the procedure involves the artificially forced reprogramming of a human somatic cell nucleus which becomes capable of the – at least rudimentary – formation of a new organism in the medium of an enucleated animal egg. It is thought likely that the physiological mismatch between the human nucleus and the enucleated animal egg would result in abnormalities and limitations in the subsequent course of the development process.

Only conjecture is at present possible concerning the potential capabilities of a human–animal cybrid after a few days of development. However, since the scientific objective is precisely that of deriving from the cybrids embryonic stem cells identical in as many respects as possible to human embryonic stem cells, it seems justifiable to assume in principle that a human–animal cybrid "successfully" yielded by the relevant technique would on the whole resemble a human rather than an animal embryo. Yet owing to its artificial, cross-species origins and to genetic defects in the transplanted nucleus, that embryo might well be so badly damaged as virtually to preclude its further development in the long term – if only because it could presumably not be successfully implanted in a uterus, at least if material from distantly related species such as cows and humans were used.

6.1.3 Assessment of the ethical legitimacy of the creation and use of human–animal cybrids

Position A: The creation and use of human–animal cybrids are ethically permissible

In the view of some members of the German Ethics Council, for the purposes of ethical appraisal it must be borne in mind that the combining of an enucleated egg with an isolated nucleus constitutes a highly specific precision-microscopic procedure that does not differ fundamentally from the standard methods used in experimental developmental and cell biology. Cell constructs of all kinds can be stimulated to grow and divide and even to form groups of cells and tissues when cultured in suitable media. Cell splitting, removal or incorporation of nuclei, cell transplantation and fusion, occasionally also involving cells of different species, are widely used methods. Pluripotent ("embryonic") stem cells too can be obtained by such techniques, as demonstrated, for example, by the recent development of the technique of somatic cell reprogramming (yielding induced pluripotent stem cells).

The production of cytoplasmic hybrids gives rise to an entity that is not created from functional germ cells, but assembled from manipulated cell components. The technique of cell nuclear transfer takes place in a completely different context from the generation of progeny and is quite different from that of (natural or artificial) fertilization. This being the case, and because the stage of possibly artificially induced totipotency must be accepted for only a few days, while the process as a whole is directed towards the creation of an entity assignable in both taxonomic and ontological terms neither to the genus *Homo* nor to that of the other animal species involved, the experimental cell construct ought not to be seen as a human embryo. The artefact's DNA has not come into being through the joining of two different sets of chromosomes, but derives predominantly from the donor nucleus; its material composition, physiology and biochemistry, as well as the first steps in its differentiation, are determined epigenetically by the enucleated animal egg. Although attempts can be made to derive pluripotent stem cells for a cell culture from the artefact, this does not mean that the artefact is an embryo as defined in the Embryo Protection Act, any more than other experiments involving the induced creation of such cells from reprogrammed somatic cells make these cells an embryo. The particular biochemical or cell-biology functions of artificially produced stem cells of this kind – for instance, whether they are or are not suitable for therapeutic use – are irrelevant to the ethical evaluation of the cybrid.

A human–animal hybrid construct could potentially lead to the attempted creation of a born mixed entity only if it were implanted in a human or animal uterus. Only then could the physical and mental welfare of the subsequently born entity be impaired; only then would there be a risk of repercussions on man's conception of himself in society; and only then might it in certain circumstances be justifiable to fear that subsequent progeny of the mixed entity might likewise be affected. None of these risks can materialize if the cell structure created remains *in vitro*. For this reason, implanting in a human or animal uterus must be prohibited.

Even if it is concluded that an artefact arising from a human nucleus and an animal zona pellucida is a human embryo or at least an entity resembling a human embryo, this by no means automatically answers the question whether the derivation and use of such an artefact is permissible. This is because the long-standing debate – which is not confined to the subject of mixed entities – on the purposes for which human embryos may be produced and used now also comes into play. If, in accordance with a widely held view, it is assumed that human dignity and the protection of life become relevant at most after implantation in the maternal uterus because an embryo *in vitro* in itself lacks sufficient potential for development, given that organic connection with a human being and the embryogenesis that depends on it are existentially necessary, there are good arguments for considering the creation and use of cybrids to be permissible. Significantly, the creation of embryos for research purposes is allowed in many countries provided that they are not transferred into a human or animal body. Such a procedure is not deemed to violate individual human dignity or the dignity of the human species. This is all the more true if, by virtue of its origins and mixed character, the embryo is not capable of implantation at all and can therefore *a priori* not develop into a mature organism able to experience feelings and pain, to form a consciousness, and to be perceived by others in a social community as one of their own. The form of generation is also relevant: even if the production of embryos by the established techniques of assisted reproduction is rejected for research purposes, their creation as cybrids and hence also as artefacts for the purposes of research can be deemed acceptable provided that there is no question of their being transferred into an animal or human uterus.

Position B: The creation and use of human–animal cybrids are ethically impermissible

Some of the members of the German Ethics Council take the view that a cybrid obtained from a human nucleus and an animal zona pellucida closely resembles a human embryo in terms of its basic structure, as all the essential characteristics needed for the development of the human individual are present in latent form in its nucleus. Almost all proteins in the cells of the cybrid are determined by the human DNA after only a short time. There remain only a tiny residue of mitochondrial animal DNA and a small number of animal proteins, which, however, do not determine any essential characteristics and higher-order functions of the potential individual. Hence the cybrid should be assigned to the taxonomic category of humans in accordance with its molecular-genetic classification. Given the genetic pattern present in the cybrid from the beginning, it can also be assumed that human-specific capabilities, which come into being only during the course of prenatal and postnatal development, exist in latent form from the beginning. The cybrid exhibits all the characteristics of a human fertilized egg. Furthermore, research deliberately seeks to achieve this "quasi-identity" of the cybrid so that it can be used for the derivation of pluripotent stem cells with applications in man. The process of generation of a cybrid – its technical creation from an enucleated egg and a nucleus – on the other hand, is not typical of the species. Having regard to all the ontological criteria – molecular-genetic classification, striving for ends, and capabilities – the overall conclusion must be that the entity should be assigned to the human species. For this reason, cybrids do not differ fundamentally in their moral status from human embryos in the earliest stages of cell division; instead, they should be assigned to the human species in the same way as a fertilized human egg. They are consequently fully entitled to protection from use and destruction for research purposes.

With regard to the position that the creation of human–animal mixtures violates human dignity, it is immaterial whether they are to be destroyed at an early stage or whether they could develop at all to the point of implantation or even birth. The capacity of a cybrid to develop presumably increases the closer the relationship to man of the animal from which the egg needed to produce the mixed entity was taken. The greater the similarity to man of the organisms created, the more applicable the results obtained in this way would be to man. The rule of caution that can be derived from this argument in terms of a possible violation of individual human dignity is as follows. Since the possibility cannot be ruled out that cybrids too might be implanted in a uterus, thereby giving rise to a human entity that would be robbed of its identity and integrity, such projects should not be undertaken. Owing to its basically fragmentary nature, the Embryo Protection Act does not provide for penal sanctions for such acts, so that the advocates of this position consider it necessary explicitly to include also the creation and use of cybrids within the prohibition of the production and use of human embryos for research purposes enshrined in Section 7 of the Act (ESchG); the Act should therefore be amended accordingly.

Unanimous recommendation

Independently of the question of a possible ban on the creation of human–animal cybrids, the German Ethics Council unanimously recommends that the implanting of human–animal cybrids into a human or animal uterus should be prohibited. An explicit provision to that effect should be incorporated in the Embryo Protection Act.

6.2 Transgenic animals with human genetic material

6.2.1 Objectives of the creation of transgenic animals

During the course of the last three decades, millions of transgenic animals with human genes have been used for research purposes in the world as a whole. Mice and rats are the preferred experimental animal models in this field of research, in which, however, fruit flies, zebra fish and other organisms are also used. Other relevant species are chickens, sheep, goats, pigs and lately also non-human primates, which raise particular ethical issues. The incorporation of human genes in experimental animals is a very important research model for investigating the functioning of these genes and the causative mechanisms and development of human diseases (see Section 2.2.2).

Genes not only code for a large number of different proteins, but may also perform control functions, so that, when switched on, they may initiate in cascade the activation of other genes capable of forming an entire organ. The developmental biology involved in the control of the genesis of tissues, organs and entire organisms is in many respects still unknown. In particular, the functioning of control genes can be properly recognized and understood only in the living organism. Their manipulation might, however, at the same time modify the entire complex system.

In medical research, certain genes that give rise to disease in humans are inserted into a mouse. The transgenic mouse then often develops similar symptoms. Study of the animal yields information on the functions of the gene and its role in the genesis and course of the relevant disorder (see Section 2.2.2).

The principal limitation of animal models so far has been that many human genetic disorders are multifactorial; in other words, they are caused by not one but a number of genes. So far it has been possible to establish only rudiments of the mechanism of multifactorial disorders by means of such research. Again, the results of animal studies have only limited applicability to man.

In addition, there are a relatively small number of medical research projects involving larger animals. In the case of the pig, the principal aim is to produce immune-tolerant cells, tissues and organs for transplant medicine, with a view to preventing rejection. Initial clinical studies have also been conducted on the transfer of insulin-producing cells from transgenic pigs into human patients suffering from diabetes mellitus. However, it is as yet impossible to determine whether, and if so when, widespread clinical application of xenotransplantation will become feasible, partly because the risk of the transfer of animal diseases to humans cannot at present be ruled out. Again, as explained in Section 2.2.2, work is in progress on the generation of pharmaceutical active substances in the form of transgenic molecules from humans for the manufacture of medicinal products in cows, goats or chickens.

6.2.2 Ontologically relevant characteristics of transgenic animals with human genes

Only individual human genes have so far been inserted into the animal genome. On the level of substance and ontogenesis, such a procedure must be clearly distinguished in ethical terms from the mixing of entire human and animal genomes. The ontological status of these animals is in this respect unaffected by the transfer of individual transgenes; they remain animals.

More far-reaching developments are, however, beginning to emerge. For instance, entire human chromosomes with some 1000 genes have already been inserted into experimental animals.[147] Work is also in hand on the production of artificial chromosomes from human material and their introduction into experimental animals. Where such large genome segments are transferred, it is at least conceivable that ontologically based assignment to a species will in future no longer be unequivocally possible, especially if the transferred genes drastically modify the shape or capabilities of the animal. However, the development of human capabilities is a theoretical possibility when individual genes are manipulated too, should it in future prove feasible to implant the control genes that are partly responsible for the development of typically human behaviour into closely related primates (see the FoxP2 example discussed below).

For this reason, appraisal of the ethical issues raised by transgenic animals depends primarily on the specific degree of manipulation involved in the experiment. This can be assessed on the basis of the stage of development of the receiving animal, the degree of relationship between the receiving and

147 See Tomizuka et al. 1997.

animal and man, and the number and potential of the human genes introduced.

In the creation of transgenic animals, manipulation takes place at such an early embryonic stage, before organ formation, that the transferred gene enters the germline of the experimental animal. In this sense, the degree of manipulation is substantial, since the evaluation must concern modifications inheritable over the course of generations. However, the majority of the transgenic animals on which research has hitherto been conducted – in particular, rodents – have remained completely unchanged in external appearance and behaviour. A protein with a slightly different structure or a receptor molecule modified in a small number of respects cannot be observed visually in the animal. Again, a mouse with an immune system that functions somewhat more or less efficiently remains a mouse, even if it produces human antibodies. Even so, as considered in more detail below, the classical issues of animal welfare still arise with regard to the effects of a transfer of human genes on the functioning of the animal organism.

In determination of the degree of manipulation involved in a gene transfer, the functioning of a transferred gene in the organism – its epigenetic effect – is also relevant, as the example of the FoxP2 gene shows.[148] The protein coded for by the FoxP2 gene is a transcription factor that regulates the activity of possibly as many as 1000 genes, providing as it does a template for RNA polymerase by binding to the DNA. FoxP2 is generally associated with genes involved in the formation of the faculty of speech, since the gene for FoxP2 was first discovered in studies of a London family of whom several members were suffering from severe speech and language disorders manifestly attributable solely to a defect in this gene. The fact that such a complex higher brain function as the articulation of speech could be critically influenced by a single gene was previously unknown to science. The vocalizations of transgenic

148 See Newbury/Monaco 2010.

mice with a human FoxP2 gene were observed to be lower in pitch. The basal ganglia of the mouse brain were also found to be conspicuously altered. However, it is unclear whether there is in fact any connection between the modification of the innate vocalizations and the faculty of speech.

In view of the distant relationship to man of transgenic animal species such as mice or rats, or indeed chickens, cows or goats, it is unlikely that their ontological status as animals would be uncertain even after the manipulations described; it is instead issues of animal welfare that arise here. Aspects of the protection of human dignity are involved at most in the creation of transgenic primates (see Section 6.2.4).

6.2.3 Assessment of the ethical legitimacy of creating transgenic experimental animals

Animal experiments are an important methodological tool for the investigation of genetic disease causation with the aim of developing new diagnostic and therapeutic procedures. As a rule, the transfer or deactivation of individual genes or groups of genes does not alter the normative status of the animal; nor is human dignity directly impaired. However, as with all other animal experiments, these actions could have animal-welfare implications. Each animal has an intrinsic value, which researchers should respect and which, when using animals, they must weigh against the benefit they themselves derive from it.

It is therefore necessary not only for the experimental animal to be kept in conditions appropriate to its species, but also for pain resulting from the insertion of a human gene to be avoided. According to the provisions of the Animal Welfare Act, departures from these requirements are acceptable only if counterbalanced by a corresponding substantial benefit in terms of establishing the causation of diseases and the development of new treatments. These considerations must be borne in mind by the animal welfare commissions of the relevant regional councils and Federal State directorates when evaluating applications to conduct such experiments. A strategy to limit the number of experiments involving transgenic animals, as well as animals in general, is required.

It will in the future also be increasingly necessary to decide how comprehensively protection of an animal's well-being is to be defined in the overall context of animal welfare. In the transfer of human capabilities and shape to an animal, irrespective of the relevance of these factors to its status, at issue will be not only protection of the transgenic animal from suffering in the classical sense, but also its social interaction, which might well be significantly impaired if its form or capabilities were distorted by the mixing of species.[149]

Having regard to the foregoing, the German Ethics Council does not consider there to be any current need for legislation in relation to transgenic animals with incorporated human genetic material, except for the introduction of a ban on procedures that might result in the formation of human egg or sperm cells in the animal. However, the application of the Animal Welfare Act should be reviewed to determine how far its aim of protecting "life and well-being" should in future include not only protection of the animal from suffering but also criteria to permit the animal created to have an appropriate life, in particular in terms of its needs for social interaction.

6.2.4 Particular problems of the creation of transgenic primates

Because of their close relationship to man, the possible creation of transgenic primates might well give rise to situations in which cognitive and mental capabilities relevant to status

149 Cf. Mark Greene's oral communication at an expert meeting of the German Ethics Council held in Berlin on 25 February 2010, accessible online at http://www.ethikrat.org/veranstaltungen/anhoerungen/mensch-tier-mischwesen [2011-06-22].

are modified significantly in the human direction by the introduction of the human control genes concerned. This would constitute an appreciable degree of manipulation.

Given that our current knowledge of the possible effects of creating transgenic primates is extremely limited and provisional, the precautionary principle should be applied in this field of research. Furthermore, such experiments should be conducted only if they are of overriding importance and there is no alternative to them. Opinions differ on the definition, for the purposes of animal welfare requirements in general, of the requirements of overriding importance and the absence of alternatives.

The creation of transgenic human–animal mixtures involving great apes should at any rate be banned.

6.3 Human–animal brain chimeras

6.3.1 Objectives of the creation of human–animal brain chimeras

As explained in detail in Section 2.2.3, human cells are transplanted into animals mainly in order to study the therapeutic potential of the implanted cells. A particular aim is the implanting of cells to improve the therapy of injury-related or degenerative neurological disorders such as Parkinson's or Alzheimer's disease. In these therapeutically oriented experiments, cells are as a rule transplanted into the brains of adult animals – principally rodents. Although the effect of the manipulation on the vegetative functions of nerve cells can be determined in rodents, a preferred experimental model, the repercussions on cognitive and other complex brain functions are of only limited applicability to man. Furthermore, in view of the significant differences in brain size between humans and rodents, the potential for the further development of applications using this model is also very limited. In the case of nerve cells, on the other hand, studies of cell types in larger animals

– in particular, primates – are in fact more promising, but present appreciable ethical problems.

Another possibility might be the injection of pluripotent human stem cells or precursor cells of human nerve cells (perhaps with human-specific mutations) into the brains of experimental animals in the embryonic or fetal state, in order to test their ability to develop and become integrated in the organism even if this "substrate" belongs to a different species. The results would probably be more readily transposable than those from cell cultures.

6.3.2 Ontologically relevant characteristics of brain chimeras

The ontological assignment of brain chimeras is based primarily on brain performance, as represented in behaviours and cognitive and other higher functions. Brain chimeras involve two particular difficulties that are less evident when other organs are used: first, the fact that the typical characteristics of the brain normally develop only after birth, so that they cannot be detected in mixed entities prenatally in real time; and, second, that, as stated in Section 4, it is in any case difficult to assign individual patterns of behaviour clearly and unequivocally to the human or animal category.

An adult mouse remains a mouse even after the transplant of human nerve cells into its brain. Functioning areas of the brain typical of the human species can no longer form as human tissue even if the transplant has high plasticity. The situation may be different in the case of a transplant of cells capable of differentiation into the prenatal, as yet immature brain. It is then conceivable that, after birth and development into an adult animal, behaviour patterns foreign to the species might arise, thus impeding the assignment of the animal to a given species, irrespective of whether it would be classified as human or otherwise.

The consequences of transplant experiments in which human stem cells are transferred to primates are particularly difficult to predict. In the case of a brain chimera with both animal and human brain components, a shift in the developing brain functions from animal towards human behaviour would not be improbable. Assignment to the human or animal category would then be even more difficult, so that the moral status of the organism would be uncertain.

Hence appraisal of the ethical issues raised by brain chimeras depends on the degree of manipulation involved in the experiment, which in turn depends essentially on the stage of development attained by the receiving animal, the closeness of its relationship to man and the number and potency of the implanted human cells. These points will be considered below.

» *Stage of development*: During embryonic development, just one transplanted cell capable of differentiation can become the precursor of large parts of the organism. In early *embryonic development* (e.g. at the blastocyst stage), an integration of pluripotent stem cells could therefore result in modifications with functional implications, since the plasticity of the environment and the involvement of even a small number of transplanted cells contribute substantially to the formation of all three "germ layers" and hence to a large number of eventual organs in the body. Within a species, the implant of embryonic or induced pluripotent stem cells into the blastocyst does indeed lead to the genesis of mixtures composed of cells from the recipient and the donor. In addition, the implanted stem cells can develop further in the mouse into human sperm or egg cells. However, it is unclear whether an introduction of stem cells on a cross-species basis (i.e. if human cells were transplanted into a mouse blastocyst) can result in the formation of chimeras, and in particular brain chimeras.

A different situation arises if human cells are implanted into a *born animal*. The number of integrated cells is then relatively limited and the environment into which the cells are implanted generates signals that limit "acceptance" by the implanted cells. In the event of the transplant of human cells into adult closely related organisms (e.g. non-human primates), again, the implantation of a small number of cells by the techniques currently available would seem to have only a limited effect on the structure and interlinking of the tissue whose formation has already begun. For this reason, the risk of substantial modification of the receiving animal due to the implant of a small number of human stem cells in the adult animal organism is likely to be very small.

- *Degree of relationship*: Transplanted cells are significantly influenced by the microenvironment into which they are transferred. Furthermore, aspects of spatial structure (for example, brain size) determine the possible biological effect of the transplanted cells. In the case of a mouse, for example, it is therefore unlikely that human-like cognitive capabilities would be acquired as a result of the transplant of neuronal stem cells. With primates (in particular, great apes), on the other hand, this possibility cannot be ruled out owing to their greater initial similarity to man.
- *Number of transplanted cells*: The number of transferred cells that integrate and multiply in the receiving organism and contribute to organ functions is an important determinant of whether the recipient is influenced at all and of the extent of any observable functional change such as, in particular, modified behaviour. The rate of integration of human embryonic stem cells or induced pluripotent stem cells after implantation in adult animals is currently relatively low.
- *Quality of transplanted cells*: In addition to the number of transplanted and/or incorporated cells, the nature of the cells and their aggregation capacity play an important part. The higher the plasticity of the cells, the more substantial the effect is likely to be.

- *Organ functions*: As discussed earlier, man's conception of himself is essentially determined by his cognitive and other faculties (for instance, cultural and moral capability), as well as his "phenotypic" appearance. Appraisal is therefore particularly necessary in the case of manipulations likely to modify the animal's cognitive capabilities, behaviour or appearance. For example, reactions to an animal that spoke or exhibited other typical human characteristics would surely differ from those to an animal with a human kidney or heart. Hence modifications with ethical implications result from manipulation of the neuronal system in particular.

6.3.3 Ethical appraisal of the generation of human–animal brain chimeras

Since, as discussed, the ethical implications differ significantly according to degree of manipulation involved in the experiment and, in particular, the species of the receiving animal, implantation in distantly related mammalian species (e.g. rodents) must here be considered separately from implantation in close relatives of humans (primates).

Ethical implications of the generation of human–rodent brain chimeras

In the present state of our knowledge, the implantation of human pluripotent cells into the adult organism of distantly related species such as rodents does not result in the assumption of functions of the donor organism, since the environmental conditions of the adult receiving animal determine the functioning and incorporation of the implanted cells. The transplant of human stem cells into the brains of adult rodents neither alters the external appearance of the receiving animal, nor is likely to give rise to a human-like modification of the receiving animal's cognitive functions, so that the problem remains confined within the ethical categories of animal welfare. The animal remains an animal. Such brain chimeras can hardly be regarded as close to man, so that the dignity of the human species is not violated by the blurring of the boundary.

When human cells are transplanted into rodents at an early stage of development, however, the quantitative contribution to organ formation may be considerable, although there is no indication at present that living mixtures of distantly related species could actually come into being, since functional integration and intercellular communication would presumably not be feasible in this case.

The generation of brain chimeras by the transfer of human cells to mammals other than primates is ethically acceptable if, first, the objective of the research is of overriding importance; second, the ethical requirements of animal welfare are satisfied; and, third, chimerization does not take place prior to the development of organ primordia. To ensure that the conditions under which the animal is kept are appropriate to its species, the degree of cell integration and the behaviour of the animal after birth should preferably be monitored.

Ethical implications of the generation of human–primate brain chimeras

The stage of development is very important in the creation of human–primate chimeras too. Behavioural modifications have been induced in closely related species by the transplant of immature nerve cells (as in the chick–quail experiment described in Section 2.2.3). For this reason, approximations in brain performance too are observable in experiments with immature cells or tissues transferred between closely related species. Body structure could also appear genuinely mixed. Should it actually prove possible to conduct an experiment resulting in the creation of a human–primate mixture, involving for example the injection of human induced pluripotent stem cells at the early embryonic stage, prior to the development of organ primordia and in particular of the brain, it would be necessary to decide whether the entity concerned should still be seen and treated as an animal or already as human. Clearly, such a situation would tend to blur the boundary between the human and animal categories. For this reason, human–primate chimeras should not be created by manipulation at the early embryonic stage.

The consequences of transplanting human stem cells into the brains of born primates have not been established. The probability of "humanized" cognitive functioning admittedly appears slight, since, so far as is known at present, the functioning of the implanted cells is determined substantially by the receiving tissue, given that the existing neuronal networks dictate circuitry and functionality. Yet the possibility cannot be ruled out that, in the event of a high rate of incorporation of cells capable of differentiation, an interaction with the recipient organism's tissue might occur, and that this might also modify the cells' environment and thereby reconfigure the surrounding circuits. The possible nature of these changes is uncertain. The degree of manipulation may be quite substantial.

In view of the possible degree of manipulation involved in the implant of brain-specific human cells into primate brains, of the vital importance of the brain and nervous system for species-specific capabilities, and of our provisional and limited knowledge of the possible effects on physiognomy and cognitive capacity, the insertion of brain-specific human cells into primate brains should be permissible only after an interdisciplinary evaluation process. Research involving the introduction of brain-specific human cells into the brains of great apes should not be carried out.

7 SUMMARY AND RECOMMENDATIONS

Research involving the mixing of human and animal cells or tissues has been well established for decades, for example with a view to the replacement of tissues or organs in human beings by animal tissue. In addition, the creation of animals as "model organisms" for research into human disorders by the insertion of disease-specific human genes is now commonplace. Considerable advances have been made in this field in recent years. For instance, neural precursor cells derived from human stem cells have been transferred into the brains of experimental animals, including primates, for the investigation and possible eventual therapy of disorders such as Alzheimer's and Parkinson's disease. In the United Kingdom, permission has been given for experiments in which a human cell nucleus is inserted into an enucleated bovine egg in order to obtain embryonic stem cells without the use of human eggs.

Such research and its possible consequences call into question the age-old presumption of a clearly defined boundary between humans and animals. Given the gathering pace of progress in research, it is essential to determine as of now whether binding limits must be set and, if so, where they should be drawn.

The present Opinion of the German Ethics Council is intended to help clarify the distinction between humans and animals, to facilitate the evaluation of developments with ethical implications in research involving the creation of human–animal mixtures, and to determine whether and where action is called for on the part of science, society or politics. This is the case even though much current research in the field of human–animal mixtures has not hitherto raised any new ethical problems.

The expression "human–animal mixture", or simply "mixture" or "mixed entity", is used here as a generic term for living organisms, even at very early stages of development, that include both human and animal components (genes, chromosomes, nuclei, cells, tissues or organs). The focus of attention is on the transfer of human material to animals. The ethical problems of transferring animal material to humans, in particular in xenotransplantation, on the other hand, are not considered.

General issues of animal-based research which do not specifically relate to human–animal mixtures are largely beyond the scope of this Opinion. The divergent views on the extent of animal protection required would merit an Opinion in their own right.

I. General recommendations

I.1 The German Ethics Council believes that the transfer of human–animal mixtures into a uterus should be prohibited where it is evident in advance that they cannot be identified with sufficient reliability as either animal or human ("true mixtures"). This is the case whether or not the experimental creation of such entities and their use *in vitro* is held to be permissible.[150]

I.2 The German Ethics Council endorses the limits set out in Section 7 of the German Embryo Protection Act (ESchG), which prohibits:

» the transfer of human embryos to an animal;
» the production of interspecies hybrids or chimeras – that is, of living organisms
  - by fertilization using human and animal gametes;
  - by the fusion of a human and an animal embryo; or
  - by the joining of a human embryo with an animal cell that is capable of further differentiation with that embryo.

150 On mixed-species embryos where this identification is unequivocal, see Recommendation I.2.

In addition to these limits, the following additional prohibitions should be incorporated in the Act:

- prohibition of the transfer of animal embryos to humans;
- prohibition of the insertion of animal material into the human germline;
- prohibition of procedures potentially resulting in the formation of human egg or sperm cells in an animal.

I.3 Under Article 49 of the European directive on animal protection, a national committee for the protection of animals used for scientific purposes must be established in Germany. The animal welfare commission provided for in Section 16b of the German Animal Welfare Act (TierSchG) could perhaps be charged with the relevant functions, and if so should specifically address the field of research involving human–animal mixtures, with particular reference to the following issues:

- the creation of transgenic animals by the insertion of a substantial proportion of human genetic material and the incorporation of regulatory genes;
- the creation of human–primate brain chimeras;
- projects resulting in drastic changes in the appearance and capabilities of an animal.

The national committee should possess the wide-ranging interdisciplinary competence necessary for the purpose; it should draw up guidelines for the work of the regional animal welfare commissions in this field; it should be involved in relevant decisions of principle; and it should perform its functions with due regard for the status of the social discourse.

I.4 More transparency is called for with regard to research involving the creation of human–animal mixtures, for instance by the inclusion of detailed information on "human–animal mixtures" in the Federal Government's animal welfare reports.

I.5 Experiments involving a high degree of manipulation – in particular, the insertion of genes or the injection of cells during embryonic development – should be permissible only if of overriding importance in terms of their scientific objectives, especially as regards the anticipated medical benefits to humanity, and their possible repercussions on the moral status of the mixed entity should be evaluated.

I.6 In biological and interdisciplinary research on the effects of the incorporation of human genes, chromosomes, cells and tissues in an animal organism, more attention must be devoted to ethical issues, including also the effects on behaviour and capabilities, as well as phenotypic changes. The results of such research should be made public to a greater extent than hitherto.

II. Specific recommendations on the creation of cybrids

A cytoplasmic hybrid, or cybrid, is defined as a living cell formed by the fusion (hybridization) of an enucleated egg (for instance, of a cow) with the nucleus of another, somatic cell (in the present case, a human somatic cell).

II.1 Irrespective of the question of a possible ban on the creation of human–animal cybrids, the German Ethics Council unanimously recommends prohibition of the implant of human–animal cybrids into a human or animal uterus. An explicit prohibition to that effect should be incorporated in the Embryo Protection Act.

II.2a The members of the German Ethics Council who consider the creation and use of cybrids to be ethically acceptable take the view that a statutory prohibition is inappropriate.

Stefanie Dimmeler, Frank Emmrich, Volker Gerhardt, Hildegund Holzheid, Weyma Lübbe, Eckhard Nagel, Jens Reich, Edzard Schmidt-Jortzig, Jürgen Schmude, Jochen Taupitz, Kristiane Weber-Hassemer, Christiane Woopen

II.2b The members of the German Ethics Council who hold that the creation and use of cybrids is ethically unacceptable call for the incorporation of a statutory prohibition in the Embryo Protection Act.

Axel W. Bauer, Alfons Bora, Wolf-Michael Catenhusen, Wolfgang Huber, Christoph Kähler, Anton Losinger, Peter Radtke, Ulrike Riedel, Eberhard Schockenhoff, Erwin Teufel, Michael Wunder

III. Specific recommendations on the creation of transgenic animals with human genetic material

An organism is considered to be transgenic if its genetic material has been modified by technical manipulation involving the integration of foreign or synthetically derived genetic material into the cell nucleus. The genes are transferred by various methods at a very early stage of individual development. All cells of the transgenic animal always carry the genetic modification, which is also passed on in the germline. However, the expression of the genetic modification may be confined to specific tissues, such as brain or blood cells. An animal is said to be transgenic if genes from other species have been inserted into it.

III.1 The incorporation of human genes into the germline of mammals (other than primates) is ethically acceptable if the objective of the research is of overriding importance in terms of the expected benefit to humanity and provided that the generally applicable ethical requirements of animal welfare are satisfied.

III.2 Owing to our provisional and limited knowledge of the possible effects on appearance, behaviour and capabilities, the insertion of human genetic material (genes or chromosomes) into the germline of primates should be permissible only after an interdisciplinary evaluation process involving the national committee. Such experiments should be carried out only if the expected medical benefit is of overriding importance and there is no alternative. Opinions differ on the definition of overriding importance and the absence of alternatives for the purposes of the general animal welfare requirements to be observed.

III.3 The creation of transgenic human–animal mixtures involving great apes should be banned.

IV. Specific requirements on the creation of human–animal brain chimeras

IV.1 The creation of brain chimeras by the transfer of human cells to mammals other than primates is ethically acceptable if, first, the objective of the research is of overriding importance especially in terms of the expected medical benefit to humanity; second, the generally applicable ethical requirements of animal welfare are satisfied; and, third, chimerization does not take place prior to the development of organ primordia. To ensure that the conditions under which the animal is kept are appropriate to its species, the degree of cell integration and the behaviour of the animal after birth should preferably be monitored.

IV.2 In view of the possible degree of manipulation involved in the implant of brain-specific human cells into primate brains, of the vital importance of the brain and nervous system for species-specific capabilities, and of our provisional and limited knowledge of the possible effects on physiognomy and cognitive capacity, the insertion of brain-specific human cells into primate brains should be permissible only after an interdisciplinary evaluation process involving the national committee as stated in Recommendation III.2.

IV.3 The insertion of brain-specific human cells into the brains of great apes in particular should be prohibited in accordance with Recommendation III.3.

DISSENTING POSITION STATEMENT

1 Preliminary remarks

The moral appraisal of "human–animal mixtures in research" necessarily entails grappling with a large number of theoretical and methodological issues and problems. Some of these are addressed in the German Ethics Council's Opinion, which contains a wealth of material and many of whose conclusions can be accepted without reservation. In the appraisal of human–animal mixtures and their creation, it considers a number of different concepts. Those to be welcomed include the precautionary principle, even if opinions may differ on the form it should take in the context of the creation of human–animal mixtures. However, I can accept most of the recommendations formulated in Section 7.

Yet precisely because the Opinion invokes so many different analytic and normative concepts, their foundations and interrelationship ultimately remain unclear, as well as the different dimensions to be taken into account in the appraisal of human–animal mixtures and their creation. This results in some cases in circular arguments, unsatisfactory decision options and disparate recommendations for action. For this reason, and because I cannot accept either of the two alternative evaluations of human–animal cybrids proposed in Section 6.1.3 (except for the unanimously advocated ban on the implant of such cybrids into a human or animal uterus), I have decided to compose this dissenting position statement.

It enables me to present three points important for the appraisal of human–animal mixtures and to justify my stance on the creation of human–animal cybrids independently of the arguments put forward in the Opinion.

2 Appraisal of human–animal mixtures

2.1 Human–animal mixtures: why are they a problem at all?

Establishing the boundary between man and animals has occupied human societies since ancient times. It is thus one of the timeless themes of cultural history.[151] In this context, the animal often assumes the role of the Other by which man is defined: the specificity of a human being – his "anthropological difference"[152] – is determined by the distinction between him and an animal. From this point of view, an animal, for Giorgio Agamben, is the indispensable substrate of the "anthropological machine"[153] that ensures the ever new "generation of the human".[154]

Humanity thus needs animals in order to recognize and define itself. The understanding of the nature of the distinction between the animal and the human has reciprocal implications, so that the two concepts are inseparable. This characterizes one of the fundamental problems in the assessment of human–animal mixtures, as any definition of the specifically human entails from the beginning a negation of the animal.

The boundary between the human and animal categories is constitutive of our society. It is the critical factor that decides who belongs to the group of privileged juridical subjects. New technical procedures call the present boundaries into question.

151 See Friedrich 2009.
152 Wild 2006.
153 Agamben 2003.
154 Höfele 2011.

What are the consequences for the present-day ethical and legal constitution of our society if the boundary between animals and humans can be shifted, or becomes more permeable, by technical means? Such shifts are brought about not only by the application of biotechnological procedures; human–animal mixtures in fact constitute just one end of what is deemed possible along the spectrum of technical feasibility. At the other end are cybernetic organisms (cyborgs, controlled by neural implants) or "humanized" robots.

In both cases the question arises of what it is that constitutes a human being, and in what respects we distinguish humans from other organisms or entities, whether formed naturally, by breeding or created by technical means. What characteristics or capabilities make an entity a member of a social or legal community enjoying equal rights or exclude it from that community? Considered from this perspective, the questions we are asking today about human–animal mixtures, and the answers given to them, are relevant also to other fields in which boundaries are shifted, and must be tested for consistency at a level over and above that of the fields concerned.

Hence the possibility of creating human–animal mixtures entails consideration of a number of problem dimensions. First, there are issues relating to the moral status of the materials (eggs, embryos, etc.) used in the creation of human–animal mixtures. The second question concerns the entities that thereby come into being. Beyond these aspects, a third issue involves the relevance of such developments to the normative constitution of societies, in which the human–animal boundary is an essential element. Each of these dimensions implies different problems and objectives for protection. With regard to the third point in particular, a more detailed consideration would have been desirable; one may hope that the discourse will be continued with greater involvement of the social and cultural sciences.

2.2 Appraisal of human–animal mixtures: concepts and criteria

From the normative perspective, our social order has a two-fold basis. It presupposes an unequivocal boundary between the human and animal categories.[155] The question arising, however, concerns the concepts that underlie the drawing of this boundary. Both categorial and graduated concepts can be identified historically, philosophically and scientifically. The categorial concepts postulate that man has characteristics (or capabilities) that distinguish him qualitatively from all other animals; that these distinctions are important particularly to our conception of ourselves; and that they are fundamental in that (all) other (important) distinctions can be derived from them. Graduated concepts, on the other hand, assume that the boundary between humans and animals is to a greater or lesser extent fluid, and that, with regard to certain characteristics that are usually attributed only to humans, no categorial or qualitative differences between humans and other animals can be discerned, but at most only quantitative differences.

The far-reaching issue of the foundations of the appraisal of human–animal mixtures arises in this context. What are the consequences of the existence of different conceptualizations of the distinction between humans and animals? What criteria can be adduced to justify a preference for one or the other conception? How can the fact that species boundaries constitute, at least in part, a construction of scientific theory and are to a certain extent empirically flexible and modifiable by evolution be reconciled with a system of appraisal based on the drawing of unequivocal boundaries between humans and animals? What normative implications follow from the conflict between

155 The seemingly clear ethico-legal boundary between humans (as subjects of human dignity enjoying the right to life) and non-humans today already appears permeable in certain respects. This applies to non-human primates (which tend to be included), on the one hand, and human embryos created *in vitro* (which tend to be excluded), on the other.

a seemingly unmodifiable "essence" of humanity and possible modifications (induced by evolution or technical means) in the field of living organisms?

How and on what basis is it to be predicted whether and under what circumstances human capabilities might arise from the transfer of genetic or cellular material? The answer to this question depends, among other factors, on one's particular hypothesis concerning the genesis of human capabilities. Are they emergent phenomena of a highly organized brain, or the result of a long process of co-evolution, in which physicochemical, biotic and sociocultural factors interact and lead to new structures and capabilities, which in turn constitute the basis for further development? In the first of these cases, the development of human capabilities could perhaps be brought about by material processes of organization and reorganization, as initiated by the transfer of genetic information or certain cells, in the course of the creation of a new human–animal mixture – that is, ontogenetically. If this hypothesis is correct, such manipulations would already be a problem on the individual level. If, however, one's premise is that specifically human capabilities arise (only) in the course of a prolonged process of co-evolution – that is, that they depend on successive stages of interaction between natural and social factors, and are the result of a phylogenetic development – one might perhaps not be very concerned by the creation, by genetic or cellular manipulation of individuals, of entities having human characteristics with normative implications.

This issue cannot be decided here. It should, however, be clear that the concepts underlying appraisal of the ethical acceptability of human–animal mixtures and their creation, as well as the fundamental theoretical assumptions, must be rendered transparent. Although the Opinion includes numerous fundamental assumptions of this kind, many of them remain concealed. Precisely for this reason, the Opinion includes a number of points worthy of further discussion.

2.3 Specific problems of appraisal

Besides the question of the perception of various problem dimensions and the conceptual framework of the appraisal, evaluation of the moral status of human–animal mixtures requires specific problems to be addressed. The concepts and approaches to their solution presented in the Opinion are not consistently convincing in this respect. A particular problem, for example, is that the normative quality of a given manipulation follows partly from the moral status of the potential product of that manipulation – that is, of a future mixed entity. This entity, however, does not (yet) exist at the time of the manipulation and indeed is perhaps not intended to be born at all.[156]

Even after the birth of a human–animal mixture, determination of its normative status presents enormous challenges. These are analogous to those confronting, for example, the investigation of morally relevant competences such as altruism in primates. In this case, the question arises as to the practical and ethically acceptable feasibility of such investigations in all individuals that may be eligible for consideration as candidates for a moral status.

Yet the possible characteristics of future entities are virtually impossible to predict with sufficient accuracy, and can therefore not readily be taken into account as criteria for appraisal. What criteria, then, should be invoked for assessing the process of their creation? The basis suggested in the Opinion is an ontological analysis and the criteria of substance, process of generation and degree of manipulation, as derived from Aristotelian philosophy. However, their normative relevance remains unclear. For instance, the process of generation

156 With regard to possibly viable human–animal mixtures, which are thus capable of development to birth and beyond, all members of the German Ethics Council have expressed the unanimous view that the transfer of an (embryonic) human–animal mixture into a human or animal uterus should be prohibited. Should this recommendation be enshrined in law, the issue of the evaluation of actually born human–animal mixtures would therefore (at least for the time being) not arise.

is mentioned as a criterion in the context of the appraisal of human–animal cybrids, but no further justification is given of its ethical relevance. But why should an entity that actually or potentially possesses human capabilities be deemed to have a lesser status on account of its artificial creation than one that comes into being naturally?

A further auxiliary construction for solving the problem of the ethical relevance of a manipulation, which can only be appraised *ex post*, according to the Opinion, is the "complex of features" involved in the degree of manipulation (Section 5.5). It is here noted that "the more the situation touches on ethical spheres of particular sensitivity, the greater the degree of [a planned] manipulation must be deemed to be". The examples given are manipulations of the germline and ones "with repercussions on capabilities relevant to an organism's moral status – as well as on drastic changes in external appearance that affect the visual foundation of intuitive distinctions". But what are "ethical spheres of sensitivity" in this context? Since the future effects of the manipulation are not known at the time when it is carried out, the criterion is based on a circular logic that is meaningless in practice.

Another point that remains unclear is the relevance of the "moral intuition" invoked in Section 5.4. Here again, the question arises whether an entity that exhibits human capabilities or the potential for such capabilities should be assigned a lesser moral status merely because it walks on four legs or has a furry coat.

The problem with these parts of the Opinion lies not so much in the fact that the proposed solutions exhibit weaknesses in relation to the fundamental difficulties of appraisal and in turn raise new problems. In my view, it is the circumstance that these difficulties are not made explicit and themselves addressed as an issue relevant to the ethical debate.

The almost insoluble problem of appraisal of an action on the basis of its presumed outcome, which, at the time of the action, is unknown and predictable only with great uncertainty, surely arises also in other fields of human activity. Precisely in those fields, however – as for example in the debate about climatological or environmental risks – the fact of acting in the context of empirical and moral uncertainty has itself become a subject of ethical and political discussion. It would be extremely rewarding to consider this issue in greater depth in the bioethical discourse on human–animal mixtures too, in order, for example, to provide a substantive basis for the precautionary principle mentioned earlier.

2.4 Conclusion

Enormous challenges are likely to be presented to society by the scientific, technical and cultural erosion of the human–animal boundary that has traditionally been perceived as firm and unequivocal and constitutive of our legal system – an erosion that commences with the creation of human–animal mixtures but by no means ends with or is confined to it. These include changes in the group of subjects enjoying ethical and legal privileges, and the possible questioning of familiar ascriptions, thus demanding unfamiliar ethical and social responses from us.

The issues raised here concerning the definition of the problem and the underlying theoretical and normative assumptions, as well as the reference to some specific problems, reflect the complexity of the appraisal of human–animal mixtures. If justice is to be done to these matters, it is appropriate to supplement the establishment of ethico-political recommendations with a careful analysis and discussion of their foundations, presuppositions and objectives, and in future to engage more thoroughly with some of these issues and to attempt their systematic resolution.

3 Appraisal of the ethical legitimacy of creating human–animal cybrids

The creation of, and research involving, human–animal cybrids using human genetic material and animal eggs is ethically acceptable and permissible provided that they are not implanted into an animal or human uterus.

This view follows, on the one hand, from the conclusion that the exclusion of embryos not capable of development from transfer into the female body is deemed to be ethically justifiable and acceptable, which features in the German Ethics Council's Opinion on preimplantation genetic diagnosis and is reflected in that Opinion's position statement in favour of a statutory prohibition of preimplantation genetic diagnosis.[157]

On the other hand, it is consistent with arguments set out in Position C of the former German National Ethics Council's Opinion on cloning.[158] Here it is considered that, in the case of clones derived from human nuclei and animal eggs (which thus constitute human–animal cybrids), it is for ethical reasons impossible to determine empirically whether these cybrids constitute human embryos – that is, entities capable of forming a whole organism – because the necessary experiment, involving the transfer of such an entity into a woman's uterus, would contravene recognized ethical precepts.

There are, however, good reasons to doubt whether the entities concerned are indeed totipotent embryos – that is, ones capable of relatively long-term development and of forming the rudiments of all organs. For example, there are various indications that the process of reprogramming a somatic cell nucleus is influenced by the nature of the eggs used. Significant differences are observed according to whether the experiment involves fresh or cryopreserved human eggs. Eggs of animal origin seem virtually or entirely unable to support embryonic

157 See German Ethics Council 2012, 115 f.
158 See German National Ethics Council 2004, 80 ff.

development on the basis of a human genome. Eggs from primates closely related to man might possibly be an exception. Having regard to current experience with and knowledge of the reprogramming of genomes in cell nuclear transfer, the assumption must be that, the more heterologous and artificial the eggs used for the purpose, the less capable such unconventionally created entities will be of development. For this reason, the status of such entities can legitimately be compared with that of human embryos which are not capable of development.

I therefore regard the creation of human–animal cybrids using animal egg cells (other than those of primates) to be ethically acceptable – but not, in accordance with the formulation of Position A, because of the (artificial) nature or the context (research) of their creation; not because the entity remains *in vitro*; and not because of the view that such entities could be sacrificed for research purposes of overriding importance even if they were human embryos. Such research is, instead, ethically acceptable solely because there are good reasons for, and arguments in favour of, the assumption that such entities do not constitute human embryos capable of development.

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GLOSSARY

AIDS	Acquired immune deficiency syndrome: a disorder in which the immune system is weakened by the human immunodeficiency virus (HIV)
Altruism	Selflessness, unselfishness; behaviour, contrasted with egoism, which benefits another individual without bringing direct advantage to the acting individual
Alzheimer's disease	Neurodegenerative disorder attributable to loss of nerve cells and nerve cell contacts and characterized by a decline in cognitive capacity in particular
Anthropocentrism	Perspective in which man enjoys priority of moral consideration
Basal ganglia	Brain structures situated beneath the cerebral cortex and performing motor, cognitive and limbic functions
Biocentrism	Perspective according to which all living things enjoy the same moral consideration
Blastocyst	A blister-like ball of about 120 cells forming during embryonic development and consisting of the trophoblast, the embryoblast and a fluid-filled cavity
Chimera	Organism composed of cells of different individuals, which may also belong to different species, but which nevertheless constitutes a unified individual
Chromosome	Carrier of genetic information; chromosomes consist of DNA and associated proteins; the genes are located on them; humans have 23 pairs of chromosomes
Cytoplasm	The basic material occupying the space within a cell, consisting of intracellular fluid (cytosol), which contains enzymes, nutrients and proteins; the cytoplasm includes not only the nucleus but also the mitochondria, separated by a membrane; the cytoplasm's outer boundary is the cell membrane
Dichotomous	Divided into two parts
DNA	Deoxyribonucleic acid; macromolecule carrying genetic information and present in every cell
Down's syndrome/ trisomy-21	Numerical chromosomal disorder in which chromosome 21 is present in triplicate; this retards development, usually involves a mental disability, and may be associated with malformations of the heart, lungs and alimentary canal in particular
Embryo	Fertilized human egg capable of development, as from the time of nuclear fusion; also any totipotent cell, removed from an embryo, which is capable of division and development into an individual given the additional conditions necessary for this to take place
Embryogenesis	Process of embryo development from fertilization of the egg to completion of organ formation

Embryonic stem cells	Undifferentiated cells derived from embryos, fetuses or by cloning and capable of development into various types of tissue
Epigenetics	Molecular mechanisms that influence the processing and action of genetic information without modification of the DNA sequence, such as DNA methylation
Extracorporeal	Outside the body
Gamete	Generic term for egg and sperm cells (also called germ cell)
Gene	Smallest functional unit of the genome; DNA segment containing the genetic information that codes for a given protein
Genome	Totality of a cell's genetic information
Genus	In taxonomy (the biological classification used for the assignment of living organisms to groups), a group above the level of the species and below that of the family
Germ cell	Generic term for egg and sperm cells
Germ layers	Layers of cells, formed in embryonic development, from which human tissues and organs develop
Germline	All cells that lead in a cell line from the fertilized egg to the egg and sperm cells of the organism that develops from it; genetic modifications in germline cells are passed on to progeny
Great apes	Family of the order of Primates; they include the gorilla, the orang-utan and the chimpanzee; owing to their close relationship to man, they are sometimes known as anthropoid apes
Huntington's disease	Neurological disorder involving severe motor disturbances and resulting in cognitive decline; onset usually in middle age; the condition is incurable and takes a lethal course
Hybrid	A mammalian hybrid is an organism formed from the union of eggs and sperm of different species, so that all its eventual cells have the same genetically mixed composition
Implantation	Adherence of the embryo to the endometrium (day 5 to 12 after fertilization)
Impregnated egg	Fertilized egg before breakdown of the pronuclear membranes ("nuclear fusion")
In vitro	Outside the living organism (literally, "in glass")
In vivo	In the living organism
Induced pluripotent stem cell (iPS)	Pluripotent stem cell obtained by reprogramming of adult somatic cells
Islet cells	Cells located in the pancreas which secrete hormones that regulate blood sugar level
Knockout animals	Animals in which specific genes have been deliberately deactivated in order to study their effect

Mitochondria	Organelles in a cell's cytoplasm possessing their own genes and supplying the cell with energy
Molecular genetics	Branch of genetics concerned with the correlations between inheritance and the chemical and physical characteristics of genes
Morphological	Relating to the form and structure of an organism
Multifactorial genetic disorders	Disorders caused by genetic factors together with additional environmental and/or lifestyle determinants
Multiple sclerosis	Chronic inflammatory disorder of the central nervous system potentially resulting in motor and sensory disturbances and other neurological symptoms
Neuron	Also called nerve cell; the particularity of a nerve cell is that it can receive excitations, produce excitations itself and transmit them
Nuclear fusion	Completion of fertilization by breakdown of the pronuclear membranes of the egg and sperm
Nucleotide	Fundamental building block of DNA
Nucleus	Component of a cell delimited by a membrane and storing the genetic information on chromosomes; it acts as the cell's information and control centre
Ontology	Branch of philosophy relating to the nature of being, and concerned with the nature of the fundamental determinants of living organisms (and other entities)
Parkinson's disease	Degenerative neurological disorder characterized by the death of nerve cells containing the messenger substance dopamine; the resulting dopamine deficiency gives rise to motor disturbances; onset usually at advanced age
Pathocentrism	Perspective according to which all sentient organisms enjoy moral consideration
Phenomenological	Relating to phenomena or appearances; choice of an intellectual and intuitive approach that seeks to apprehend essential and significant characteristics in phenomena
Phenotypic	Relating to the appearance of an organism
Pluripotent	Ability of a cell to differentiate into various, but no longer all, types of cells
Poliomyelitis	Viral disorder affecting the nerve cells of the spinal cord and potentially leading to permanent paralysis or death
Preclinical	Prior to use in clinical medicine; a study is said to be preclinical if it is conducted not (yet) in humans but with cell or animal models
Preimplantation genetic diagnosis	Procedure for genetic testing of artificially produced embryos before transfer to the uterus
Primates	Mammalian order comprising all prosimians, monkeys and apes, including great apes, to which man too belongs in biological terms
Reproductive medicine	Branch of medicine concerned with reproduction

Retroelements	Mobile genetic elements consisting of RNA; they can be excised from their original position and integrated elsewhere in the genome
Retroviruses	Viruses that infect mammalian cells and insert their genetic information into the host cell
RNA	Ribonucleic acid; in human cells, RNA transmits information that directs protein synthesis
SARS	Severe acute respiratory syndrome: an infectious viral disorder with symptoms such as raised temperature, coughing and shortness of breath
Somatic cell nuclear transfer	Transfer of a cell nucleus of any kind from one species into an enucleated egg of another species; the resulting embryo has the nuclear genome of the former species, but also includes a small number of genes of the other species, located in the mitochondria of the egg's cytoplasm
Species	A biological species is a self-contained reproductive community of shared descent empirically recorded up to the time of observation and forming a genetic, ecological and evolutionary unity; as a rule it exhibits shared characteristics (anatomy, physiology, immunology, behaviour and cognition) that distinguish it from members of other species
Stem cell	Undifferentiated cell that can develop into a differentiated somatic cell
Taxonomy	Ordering and classification system of living organisms
Totipotent	In embryology, a cell or group of cells is said to be totipotent if it is capable of developing into a complete organism given the necessary conditions
Transgene	A transgenic organism includes one or a small number of newly integrated foreign genes
Tuberculosis	Chronic bacterial infectious disorder affecting in particular the lungs
Typology	Classification based on the totality of an organism's features that characterize a given type
Viral hepatitis	Viral inflammation of the liver
Xenotransplantation	Transfer of animal material to humans
Zona pellucida	Outer layer of cells around an egg; when an egg is enucleated, not only the zona pellucida but also cell components such as mitochondria remain in the cytoplasm

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