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## Introduction

1. The Academy of Medical Sciences welcomes the opportunity to respond to the Home Office consultation on options for the transposition of European Directive 2010/63/EU. The Academy promotes advances in medical science and campaigns to ensure these are translated into healthcare benefits for society. Our Fellowship is drawn from leading medical scientists across academia, industry, hospitals and the public service, and includes many pre-clinical scientists who undertake research using animals.
2. In July 2011, the Academy published *Animals containing human material* (ACHM), the report of a working group study chaired by Professor Martin Bobrow CBE FRS FMedSci.<sup>1</sup> The study was part funded by the Department of Health, Department for Business, Innovation and Skills through the Sciencewise-ERC programme, Medical Research Council, and Wellcome Trust. The report's recommendations are directly relevant to aspects of the Home Office's consultation, and are included in full as Annex A. The Academy welcomes the commitment made by Lynne Featherstone MP, Home Office Parliamentary Under Secretary of State, that the Home Office will consider the report's recommendations carefully and we look forward to continuing engagement with the Home Office, Department of Health and other Government Departments in taking them forward.
3. In this submission, we respond to questions in the Home Office consultation which are closely associated with the recommendations of the ACHM report. These address:
  - Subject matter and scope: Limits on protection of fetal forms of mammals, birds and egg laying reptiles (*Consultation Questions 1 and 2*).
  - Requirements for projects: the role of the Animal Procedures Committee (APC) in reviewing project license applications (*Consultation Question 45*).
  - National committee for the protection of animals used for scientific purposes (*Consultation Question 53*).

In response to paragraph 32, we comment on the importance of maintaining UK competitiveness as an environment in which excellent pre-clinical research can be undertaken. We would welcome further opportunity to expand on the points in this submission.

4. The Academy supports, and has contributed to, the response from the UK Bioscience Sector which addresses wider aspects of the Home Office consultation.

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<sup>1</sup> Academy of Medical Sciences (2011). *Animals containing human material*.  
<http://www.acmedsci.ac.uk/p47prid77.html>

## **Subject matter and scope: limits on protection of fetal forms of mammals, birds and egg laying reptiles**

5. Directive 2010/63/EU applies to live non-human vertebrate animals, including independently feeding larval forms; fetal forms of mammals as from the last third of their normal development; live cephalopods; and fetal forms of vertebrates at an earlier stage of development if they are to be allowed to live beyond the last third of development, and as a result of the procedures performed are likely to experience pain, suffering, distress or lasting harm after they have reached that stage of development. For mammals, these provisions differ from those in place under the Animals (Scientific Procedures) Act 1986 (ASPA), which protects mammals from half way through their gestation period. Under Directive 2010/63/EU birds and reptiles are not protected until hatching (or for viviparous reptiles, birth), whilst ASPA protects birds and reptiles from half way through their incubation period.
6. Besides the evidence cited in the consultation<sup>2,3</sup> we are aware of a recent report from a working group of the Royal College of Obstetricians and Gynaecologists '*Fetal Awareness, Review of research and recommendations for practice*', which, although focused on humans, includes relevant discussion and references to other mammalian species.<sup>4</sup>
7. On the basis of evidence of which we are aware, we have no objection to the harmonisation of UK legislation with Directive 2010/63/EU with respect to the protection of fetal forms of mammals. We note that harmonisation would result in an extension of the period (from half- to two-thirds through gestation) during which fetal mammals could fall outside the scope of legislation, although we recognise that maternal animals carrying fetuses at this stage of development may themselves be regulated under ASPA. We encourage the use of an evidence-based approach in establishing start points for the protection of birds and egg laying reptiles, rather than a generic exclusion of all such species from the scope of legislation prior to hatching or birth.
8. Within the UK, particular provisions are made for the regulation of research involving human embryos by the Human Fertilisation and Embryology Authority (HFEA) under the Human Fertilisation and Embryology Act (HFE Act, as revised in 2008).
9. As our ACHM report emphasised, there are situations in which the regulation of human embryo research (under the HFE Act) and research involving modified animal embryos (under ASPA) interface very closely, and may partly overlap. Chimeric embryos containing both human and animal cells are examples, because whether they are considered 'human' for the purposes of regulation depends on the proportion of human cells, their distribution and, most importantly, their expected effect on the phenotype of the resultant embryo.

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<sup>2</sup> Mellor, et al. (2007). *Birth and hatching: Key events in the onset of 'awareness' in lambs and chicks*. NZ Veterinary Journal **55** 51-60.

<sup>3</sup> Legal and animal welfare implications of when consciousness first appears in developing young and of the potential for delayed onset of increased pain sensitivity. AAWAS International Conference.

<sup>4</sup> Royal College of Obstetricians and Gynaecologists (2010). '*Fetal Awareness, Review of research and recommendations for practice*' <http://www.rcog.org.uk/files/rcog-corp/RCOGFetalAwarenessWPR0610.pdf>

10. Research involving chimeric embryos, which contain both human and animal material, and where the human component has the potential to contribute to sensitive parts of the developing embryo (as illustrated in the ACHM report), requires careful scrutiny. For such embryos, provision should be made to enable expert oversight from the point of their creation and throughout gestation.
11. We recommend that the Home Office and the Department of Health work closely together to ensure that there are no regulatory gaps, overlaps or inconsistencies, between their respective regulatory systems in this area. We consider it essential that the Home Office and the HFEA (or, as appropriate, the Department of Health) work together to develop and maintain a smooth, functionally integrated operational interface, at the boundaries of their areas of responsibility. This should be supported by clear guidance to the research community, to ensure the timely and appropriate adjudication of innovative scientific projects without undue bureaucracy. Such an interface may well involve the expert advisory bodies in the two systems, as well as officials acting for the agencies concerned.
12. We emphasise our recommendation, that particular categories of experiments involving the combination of human and animal material require additional expert scrutiny. We recommend that such experiments should be included in the list of types of research that are always referred to the Home Office's expert advisory body. This would not necessarily be the case under ASPA or Directive 2010/63/EU. We recommend the Home Office takes the opportunity presented by the transposition of Directive 2010/63/EU to ensure that a national expert body with a duty to advise on the use of ACHM in research is put in place.

### **Requirements for projects: the role of the APC in reviewing project license applications**

13. Directive 2010/63/EU defines a 'project' as 'a programme of work having a defined scientific objective and involving one or more procedures'. Under the Directive, projects require prior authorisation by the competent authority. In the UK, the assessment of project applications is currently performed by the Home Office Inspectorate with referral of certain types of applications to the APC or, less frequently, to an external advisor.
14. We are aware that, in implementing Directive 2010/63/EU, the UK is required to establish a 'national committee for the protection of animals used for scientific purposes' ('national committee'). We anticipate this body will succeed the current APC in the UK.
15. As currently constituted, the APC is an advisory non-departmental public body, set up to provide strategic advice to the Secretary of State on policy, practice, ethics, science and animal welfare related to ASPA.<sup>5</sup> The APC reviews any applications referred to it by the Home Office Inspectorate and can review further applications on

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<sup>5</sup> <http://www.homeoffice.gov.uk/agencies-public-bodies/apc/>

request. It automatically reviews all applications that fall within four categories agreed with the Secretary of State. These cover research including:

- The proposed use of wild-caught non-human primates.<sup>6</sup>
- The proposed use of cats, dogs, equidae, or non-human primates in procedures of substantial severity.
- A substantial severity banding or major animal welfare or ethical implications, involving:
  - a. Xenotransplantation of whole organs.
  - b. Chronic pain models.
  - c. Study of the central nervous system.
- Applications of any kind raising novel or contentious issues, or giving rise to serious societal concerns.<sup>7,8</sup>

We consider it appropriate for project applications in these categories to continue to be referred for expert review by the APC (or its successor) in the future.

16. To ensure a consistent approach in ethical and animal welfare matters we consider it desirable that research applications involving some types of ACHM are considered by the same body that advises Government on other aspects of animal research. We emphasise that the Home Office should ensure that the body which meets the requirement of the 'national committee' in the UK has within its remit and competence, the function of the national expert body for ACHM.<sup>9</sup>

17. Our report set out a proposed system of categorisation for ACHM research. Under this system, a limited number of types of ACHM research (Category 2) should be permissible subject to additional specialist scrutiny by the national expert body for ACHM. Although we would expect this list to evolve over time as knowledge advances, the major types of research that we would currently include in this category are:

- Substantial modification of an animal's brain that may make the brain function potentially more 'human-like', particularly in large animals.
- Experiments that may lead to the generation or propagation of functional human germ cells in animals.
- Experiments that could be expected to significantly alter the appearance or behaviour of animals, affecting those characteristics that are perceived to contribute most to distinguishing our species from our close evolutionary relatives.
- Experiments involving the addition of human genes or cells to non-human primates (NHPs).

The national expert body for ACHM should provide specialist scrutiny for such research, including close consideration of the ethical and any safety issues in addition to the potential value of the research. Proposed studies should be assessed on a case-by-case basis, at least until experience allows the formulation of

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<sup>6</sup> We note that a proposed limitation on the use of NHPs to the offspring of animals bred in captivity (F2+) will be subject to a feasibility study under Directive 2010/63/EU Article 10.

<sup>7</sup> Omand D (2010). *Report of the 2009/10 NDPB Review of the Animal Procedures Committee*.

<http://www.homeoffice.gov.uk/publications/apc/publications-2010/review-apc-0910?view=Binary> (para 8)

<sup>8</sup> <http://www.homeoffice.gov.uk/agencies-public-bodies/apc/>

<sup>9</sup> Academy of Medical Sciences (2011). *Animals containing human material*.  
<http://www.acmedsci.ac.uk/p47prid77.html>

guidelines. Authorisation may require studies to adopt an incremental (graduated) approach.

18. The report also identifies a very narrow range of experiments that should not for now be licensed because they either lack compelling scientific justification or raise very strong ethical concerns. The list of such experiments should be kept under review by the national expert body for ACHM (see Annex A).

## **National committee for the protection of animals used for scientific purposes**

19. Directive 2010/63/EU requires each Member State to establish a 'national committee' to advise the competent authority and animal welfare bodies on the acquisition, breeding, accommodation, care and use of animals in procedures and ensure sharing of best practices. National committees are also to exchange information on the operation of animal welfare bodies and project evaluation and share best practices with the national committees of other Member States. The consultation indicates that 'these functions are in some respects similar to those of the Animal Procedures Committee (APC) set up under ASPA ... They are, however, more narrowly focused on animal welfare issues than is the case with the APC, which also considers wider ethical issues. The requirement to 'ensure the sharing of best practice' and the direct relationship with animal welfare bodies suggest a more direct involvement with establishments than is currently exercised by the APC. Similarly, the requirement to exchange information with national committees in other Member States also involves a wider role.'
20. We suggest it is appropriate for the current Animals Procedures Committee to form the basis for the new 'national committee'. However, to undertake the role of the national expert body for ACHM, we suggest that this committee should:
  - Be transparent, making its proceedings, deliberations, reasoning, conclusions and recommendations available for public scrutiny.
  - Be outward facing so that interested persons are aware of its function and feel able to input into its work programme.
  - Be actively involved in public engagement and consultation; and maintain regular forward-looking dialogue with the scientific community. This will enable it to anticipate future scientific directions. A major strength of this approach would be the ability to ensure that scientific work in this area proceeds with reasonable public understanding and support, and is not unduly influenced by extreme views. Responses from public participants in our dialogue programme, conducted as part of the ACHM study, indicated that the UK public would be receptive to such an approach.
  - Have the power to develop guidelines to promote consistency and transparency in the regulatory process. The expert body should take note of advances in scientific knowledge and take a proactive approach to the development and adjustment of guidelines.

Although we recommend these characteristics specifically in relation to the national expert body for ACHM, we consider them to be beneficial for the effective function of the future 'national committee' in relation to other types of animal experiments.

21. We suggest that an important aspect of the role of the 'national committee' will be to take ethical and social aspects into account as part of 'benefit:harm analysis'. Benefits and harms are not only matters of animal welfare, important as these are, but should also include potential harms, for example, to public confidence in medical research and regulation.
22. We would welcome increased transparency around the new national committee's working practices and composition. This might be achieved through the development of a working protocol.
23. We recommend that the committee should be balanced and multidisciplinary, with a membership drawn from people with knowledge of:
  - Law
  - Relevant biological sciences (including, for example, experts in animal behaviour, reproductive biology, genetics, stem cell biology, physiology, immunology, neurobiology, and virology). It is likely that more than one biological scientist may be needed to ensure a sufficiently broad range of expertise
  - Social sciences
  - Ethics
  - Humanities
  - Lay members without specific expertise in these fields

Given the special issues associated with experiments on NHPs, we recommend that the national expert body should include, either in its membership or as an advisor, an independent scientist with experience in NHP research who should be present to advise the group when such issues are discussed.

The committee should be able to co-opt additional expertise when needed. The list of relevant expertise should be kept under review by the committee itself and the Home Office. The Academy of Medical Sciences would be willing to advise on the membership of the committee.

24. The impact assessment associated with the consultation indicates that 'it is assumed that the establishment of a national committee can be satisfied without adding to the resources currently provided to the APC and the National Centre for the 3Rs'. We encourage the Home Office to ensure that the new national committee is adequately resourced to carry out its functions effectively. In particular, it would be important to ensure that sufficient resources should be available to enable the national committee to undertake public engagement and consultation; and activities to maintain regular forward-looking dialogue with the scientific community. We are aware of existing programmes within Government (e.g. the BIS Sciencewise-ERC programme) to support public dialogue. This programme supported the public dialogue which was an important element of the Academy's study. The Home Office should consider how these, or additional resources, might be utilised.

## Competitiveness

26. The UK has an outstanding record of preclinical biomedical research, which is an important element of the UK science base. Experiments conducted in the UK involving research animals or cellular material make invaluable contributions throughout the development of treatments, from basic investigative research to preclinical testing of new drugs and devices. The UK is, perhaps uniquely, positioned to attract the whole research and development chain for new medicine. It is to the UK's advantage to maintain expertise across the entire spectrum of biomedical research from basic science discovery to clinical application – to improve the health of the population both here and abroad.<sup>10</sup>
27. The Academy emphasises the value of a proportionate approach to research regulation, with clear guidelines and appropriate assessment systems in all areas of medical research.<sup>11</sup> As in clinical research, there is a need for animal research regulation to be proportionate and kept under regular review. Our ACHM report recognises that, to protect and strengthen pre-clinical research in the UK, there is a need to ensure a comprehensive system for its regulation that protects animal welfare, maintains the highest standards of safety and ethics, and keeps the issues of public acceptability of research to the forefront.
28. Through its integrated public dialogue programme, the ACHM report took into account the public's views on a specific, and relatively complex, area of animal research.<sup>12</sup> We believe it important that public discussion of animal research takes place and so encourage the Home Office to foster a more open style of regulation, and communication, around the use of animals in research. An outward facing approach could be beneficial in avoiding public concern resulting from unexpected scientific developments. The voice of a more broadly informed public may also help to moderate the influence of vocal minorities, and so help to avert any tendency towards over-regulation to address minority concerns.
29. We emphasise the value of consistent regulation across Europe. It is imperative that EU-wide legislation promotes consistency of research practices and movement of skilled researchers. Equally, new legislation must not compromise or unduly restrict the UK's ability to undertake animal research, including that involving non-human primates, in academic or industrial sectors.<sup>13</sup> We welcome the current transposition of the EU Directive, and the opportunities it brings to renew our regulatory system to ensure that excellent pre-clinical science will continue to flourish in the UK.

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<sup>10</sup> Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*. <http://www.acmedsci.ac.uk/p99puid172.html>

<sup>11</sup> Academy of Medical Sciences (2011). *A new pathway for the regulation and governance of health research*. <http://www.acmedsci.ac.uk/p99puid209.html>

<sup>12</sup> Ipsos MORI (2010). *Exploring the boundaries: report on a public dialogue into animals containing human material*. <http://www.acmedsci.ac.uk/index.php?pid=209>

<sup>13</sup> Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*. <http://www.acmedsci.ac.uk/p99puid172.html>

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This response was approved on behalf the Academy's Council by our Vice-President Professor Ronald Laskey CBE FRS FMedSci. We are grateful to Professor Martin Bobrow CBE FRS FMedSci, Dr Robin Lovell-Badge FRS FMedSci and Professor Maria Fitzgerald FMedSci for their contributions and assistance. Contributions were made in an individual capacity.

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## **Academy of Medical Sciences**

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## 8 Conclusions and recommendations

### 8.1 Overview

We have reviewed the types of research conducted using animals incorporating human gene sequences or human cells. The overall purposes of such work are to study the function of human genes and cells, to create improved animal models of human disease, and to develop, produce and test novel therapeutic products. Not all such experiments are successful, as in all types of science, but this research has yielded important new knowledge and significant insights with promise for the future, as well as methods and products that have considerable clinical value.

#### 8.1.1 ACHM and animal research

Consideration of the research use of ACHM must always be set in the general context of animal research, which is tightly regulated in the UK under the Animal (Scientific Procedures) Act (ASPA), such that any suffering inflicted on a protected animal must be justified by the potential value of the research, and animal welfare principles, as commonly embodied in 3Rs, must be applied.<sup>469</sup> Comparable national regulation exists in many scientifically advanced countries, and is incorporated in the European Directive (2010/63/EU). We see no reason to either relax or tighten UK standards in the case of ACHM. However, we have considered whether any additional scrutiny might be required for ACHM research.

#### 8.1.2 ACHM history and prospects

Research involving ACHM has a long history. No specific safety or regulatory concerns have emerged from such research to date, although a few issues have prompted ethical debate (see 8.5 for discussion of safety issues). Developments in transgenesis and particularly in stem cell research lead us to anticipate a major increase in the use of these techniques to investigate the biological effects of normal and abnormal human genes and cells in animals: to

study their roles in development, normal function and human disease processes; to test the safety and efficacy of novel therapeutics (particularly biological therapeutics); and to produce clinically useful proteins, cells and tissues.

These approaches hold promise for advancing biomedical and biological research but, as with virtually all scientific developments, we repeat our caution that not all avenues explored will prove fruitful; and that the timescales between initial research and applicable health interventions are long (up to decades), variable and impossible to predict with confidence. The use of ACHM can also offer approaches which may advance the 3Rs principles, improving the effectiveness of animal use by making individual experiments more informative about human biology.<sup>470</sup>

#### 8.1.3 ACHM ethical and societal aspects

The great majority of experiments that we can currently anticipate do not present novel ethical issues and should continue to be satisfactorily regulated under the existing framework governing all animal research. They include familiar experiments such as the creation of transgenic rodents containing relatively small numbers of human genes, tissue grafting, and the transfer of tissue-specific stem cells to humanise individual organs.

Evidence we received, the public dialogue, the published literature and our own deliberations, identify a limited number of research areas which may require greater scrutiny. These include research that may raise issues of ethical and social acceptability or have unusual implications for the animals involved. Experiments that approach these sensitive areas may, however, be of substantial medical and scientific importance. We therefore propose that such research projects should remain eligible for consideration for licensing by the appropriate regulatory authorities (see sections 8.3 and 8.6), but subject to additional expert scrutiny.

<sup>469</sup> The 3Rs principles are that experiments involving animals can be licensed only if there are no scientifically suitable alternatives that *replace* animal use, *reduce* the number of animals needed or *refine* the procedures used to cause less suffering (see 4.1 and 6.2.1).

<sup>470</sup> This is not to imply that we expect *overall* use of animals in medical research to diminish in the short term as a result of research involving ACHM, in part because their development will open up new avenues of research involving animal experimentation.

## 8.2 Categorisation of ACHM

We propose that experiments involving ACHM could be usefully classified into three categories:<sup>471</sup>

### 8.2.1 Category 1

The great majority of ACHM experiments, as outlined in section 8.1.3 above, which do not present issues beyond those of the general use of animals in research, should be subject to the same oversight and regulation under ASPA as other animal research.

### 8.2.2 Category 2

A limited number of types of ACHM research, outlined below in this section (8.2.2), should be permissible subject to additional specialist scrutiny by the national expert body we propose in section 8.3. Such experiments should be approached with caution. Strong scientific justification should be provided to the national expert body, who should closely consider the ethical and any safety issues in addition to the potential value of the research. Authorisation may require studies to adopt an incremental (graduated) approach as described in section 8.2.4 and Box 3.8. Proposed studies should be assessed on a case-by-case basis, at least until experience allows the formulation of guidelines. Although we would expect this list to evolve over time as knowledge advances, the major types of research that we would currently include in this category are:

- Substantial modification of an animal's brain that may make the brain function potentially more 'human-like', particularly in large animals.
- Experiments that may lead to the generation or propagation of functional human germ cells in animals.
- Experiments that could be expected to significantly alter the appearance or behaviour of animals, affecting those characteristics that are perceived to contribute most to distinguishing our species from our close evolutionary relatives.

- Experiments involving the addition of human genes or cells to NHPs. We recognise that research on NHPs is appropriate, and in some types of research probably essential if it is to lead to clinical benefit, but such research should remain under a high degree of regulatory scrutiny.<sup>472</sup>

### 8.2.3 Category 3

A very narrow range of experiments should not, for now, be licensed because they either lack compelling scientific justification or raise very strong ethical concerns. The list of such experiments should be kept under regular review by the proposed national expert body, but should at present include:

- Allowing the development of an embryo, formed by pre-implantation mixing of NHP and human embryonic or pluripotent stem cells, beyond 14 days of development or the first signs of primitive streak development, (whichever occurs first), unless there is persuasive evidence that the fate of the implanted (human) cells will not lead to 'sensitive' phenotypic changes in the developing fetus.<sup>473,474</sup> This supplements the 14 day provision applied to human admixed embryos under the HFE Act, so that mixed embryos that are judged to not quite meet the criteria for being 'predominantly human', should nevertheless be regulated on the basis of the likely phenotypic effect on the embryos created. Currently, any mixed origin embryo judged to be 'predominantly human' is regulated by HFEA and cannot be kept beyond the 14 day stage, whereas an embryo judged to be predominantly animal is unregulated until the mid-point of gestation (likely to be increased to two-thirds on implementation of the European Directive 2010/63/EU) and can in principle be kept indefinitely. As to whether or not an admixed embryo is predominantly 'human' is an expert judgement, including an assessment of likely phenotype, but neither

<sup>471</sup> A graded approach already operates to some degree under ASPA. Project licenses including certain types of experiment, including those that raise 'novel or contentious' issues, must be referred to the Animal Procedures Committee for review (see Box 6.2). The principle of a graded approach has also been enunciated by the International Society for Stem Cell Research (see 7.4.2), the US National Academy of Sciences (Box 7.2-3), and in reference to the 'human neuron mouse' by Greely *et al.* (see 3.4).

<sup>472</sup> For example, stem cell therapeutic approaches may need to be tested on NHPs because their greater similarity (cell cycle time, brain structure, molecular homology) to humans will provide better assessment of colonisation and neural contact development.

<sup>473</sup> This applies whether the embryo is implanted within an animal uterus or maintained as an intact embryo *in vitro*.

<sup>474</sup> Equivalent statutory restrictions are applicable to human and human admixed embryos under the HFE Act (see 6.2.2).

the precise eventual composition of an individual embryo nor the phenotypic effect of the admixture will be easily predictable in the current state of knowledge.

- Transplantation of sufficient human-derived neural cells into an NHP as to make it possible, in the judgement of the national expert body, that there could be substantial functional modification of the NHP brain, such as to engender 'human-like' behaviour. Assessing the likely phenotypic effect of such experiments will be informed by prior work on other species (possibly including stem cell transfer between NHPs) or by data on the effects of 'graded' transplantation of human cells into NHPs.
- Breeding of animals that have, or may develop, human-derived germ cells in their gonads where this could lead to the production of human embryos or true hybrid embryos within an animal.<sup>475</sup>

#### 8.2.4 Graduated licensing

Since the outcome of many of the experiments outlined in category 2 (8.2.2) will be somewhat unpredictable until initial studies have been conducted, we recommend consideration of graduated licensing. By this we mean licensing limited initial experiments, involving small numbers of animals, starting with those species considered least likely to experience pain, suffering, or long-lasting harm, and with careful monitoring of the outcomes according to agreed measurable criteria, before further work is permitted.<sup>476</sup> Given the exploratory nature of the work, there should be active dialogue between investigator and the national expert body, and the results of such experiments should in turn inform the future regulatory process for similar experiments. In Chapter 3 (Box 3.8) we outline an example of this approach in neuroscience, but the principles are generic.

#### 8.2.5 Flexibility of regulation

The types of experiment in these categories, and the boundaries which are set, are virtually

certain to evolve with time, new knowledge and changing social norms. Regulators should monitor and respond to changes in societal views and scientific knowledge, and regulatory mechanisms should be sufficiently flexible to accommodate such change.

### 8.3 National expert body

The limited number of such experiments, the specialist knowledge required to evaluate their likely outcomes and the socially sensitive nature of the judgements to be made, dictate that oversight of research involving ACHM should be carried out by a single, national, expert, review body. **We recommend that the Home Office ensures that a national expert body with a duty to advise on the use of ACHM in research is put in place.**

**We recommend that this national expert body should:**

- **Be multidisciplinary, involving people with knowledge of ethics, the humanities, social sciences, law and the biological sciences as well as people without specific expertise in these fields, and be able to co-opt additional expertise when relevant.**<sup>477</sup>
- **Be transparent, making its proceedings, deliberations, reasoning, conclusions and recommendations available for public scrutiny.**
- **Be outward facing so that interested persons are aware of its function and feel able to input into its work programme.**
- **Be actively involved in public engagement and consultation; and maintain regular forward-looking dialogue with the scientific community.**

This will enable it to anticipate future scientific directions. A major strength of this approach would be the ability to ensure that scientific work in this area proceeds with reasonable

<sup>475</sup> Placement of human embryos into animals is prohibited by the HFE Act, and this seems likely to be interpreted to include placement of human embryos into animals modified to contain human uterine tissue.

<sup>476</sup> We do not intend this to lead to the duplication of animal experiments. Where there is satisfactory evidence from previous experiments this should be taken into account and not repeated.

<sup>477</sup> Given the special issues associated with experiments on NHPs, we recommend that the national expert body should include, either in its membership or as an advisor, an independent scientist with experience in NHP research who should be present to advise the group when such issues are discussed.

public understanding and support, and is not unduly influenced by extreme views. Responses from public participants in our dialogue indicated that the UK public would be receptive to such an approach.

- **Have the power to develop guidelines to promote consistency and transparency in the regulatory process.**

To ensure a consistent approach in ethical and animal welfare matters (see Chapters 4 and 5), we consider it desirable that research involving ACHM is considered by the same body that advises Government on other aspects of animal research. We are aware that, in implementing the EU Directive 2010/63/EU, the UK is required to establish a 'national committee for the protection of animals used for scientific purposes'.<sup>478</sup> We anticipate this body will succeed the currently constituted Animal Procedures Committee. **We recommend that the Home Office ensures that the body which meets the requirement of the 'national committee for the protection of animals used for scientific purposes' in the UK has within its remit and competence the function of the national expert body for ACHM.**

#### 8.4 Welfare

We have commented that research involving ACHM does not have a generally increased potential for causing animal suffering compared with other experiments permitted under existing regulation, and that the development and use of ACHM could contribute to 3Rs principles. There may, however, be a few specific situations in which modification of the appearance or behaviour of a normally social animal may cause it to experience distress, including as a result of the actions of others of its own species, or of its human carers. Such effects can also occur in other experimental situations. This type of harm should be taken into account in the overall assessment

of potential animal suffering in ACHM experiments, as it would with similar changes induced by other experimental procedures. We emphasise that research involving ACHM should be subject to scrutiny, and advancement from the perspective of animal welfare, in a manner no different from other animal research.

#### 8.5 Safety

We have considered a variety of safety issues that could arise from experiments involving ACHM. There are some hazards that are specific to the purpose and nature of individual research protocols, such as those altering an animal's susceptibility to human infections, which must be appropriately regulated and managed according to established procedures. We have also considered more generic issues, predominantly relating to the risk of activating endogenous viruses or altering the host range of infectious agents. The risk levels are thought to be very low, but not zero.<sup>479</sup> Any manipulation which is known to, or could, alter viral or other pathogen recognition sites, or in any other way affect susceptibility to pathogens, or which deliberately involves the activation of human and animal proviruses within the same ACHM (such that they could recombine) should be carefully risk-assessed and appropriate control mechanisms put in place. It is critical that the provenance of human material to be used clinically is known and considered during the risk assessment.

The nature of the risks, and ways of mitigating them, are similar to those regularly used for other research involving potentially infectious materials. **We recommend that, for those classes of ACHM where it is relevant, a risk assessment should be undertaken and appropriate containment levels specified. The risk assessment is the responsibility of investigators, research institutions, and regulators; and should where relevant take the advice of an independent virologist.**

<sup>478</sup> Article 49, Directive 2010/63/EU on the protection of animals used for scientific purposes. Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31986L0609:en:HTML>

<sup>479</sup> Notably when human cells are isolated from ACHM and then maintained in culture or introduced into humans.

## 8.6 Interfaces between regulatory authorities

Research involving human embryos is regulated by the HFEA under the HFE Act (see 6.2.2). As was recognised during the passage of this Act, there are situations in which this regulation of human embryo research and the matters discussed in the current report interface very closely, and may partly overlap. Chimæric embryos containing both human and animal stem cells are examples, because whether they are considered 'human' for the purposes of regulation depends on the proportion of human cells, their distribution and, most importantly, their expected effect on the phenotype of the resultant embryo. The proportions and distribution of cells of different species in a single structure may evolve over time; such change may be unanticipated or result from experimental design; and the state of current knowledge is such that predicting phenotypic effects may be difficult. In each case, an expert judgement will have to be made, as to whether and how to proceed. The technical potential to create transgenic animals containing ever larger amounts of human DNA sequence raises similar issues.

The existing UK legislative structure is such that some awkward cases may fall at the boundary of jurisdiction. **We recommend that the Home Office and the Department of Health work closely together to ensure that there are no regulatory gaps, overlaps, or inconsistencies, between the two regulatory systems.** They should bear in mind that animal embryos are not regulated until the middle of gestation (likely to be increased to two-thirds of gestation under the new European Directive), although we recognise that maternal animals carrying these embryos may be regulated under ASPA.

**We consider it essential that the Home Office and the HFEA (or, as appropriate, the Department of Health) work together to develop and maintain a smooth, functionally integrated operational**

**interface at the boundaries of their areas of responsibility. This should be supported by clear guidance to the research community, to ensure the timely and appropriate adjudication of innovative scientific projects without undue bureaucracy. Such an interface may well involve the expert advisory bodies in the two systems, as well as officials acting for the agencies concerned.**

The Home Office (and, where relevant, the Department of Health) should consult, as appropriate, with other bodies who may sometimes have a role in the regulation of ACHM, namely, the Human Tissue Authority, the Health and Safety Executive, the Department for the Environment, Food and Rural Affairs and the Steering Committee of the National Stem Cell Bank.

## 8.7 International regulation

We have considered other recent (non-UK) national and international studies which have examined aspects of the use of ACHM in research (Chapter 7). To date, consideration of ACHM research from policy, societal, ethical and regulatory perspectives is limited. We have also noted that this field of science, like so many, could take place across several jurisdictions with differing regulatory requirements, allowing funders and researchers to exercise choice about the location of their research. **We recommend raising international awareness of ACHM, promoting international consistency in research practice involving their use, and exploring the development of international standards or guidance. This might be achieved through international collaboration amongst regulators, policy-makers, national and international bioethics bodies and medical research councils, or initiatives within the research community. This is an area in which the UK should provide leadership.**

### **8.8 Summary**

In short, we advocate a tiered approach to regulation such that the great majority of uncontentious experiments proceed as under current ASPA regulation, while a small number of categories of experiment are referred for more expert scrutiny, with graduated licensing allowing progress to be made under regular

review. A very limited number of experiments should not be licensed at the current time. The graduated licensing process should be interfaced with the corresponding processes that regulate human embryos so that the regulators are aware of each other's activities and so that there is no gap or unnecessary overlap between their jurisdictions.

## Categorisation of ACHM

We propose that experiments involving ACHM could be usefully classified into three categories:

### **Category 1**

The great majority of ACHM experiments, which do not present issues beyond those of the general use of animals in research, should be subject to the same oversight and regulation under ASPA as other animal research.

### **Category 2**

A limited number of types of ACHM research (outlined below) should be permissible, subject to additional specialist scrutiny by the national expert body we propose<sup>1</sup>. Although we would expect this list to evolve over time as knowledge advances, the major types of research that we would currently include in this category are:

- Substantial modification of an animal's brain that may make the brain function potentially more 'human-like', particularly in large animals.
- Experiments that may lead to the generation or propagation of functional human germ cells in animals.
- Experiments that could be expected to significantly alter the appearance or behaviour of animals, affecting those characteristics that are perceived to contribute most to distinguishing our species from our close evolutionary relatives.
- Experiments involving the addition of human genes or cells to non-human primates (NHPs). We recognise that research on NHPs is appropriate, and in some types of research probably essential if it is to lead to clinical benefit, but such research should remain under a high degree of regulatory scrutiny.

### **Category 3**

A very narrow range of experiments should not, for now, be licensed because they either lack compelling scientific justification or raise very strong ethical concerns. The list of such experiments should be kept under regular review by the proposed national expert body, but should at present include:

- Allowing the development of an embryo, formed by pre-implantation mixing of NHP and human embryonic or pluripotent stem cells, beyond 14 days of development or the first signs of primitive streak development (whichever occurs first); unless there is persuasive evidence that the fate of the implanted (human) cells will not lead to 'sensitive' phenotypic changes in the developing fetus.<sup>1,2,3</sup>
- Transplantation of sufficient human-derived neural cells into an NHP as to make it possible, in the judgement of the national expert body, that there could be substantial functional modification of the NHP brain, such as to engender 'human-like' behaviour. Assessing the likely phenotypic effect of such experiments will be informed by prior work on other species (possibly including stem cell transfer between NHPs) or by data on the effects of 'graded' transplantation of human cells into NHPs.
- Breeding of animals that have, or may develop, human derived germ cells in their gonads, where this could lead to the production of human embryos or true hybrid embryos within an animal.<sup>4</sup>

1 Such experiments should be approached with caution. Strong scientific justification should be provided to the national expert body, who should closely consider the ethical and any safety issues in addition to the potential value of the research. Authorisation may require studies to adopt an incremental (graduated) approach. Proposed studies should be assessed on a case-by-case basis, at least until experience allows the formulation of guidelines

2 This applies whether the embryo is implanted within an animal uterus or maintained as an intact embryo in vitro. Equivalent statutory restrictions are applicable to human and human admixed embryos under the HFE Act (see 6.2.2).

3 This supplements the 14 day provision applied to human admixed embryos under the HFE Act, so that mixed embryos, which are judged to not quite meet the criteria for being 'predominantly human', should nevertheless be regulated on the basis of the likely phenotypic effect on the embryos created. Currently, any mixed origin embryo judged to be 'predominantly human' is regulated by HFEA and cannot be kept beyond the 14 day stage, whereas an embryo judged to be predominantly animal is unregulated until the mid-point of gestation (likely to be increased to two-thirds on implementation of the European Directive 2010/63/EU) and can in principle be kept indefinitely. As to whether or not an admixed embryo is predominantly 'human' is an expert judgement, including an assessment of likely phenotype, but neither the precise eventual composition of an individual embryo nor the phenotypic effect of the admixture will be easily predictable in the current state of knowledge.

4 Placement of human embryos into animals is prohibited by the HFE Act, which seems likely to be interpreted to include placement of human embryos into animals modified to contain human uterine tissue.

## Recommendations

1. We recommend that the Home Office ensures that a national expert body with a duty to advise on the use of ACHM in research is put in place.
2. We recommend that this national expert body should:
  - 2.1 Be multidisciplinary, involving people with knowledge of ethics, the humanities, social sciences, law and the biological sciences as well as people without specific expertise in these fields, and be able to co-opt additional expertise when relevant.<sup>5</sup>
  - 2.2 Be transparent, making its proceedings, deliberations, reasoning, conclusions and recommendations available for public scrutiny.
  - 2.3 Be outward facing so that interested persons are aware of its function and feel able to input into its work programme.
  - 2.4 Be actively involved in public engagement and consultation; and maintain regular forward-looking dialogue with the scientific community.
  - 2.5 Have the power to develop guidelines to promote consistency and transparency in the regulatory process.
3. We recommend that the Home Office ensures that the body that meets the requirement of the 'national committee for the protection of animals used for scientific purposes' in the UK has within its remit and competence the function of the national expert body for ACHM.
4. We recommend that, for those classes of ACHM where it is relevant, a risk assessment should be undertaken and appropriate containment levels specified. The risk assessment is the responsibility of investigators, research institutions and regulators, and should where relevant take the advice of an independent virologist.
5. We recommend that the Home Office and the Department of Health work closely together to ensure that there are no regulatory gaps, overlaps or inconsistencies, between the two regulatory systems. We consider it essential that the Home Office and the Human Fertilisation and Embryology Authority (HFEA) (or, as appropriate, the Department of Health) work together to develop and maintain a smooth, functionally integrated operational interface, at the boundaries of their areas of responsibility. This should be supported by clear guidance to the research community, to ensure the timely and appropriate adjudication of innovative scientific projects without undue bureaucracy. Such an interface may well involve the expert advisory bodies in the two systems, as well as officials acting for the agencies concerned.
6. We recommend raising international awareness of ACHM, promoting international consistency in research practice involving their use, and exploring the development of international standards or guidance. This might be achieved through international collaboration among regulators, policy-makers, national and international bioethics bodies and medical research councils, or initiatives within the research community. This is an area in which the UK should provide leadership.

<sup>5</sup> Given the special issues associated with experiments on NHPs, we recommend that the national expert body should include either in its membership or as an advisor, an independent scientist with experience in NHP research who should be present to advise the group when such issues are discussed.