Ethical Review of Projects Involving Non-human Primates Funded Under the European Union's 7th Research Framework Programme

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Summary — Internet searches were performed on projects involving non-human primates ('primates') funded under the European Union (EU) 7th Research Framework Programme (FP7), to determine how project proposals are assessed from an ethical point of view. Due to the incompleteness of the information publicly available, the types and severity of the experiments could not be determined with certainty, although in some projects the level of harm was considered to be 'severe'. Information was scarce regarding the numbers of primates, their sourcing, housing, care and fate, or the application of the Three Rs within projects. Project grant holders and the relevant Commission officer were consulted about their experiences with the FP7 ethics review process. Overall, it was seen as meaningful and beneficial, but some concerns were also noted. Ethical follow-up during project performance and upon completion was recognised as a valuable tool in ensuring that animal welfare requirements were adequately addressed. Based upon the outcome of the survey, recommendations are presented on how to strengthen the ethical review process under the upcoming Framework Programme 'Horizon 2020', while adequately taking into account the specific requirements of *Directive 2010/63/EU*, with the aim of limiting the harms inflicted on the animals and the numbers used, and ultimately, replacing the use of primates altogether.

Key words: *7th Research Framework Programme, Directive 2010/63/EU, ethical review, evolutionary biology, infectious disease research, neuroscience, non-human primates, severity classification.*

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Introduction

Aims of the study

Non-human primates (hereafter referred to as 'primates') are man's closest relatives in the animal kingdom, and this phylogenetic proximity has made them desirable research subjects for a broad variety of scientific purposes (1). However, their cognitive capacities and complex behaviour mean that there are serious animal welfare and ethical concerns about their use in procedures that would be unethical if performed in humans (2). The use of any animal in scientific procedures that cause pain or distress is a contentious issue and a cause of public concern, but, in the case of primates, public concern is particularly high (3). This is reflected within the European Parliament which, in 2007, adopted a written declaration calling for an end to primate use (4), and in recent legislation regulating animal use in scientific procedures, *Directive 2010/63/EU on the protection of animals used for scientific purposes* (5).

There are two key opportunities for balancing the conflicting pressures with regard to primate use that arise — stemming, on the one hand, from the desire within science and industry to use them in research as 'models' of human disease, and on the other hand, from the desire to protect them from the harms associated with such research. *Directive 2010/63/EU* includes a number of provisions that confirm the special status of primates and restrict the purposes for which they may be used. The special status of these animals is also recognised in EU (European Union) research funding programmes, such that a specific ethical review process for applications for funding of research projects involving primates was implemented in the Seventh EU Framework Programme for research, technological development and demonstration activities (FP7; 6–8).

Research within the Framework Programmes (FPs) is largely funded by public money, and is purported to be carried out in the public's interests. Therefore, the public have the right to be able to access information about the research their money supports, the benefits it delivers, and the costs it entails, especially with respect to the harms to the animals that people are clearly also concerned about. Openness on all of these issues is therefore essential, and there are

European Commission (hereafter referred to as 'Commission') initiatives on transparency of policy (9) that should be applied to primate use.

Against this background, the goal of the study presented in this report was:

— to review and evaluate the information on primate use in FP7 that is accessible in the public domain, in order to gain a better understanding of the use of these animals in FP7-funded projects. This included the type of research funded, the numbers of animals used, the nature and level of suffering that the animals experienced, how suffering was assessed and relieved, and how the Three Rs principle to replace, reduce and refine animal experiments (10) was applied;

— to determine how FP7 project proposals are assessed from an ethical point of view and the impact of this ethical review of projects conducted;

— to consider whether any changes are required to the ethical review process for the next Framework Programme for Research and Innovation 2014–2020 — Horizon 2020 (final provisions outstanding; Commission Proposal published as [11]), by taking into account relevant requirements of the revised *Directive 2010/63/EU on the protection of animals used for scientific purposes*.

Since many of the FP7 projects evaluated were still ongoing while the survey was being conducted, the information collected was *not* used to evaluate the scientific outcome of the projects or the specific procedures involving non-human primates. Therefore, a harm–benefit analysis of the procedures was also *not* performed.

Background Information

FP7 provisions on the ethical review process for research proposals

FP7 is a research funding programme that aims at "*strengthening the scientific and technological bases of Community industry by promoting all the research activities deemed necessary, in particular by encouraging undertakings, including small and medium-sized enterprises, research centres and universities in their research and technological development activities*" — see Preamble 1 of *Decision 1982/2006/EC* concerning FP7 (6). The need for research activities supported by FP7 to respect ethical principles, including those reflected in the Charter of Fundamental Rights of the EU, is set out in this Decision. The opinions of the European Group on Ethics in Science and New Technologies, and the Protocol on the Protection and Welfare of Animals, as it has been implemented in Article 13 of the Treaty of the Functioning of the European Union (12), also have to be taken into account "*and reduce the use of animals in research and testing, with a view to ultimately replacing animal use*" (*Decision 1982/2006*; Preamble 30). Article 15(2) of *Regulation (EC) No 1906/2006* laying down the rules for the participation of undertakings, research centres and universities in actions under FP7, and for the dissemination of research results (7), states that project proposals that contravene fundamental ethical principles must not be selected for funding.

The specific rules for submitting project proposals under FP7, as well as for their evaluation, selection and support, are laid down in the Annexes of a separate Commission Decision, amended for the fourth time on 28 February 2011 to introduce modifications considered necessary based on previous experience (8). These rules encompass the following steps:

Commission calls and project submission

The Commission defines and publishes calls for proposals ('calls') in specific research areas corresponding to major fields in science and research. In response, project proposals are submitted, making use of the web-based Electronic Proposal Submission Service (EPSS).

Where appropriate, the project proposals must include an *Ethics Annex*. This should identify and discuss the potential ethical issues that the research raises. It should describe and justify the design and methodology of the research project, and discuss the potential implications of the expected results from an ethical viewpoint. It should also describe how the proposal meets the national legal and ethical requirements of the country where the research is to be performed, indicate the time-frame for applying the opinion of an appropriate local ethics committee and, where necessary, for approval by the national competent authority.

Research proposals should also include the *Ethical Issues Table* (ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-issues-table-annex4.pdf). This requires applicants to state whether the proposals involve research on animals, and if so, whether the animals are genetically-modified small laboratory animals or farm animals, cloned farm animals, or primates.

Once the proposal has been submitted, the EPSS carries out a number of *basic verification checks*. After the call closure, the submitted proposals are entered into databases. An initial eligibility check is carried out and any proposals

that do not fulfil the basic eligibility requirements are withdrawn.

Project evaluation

The main project evaluation procedure then begins. The initial focus is on scientific issues, and the evaluation is performed by external experts, independent observers, and, occasionally, internal Commission staff experts. It can take place as a "*remote review*" or "*panel review*"; the latter may include a hearing of the applicants. The experts present the outcome of their evaluation to the Commission in the form of an *Evaluation Summary Report* (ESR). Where relevant, the ESR also identifies any ethical issues, and indicates whether the proposal requires a specific ethics review. This is mandatory for proposals that involve interventions on humans, research involving human embryonic stem cells and human embryos, or primates (see Annex A in Reference 11). For this purpose, the experts produce an *Ethical Issues Report* (EIR) alongside the ESR. The outcome of this stage of the evaluation is sent to the applicants in the form of an "*initial information letter*", which may lead to further negotiations with the applicant and, ultimately, the award of the grant.

Any ethical issues identified are dealt with in a two-step *Ethics Review Procedure*, consisting of ethics screening and ethics review (described in Annex A of Reference 11). This is conducted in parallel to the ongoing negotiations over proposals that have successfully passed the first stage of evaluation, and is carried out by independent experts with appropriate skills in ethics.

The *ethics screening* takes into account the EIR, and serves to identify those proposals that fall under EU legislation (in the case of research animals, originally *Directive 86/609/EEC*, now replaced by *Directive 2010/63/EU*; see below), and require approval by a national authority, including those that, in addition, require an Ethical Review by the Commission. For each proposal screened, the experts of the *ethics screening panels* prepare and sign an *Ethics Screening Report*, which includes requirements that will form the basis for specific obligations for adaptations to the work plan of the project.

The *ethics review* of proposals is performed under the auspices of the *Ethics Review Sector* of the Commission's Directorate General on Research and Innovation (DG RES), and is carried out by independent *ethics review panels*. These produce an *Ethics Review Report*, which may set certain requirements and recommendations, and indicates whether there is a need to organise an *ethics follow-up audit* (EFA) during the performance of the project.

Directive 2010/63/EU on the protection of animals used for scientific purposes: Special provisions for primates

When FP7 started, the legislation regulating laboratory animal use in the EU was *Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes* (13). This had no requirement for a harm–benefit analysis of research projects, no specific mention of the Three Rs, and no special provisions for primates, other than a need for each animal to have an "*individual identification mark*" (Article 18). However, some Member States, e.g. the UK, included project evaluation and special concerns for primates when they transposed the Directive into their national legislation.

Directive 2010/63/EU, which came into force in the EU in November 2010, imposes an authorisation process for projects involving vertebrate animals and cephalopods. This process includes an evaluation of the project, including its objectives, compliance with the Three Rs principle, classification of the severity of procedures to be used, and a harm–benefit analysis to assess whether the harms to the animals are justified by the expected outcome (Articles 36–38; Annexes VI and VIII).

In the case of projects involving primates, Article 8 restricts the purposes of procedures for which primates may be used to translational or applied research "*undertaken with a view to the avoidance, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical conditions in human beings*", basic research, and research aimed at preservation of the species (although with a safeguard clause in Article 55[1]). A 'debilitating clinical condition' is defined as "*a reduction in a person's normal physical or psychological ability to function*". Article 8 also requires a "*scientific justification to the effect that the purpose of the procedure cannot be achieved by the use of species other than non-human primates".*

Recital 17 further describes that the evaluation of projects involving primates should ensure that these animals are only used "*in those biomedical areas essential for the benefit of human beings, for which no other alternative replacement methods are yet available*" (emphasis by the authors of the present report). This Recital explicitly mentions xenotransplantation as an acceptable purpose, and imposes the qualification that primate experiments performed in the context of translational or applied research should only be "*carried out in relation to potentially life-threatening conditions in humans or in relation to cases having a substantial impact on a person's day-to-day functioning, i.e. debilitating conditions*" (emphasis by the authors of the present report).

Specific concerns about the use of primates are also reflected in the requirement for the retrospec-

tive assessment of all projects that use primates (Article 39), and in the priority given to primates in the thematic review of the Three Rs (Article 58). The retrospective assessment should evaluate whether the objectives of the project were achieved, the actual harm inflicted on the animals (including the numbers of animals used and the severity of the procedures), and any elements that may contribute to the further implementation of the Three Rs principle. The thematic review of the Three Rs, which the Commission is required to submit by 10 November 2017, "*should examine the possible replacement of the use of animals, and in particular primates, as a matter of priority where it is possible, taking into account the advancement of science*" (Recital 49, implemented in Article 58; emphasis by the authors of the present report).

A non-technical project summary will also be required for all projects involving primates (Article 43). This must include information on the objectives, the predicted harms and benefits, the number and types of animals to be used, and a demonstration of compliance with the Three Rs. It has to be updated with the results of the retrospective assessment and must be published, albeit anonymously.

Public concern over the use of primates for scientific procedures

There are a number of activities within the EU and individual EU Member States that underline the extent of public concern with regard to the use of primates for scientific purposes and the need to ensure transparency in this matter. A few examples are given below.

In 2002, a report by the United Kingdom's (UK) Animal Procedures Committee recognised serious ethical and animal welfare concerns regarding the use of primates in experiments and "*considerable public disquiet*" with regard to such use. It recommended that the UK Secretary of State convene a forum for all interested stakeholders to address these concerns (14). Several years later, a committee set up by major UK research funders (the Medical Research Council and The Wellcome Trust), together with the Royal Society and the Academy of Sciences, chaired by Sir David Weatherall, reviewed the use of primates in research. One of the committee's recommendations was that there should be "*much greater openness about every aspect of primate research on the part of all those involved*" (15).

In 2005, a resolution to end the use of primates in research and testing, presented at the Fifth World Congress on Alternatives and Animal Use in the Life Sciences in Berlin, was signed by world-renowned primatologist Dr Jane Goodall and 57 individuals and organisations from 19 different countries (available at: http://www.rspca.org.uk/sciencegroup/researchanimals/implementing3rs/primateuse).

During the 2006 public consultation carried out by the Commission on the revision of *Directive 86/609/EEC*, over 93% of citizens considered it important to improve the current level of welfare and protection of great apes and other primates. Furthermore, almost 89% of those responding asked that there be more transparency and public participation in determining when and how animals are used in experiments (available at: http://ec.europa.eu/environment/chemicals/lab_animals/pdf/results_citizens.pdf).

The concerns of European citizens were taken up by their elected representatives in the European Parliament in 2007, when 433 of the 786 members of the Parliament voted to adopt a written declaration calling for an end to the use of great apes and wild-caught monkeys in scientific procedures, and for the establishment of a timetable for replacing the use of all primates in scientific procedures (4). In response, the Commission announced that the revised Directive (i.e. *86/609/EEC*) could "*incorporate strong incentives combined with a specific review clause to provide the appropriate and effective mechanism to move towards the ultimate goal of phasing out the use of primates in experiments*" (implemented in Article 58 of *Directive 2010/63/EU*). It further expressed its conviction that this goal could "*only be achieved with a vision, close cooperation and combined effort of all concerned*" (16). A similar comment had been made in the 2005 World Congress resolution.

Commission commitment to transparency

In 2006, the Commission made a firm commitment to promote transparency of policy issues in its Commission Transparency Initiative, by stressing "*the importance of a high level of transparency to ensure that the Union is open to public scrutiny and accountable for its work*" (9).

This commitment is backed up by the European Research Council (ERC)'s Scientific Council guidelines for open access, which underline that "*free and efficient access to information, including scientific publications and original data, will be the key for sustained progress*". The guidelines (available at: http://erc.europa.eu/sites/default/files/document/file/erc_scc_guidelines_open_access.pdf) require that all peer-reviewed publications from ERC-funded research projects be deposited into an appropriate research repository and subsequently be made open access within six months of publication. The ERC complements other funding activities in Europe, such as those of the national research funding agencies, and is a flagship component of the 'Ideas Programme' of the European Union's FP7.

Since the Lisbon Treaty, the right of access to documents has been extended to documents from all EU institutions, bodies, agencies and offices, whatever their medium (Article 15 of the Treaty of the Functioning of the European Union).

In addressing the problem of the public availability of research-related information, a three-year EU-funded project, OpenAIRE (Open Access Infrastructure for Research in Europe; www.openaire.eu), was launched at the end of 2009, to establish and operate an electronic infrastructure for researchers to assist them in handling peer-reviewed articles and other relevant forms of publications, such as pre-prints or conference publications. Thus, OpenAIRE supports researchers in complying with the ERC's guidelines.

In addition, in the case of research involving animals, *Directive 2010/63/EU* requires "*objective information concerning projects using live animals [to be] made publicly available*" (Recital 41 and Article 54) and, as stated above, requires the publication of non-technical project summaries.

Survey Methods

Collection of information on FP7-funded projects involving the use of primates: Internet and literature searches

At the start of 2012, an internet and literature review was performed, to compile the information available on FP7-funded projects that were likely to involve the use of primates. This provided an overview of the project-related information available in the public domain.

First, the Framework Programme Community Research and Development Information Service (CORDIS; http://cordis.europa.eu/fp7/projects_en.html) was searched, by using the terms: *primate(s)*, *monkey(s)*, *macaque(s)*, *marmoset(s)*, *tree shrew(s)*, and *ape(s)*. The information accessible with the CORDIS search engine consists of: a project overview page containing the project names and acronyms; an abstract (entitled 'objectives'); details of the type of project in regard to the specific FP7 sub-programme and contract type, and its duration; the amount of funding; the participants in the project and links to their affiliations; and any reports published.

This search retrieved projects where any mention of primates was made. Hence, the information retrieved was evaluated to distinguish between those projects where primates were referred to but not used, and those where their use was explicit. Individual projects were then categorised according to the following research topics: neurosciences, infectious disease research, evolutionary biology, and 'other topics'.

The information retrieved from the CORDIS pages does not contain details of the procedures that primates are subjected to. Therefore, an in-depth internet search was carried out for further information on individual projects. Lists of project-related publications presented on the respective CORDIS websites, linking to the OpenAIRE (Open Access Infrastructure for Research in Europe) website, were also evaluated, together with any project-specific websites, or websites of institutions where the research was carried out.

In addition, the names of CORDIS project contact persons, as well as combinations of relevant project-specific search terms, were used for PubMed literature searches, with the aim of retrieving relevant peer-reviewed publications indexed in the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed). These were included in the survey, if they involved primate use:

— *and* had been referred to in the project reports;
— *or* if they had been listed on project websites;
— *or* if the first author or senior author was project coordinator or scientific coordinator of the project's work package using primates;
— *and* the topic addressed was directly project-related;
— *and* if the full-text version was available free of charge.

Finally, general Google searches were performed by using the project acronyms and the project-specific search terms.

Collection of information on FP7-related ethics review process from grant holders and responsible Commission official

Later in 2012, CORDIS project contact persons, project coordinators and scientific coordinators of project work packages, including procedures involving non-human primates that had been identified during the literature review, were contacted via the CORDIS contact form, by post and, in some cases, also by telephone. The aim was to explore their experiences with the performance and outcome of the FP7 ethics review process. Specifically, they were asked which aspects of the FP7 ethics review process they considered beneficial, and why, and which parts of the process worked well or might require amendments. The Head of the Ethics Review Sector of the Commission Directorate General for Research was also contacted with regard to his experience with the process. His views were also sought on adaptations envisaged under the next FP, Horizon 2020, and in the light of *Directive 2010/63/EU*.

Results of Internet and Literature Searches

Numbers of projects retrieved and invasiveness of procedures involving primates

The CORDIS searches returned a total of 70 individual FP7 projects that could involve the use of primates. An overview of these, together with the general research areas they cover and an indication of whether invasive procedures were likely to be performed, are presented in Table A1 of *Appendix*.

Of the 70 projects retrieved, 23 were judged not to involve experiments with primates (see Table A2 of *Appendix*). This was either because the reference to primates made in the abstract was only in general terms, or referred to previous primate work, or stated that another model was to be used instead of a primate. For example, one of these projects, NEURONAGE (Molecular basis of neuronal ageing), uses nematodes in ageing research, and could be regarded as a 'replacement' project. Another was EUPRIM-NET II (European Primate Network: Advancing 3Rs and international standards in biological and biomedical research), which is aimed at disseminating best practice and the Three Rs in primate research, but does not itself seem to involve research on primates.

Forty-one projects either explicitly involved the use of primates in experiments, or were judged very likely to do so. Of these, 31 were considered to involve invasive experiments (i.e. involving procedures resulting in some form of interference with the animal's integrity), and 10 were judged to involve non-invasive procedures, i.e. non-invasive, behavioural experiments or the use of primate tissues (see Table A1 of *Appendix*).

Examples of statements in the CORDIS project summaries that were taken as evidence for the use

Table 1: Examples of statements in CORDIS project summaries taken as evidence for the use of invasive procedures

Acronym	Project title	Statement
AGELYSPARK	'Role of lysosomal dysfunction during aging, and implication for Parkinson's disease' (see also Table A3)	"…injecting filtrated fractions coming from cerebrospinal fluid from Parkinson Disease patients in non-human primates brains, and we will let those animals get older for years"
COGSYSTEMS	'Understanding actions and intentions of others' (see also Table A3)	"...we investigate the neural organization of monkey area F5, an area deeply involved in motor act understanding. By using a new set of electrodes…"
HIVNONILV	'A novel non-integrating replication limited lentiviral-based vector for HIV vaccination' (see also Table A4)	"…evaluate the immunogenicity and the safety of our novel NONI-LV vectors and the protection against pathogenic viruses in the non-human primate model of HIV… explore the immune responses induced in monkeys [and] the efficacy of induced immune responses to protect immunized monkeys against heterologous pathogenic viruses"

Table 2: Examples of statements in CORDIS project summaries taken as evidence for procedures involving tissues from primates

Acronym	Project title	Statement
EMREP	'A comparative genomic study of the contribution of epigenetic mechanisms to regulatory evolution in primates' (see also Table A5)	"...high-resolution gene expression data, methylation state, and histone modification profiles from a set of five tissues from multiple human, chimpanzee, and rhesus macaque individuals"
PRIMATE HETEROTACHY	'The speed of molecular evolution: Rate shifts, gene function and natural selection in primate history' (see also Table A5)	"…investigate changes in the speed of primate gene evolution, using complete genome sequences from at least six species of primates…"

of invasive procedures are presented in Table 1; those taken as evidence for procedures involving tissues from primates in Table 2; and an example of a statement taken as evidence for a non-invasive behavioural experiment in Table 3.

For six of the 70 projects, it was difficult to ascertain whether primates were used at all, and if they were, which types of procedures were involved. For instance, in the CORDIS summary of the project CONEURON (Drawing neuronal circuits without seeing them), primates are referred to as follows: "*We will analyze and model data from multi-electrode recordings in monkey primary visual cortex using state of the art and our own developments of analytical, computational and simulation techniques in order to address the fundamental question of how neurons interact to lead to complex activity patterns*" (Table A3). It is unclear whether the data from multi-electrode recordings in monkey primary visual cortex were already available at the onset of the project, or whether they would be obtained as part of the project.

Similarly, the CORDIS summary of the project NEUROMAN (Identifying the genes responsible for the expansion of the human cerebral cortex) states: "*…human-specific features of cortical progenitor cells will […] be identified by comparison with various non-human primates*" (Table A3). It is unclear whether this comparison involves live animals, or cells or tissues from animals, and whether or not the respective data were already available at the start of the project.

Project-related information supplementing CORDIS information

For 22 of the 47 projects judged to involve primate use, or where their use was possible, project-specific websites were available. These were either independent websites, or topic-related parts of institutional websites. This provided some additional information for five of 21 neuroscience projects, 10 of 12 infectious diseases research projects, three of six projects on evolutionary biology, and four of eight projects assigned to the category 'other topics' (see Tables A3–A6 of *Appendix*).

In some cases, the project-specific websites provided further information on the methodologies applied or, at least, a list of relevant publications. In addition, publications were looked for in PubMed and OpenAIRE. Since publications are linked to relevant project acronyms in the latter database, it was found to be a valuable tool for obtaining relevant additional information on FP7-funded projects, even though not all of the projects have uploaded documents in OpenAIRE.

In determining whether a publication was related to a given project, its *Acknowledgements* section was also evaluated, since many publishers require an acknowledgement of the sources of funding received. However, even where a specific publication was listed on a project website or linked to the respective project in OpenAIRE, its *Acknowledgements* did not, in all cases, refer specifically to the EU-funded project in question, but to other projects or sources of funding.

A total of 33 peer-reviewed original publications, review articles, project report summaries, or project presentations were retrieved, related to 20 of the 47 projects. This included 11 of 21 neuroscience projects, four of 12 infectious diseases projects, three of six projects on evolutionary biology, and two of eight projects assigned to the category 'other topics'. For a total of 11 projects, information was available from both project-related websites and publications. These 33 documents are listed in the *References* section of the present survey, with indications to the projects to which they are related. In addition, the projects for which publications were retrieved are indicated in *Appendix* (Tables A3–A6).

The documents retrieved were evaluated, in order to obtain more-detailed information on the procedures to which the non-human primates were submitted. As a rule, publications provide, in their *Materials and Methods* sections, a brief description of such procedures, as well as an indication of the animal species and numbers used. However, comprehensive descriptions of all parts of the procedures, up until the fate of the animals at the end of the experiments, were hardly ever presented.

Table 3: Example of a statement taken as evidence for procedures involving non-invasive, behavioural experiments

Acronym	Project title	Statement
HYBRIDBAB	'Baboon population studies; non-invasive sampling' (see also Table A6)	"…gaining a detailed understanding of the genetic, behavioural, and demographic consequences of hybridization in the well-studied wild Amboseli baboon population"

Factors limiting the comprehensiveness of the review

Generally, the information about FP7 projects that is available on CORDIS is limited, and as a rule, the links provided did not lead to more information. The titles and abstracts of the projects are often very vague, and there are no key words describing the animal species used or the methodologies applied. Therefore, primate projects might not appear, despite searches by using primate-related terms. Even where the abstracts are explicit about the use of primates, very few gave any indication of the procedures that the animals would be subjected to, and none gave any estimates of the numbers involved.

During CORDIS searches, some projects were returned by the search for 'primate', because the list of participants included a primate centre, even if there was no primate-relevant word in the project title or abstract. In these cases, it was not possible to tell whether primates would be used. It was also possible that some projects involving the use of primates were not found, because none of the primate-related search terms were contained in the abstract, and a primate centre was not involved. Many project abstracts in CORDIS merely refer to 'animal models', '*in vivo* studies' or 'preclinical work', without specifying which animal species are involved, or which procedures the animals are subjected to. In fact, some CORDIS abstracts seem so vague that it is not clear whether any animal use is involved at all.

A brief search by using terms covering scientific topics where primates have been used (e.g. 'Parkinson's' and 'ageing'), produced many projects that referred just to 'animal models', or other similarly vague terms. Some of these might indeed involve primates. For instance, the CORDIS objective to SNAP-PD (Striatal neuron anatomy and physiology in Parkinson's disease) includes the definition of "*in vivo physiological properties*" of neurons and application of multi-electrode recordings. An extensive search of the host institution and publications on the subject suggest that this project will use rats, but the use of primates cannot be ruled out.

Almost all CORDIS project descriptions provide a link to the homepage of one of the participating institutions. However, as a rule, very little additional information could be obtained by searching the institutional websites of the project partners. Finding a reference to the specific project on these websites is very difficult, and in many cases proved impossible. Some projects have a 'to know more' or 'for more information, please visit' link at the bottom of their respective CORDIS project pages. This link leads to the ERC website, which, however, has only a list of project titles — so this does not, in fact, provide the 'more information' promised.

Where principal investigators are named, it is often possible to find their publications, e.g. in PubMed, and to determine what methods they tend to use, then to relate this back to the project. However, many projects only provide an administrator as the CORDIS contact person, who is not involved in the scientific research, so further information cannot be obtained by this route.

Overall, free public access to the outcome of EU-funded research is limited by the fact that not all projects have published their results in open access journals. With respect to scientific publications in general, it is possible that 2012 was too early to expect publications from projects funded during the FP7 period, and it might be easier to find peer-reviewed publications from projects funded in earlier FPs. Nevertheless the problem of linking publications to FP projects remains, and has serious implications for the Commission's aim of greater transparency.

Research areas involving primates

The 47 projects discussed above mainly fall into three broad research areas, i.e. neuroscience, infectious disease research and evolutionary biology. Eight address a variety of scientific topics, and are summarised under *Other topics*.

Neuroscience

Covering 21 projects, neuroscience (Table A3) is the largest category, and contains the most projects with explicit and pivotal use of primates. The majority involve basic research on cognition, attention, memory and vision. Four projects focus on neurodegeneration, particularly Parkinson's disease, and three are related to robotics and prosthetics.

Sixteen of the 21 projects were judged to involve invasive research, and three projects to involve non-invasive research. In two projects the extent and type of primate use was unclear.

Infectious disease research

Infectious disease research (Table A4), in which primate 'models' are used for the development and testing of treatments (mostly vaccines) for human health problems, was the general topic of 12 projects. These involve research on malaria (three projects), human immunodeficiency virus infections (three projects), tuberculosis, Mexican influenza A (of avian/swine origin), chikungunya fever, West Nile virus, trypanosomiasis, and vaccine development in general.

Eleven of these projects were judged to involve invasive research, but the extent and type of primate use in one project was unclear.

Evolutionary biology

Six projects were classified as evolutionary biology (Table A5). Five of these involve molecular genetic studies, presumably requiring DNA samples from a variety of primate species. The samples may in some cases be archive material, but the collection of blood samples from captive or wild individuals also seemed to be involved.

Thus, these five projects involved some kind of 'sampling' rather than more severe procedures. The sixth project, on the other hand, reports performing cranial measurements, which, based upon the information obtained on the institutional website, most likely were performed on available skulls or non-invasively *in vivo*.

Other topics

The remaining eight projects involved primate use for a variety of purposes not covered by the above three categories (Table A6). One of these involves population studies in baboons. Others use primates to test treatments for retinitis pigmentosa or to test *Botulinum* antibodies, or for research on autoimmune disease.

Four projects were judged to involve invasive research and one project non-invasive research; for three projects, the extent and type of primate use was unclear.

Amount of project funding

The funding for individual projects is listed in CORDIS, but this is the total figure for each project, and the relative contributions of primate experiments to the entire project work plan vary. In some cases, for example, in TWOPAN (Genomic and phenotypic evolution of bonobos, chimpanzees and humans), primate experiments form the main focus of a project, whereas in others, they are part of a larger research strategy. NEUROCONSC (Converging criteria for consciousness: Using neuroimaging methods to characterize subliminal and conscious processing), for example, is a €2.4 million project that uses imaging techniques to study conscious processing in the brain. Experiments on primates are mentioned, but it is clear that a substantial proportion of the work will be on human subjects. Procedures involving primates might even be optional, depending on the outcome of the initial work packages, e.g. the development of a treatment that would only be tested on primates if preceding studies were successful.

Therefore, it is not possible to say how much the EU spends specifically on primate studies. However, the total funding for the projects in each of the four categories listed above is: neuroscience, €41.2 million; infectious disease research, €56.5 million; evolutionary biology, €4.2 million; and 'other', €23 million.

Numbers of primates used in FP7-funded projects

References in CORDIS information

The total number of primates to be used was not stated for any of the 47 projects listed above, and for only two of the projects was any reference to animal numbers found in the CORDIS information — in both cases, in the CORDIS periodic summary report (shown in Table 4).

References in project-related publications

It is not possible to tell from the publications arising from a project, how many animals were used in the project overall, since it is possible that not all of the results are published in a single paper and not all of the animals used are reported. The fig-

Table 4: Reference to animal numbers in CORDIS periodic summary reports

Acronym	Project title	Statement on animal numbers
NGIN	'Next generation HIV-1 immunogens inducing broadly reactive neutralising antibodies' (see also Table A4)	"…To date screening for neutralising activity occurred in 351 subjects: 285 HIV-1-infected adults, 20 HIV-1-infected mothers, 14 HIV-1-infected children, 20 HIV-2-infected adults, 12 SIV-infected macaques" (emphasis by the authors of the present report).
AMY-MPFC-EXTINCTION	'Functional connectivity between the primate amygdala and the medial prefrontal cortex: Role in extinction of emotional memories' (see also Table A3)	"…recordings of over 1000 neurons in the amygdala and prefrontal cortex of three behaving monkeys" (emphasis by the authors of the present report).

ures can only give an indication of the *minimum* number used in any given EU project.

By reviewing the publications that directly linked to an FP7 project (such direct links were either provided in the OpenAIRE repository, on the respective project website, or in the publication's acknowledgements), the numbers of primates used could only be obtained for nine of the 47 projects. The figures obtained are shown in Table 5.

Animal welfare-relevant information in publications arising from FP7-funded projects involving primates

The publications that related to FP7-funded projects involving primates were evaluated with regard to the provision of information considered relevant from the point of view of animal welfare. In the following sections, all of the animal welfare-related information found in the publications evaluated is presented. Whereas many publications made reference to legal provisions and guidelines, reference to the animals' housing conditions or to their sourcing, as well as to Three Rs measures applied, was scarce and often very general (see below). The severity of the procedures or the application of humane endpoints were never mentioned. In the CORDIS information, however, such animal welfare-related information was not found at all. In consequence of this lack of information, it was not possible to perform independent and comprehensive assessments of the severity of the procedures (see *Examples for specific procedures involving primates in FP7-funded projects and their severity classification*).

Reference to animal welfare-related legal provisions and guidelines

Indications of the legal framework under which the procedures were performed, not only underline the authors' awareness of, and compliance with, animal welfare-relevant provisions, but also reveal the framework under which the procedures were conducted. Hence, even if the location of the institute in which the experiments were performed is not explicitly stated in the publications, reference to the legal provisions complied with point to the country in which the procedures involving primates were conducted. Accordingly, quite a number of experiments of FP7-funded projects seem to have taken place outside the EU.

A number of publications arising from the FP7 projects mention compliance with the relevant EU or national legislation on the protection of laboratory animals (17–21). Others mention approval of the procedures by an Institutional Animal Care and Use Committee (IACUC). In this context, Klavir *et al.* (22), and Livneh and Paz (23) refer to

Table 5: Reference to animal numbers in publications with direct links to the respective projects

Acronym	Publication	Number of animals/species
AGELYSPARK	Berthet *et al.* (31) Porras *et al.* (21)	45 Macaques 37 Macaques
AMY-MPFC-EXTINCTION	Klavir *et al.* (22) Livneh and Paz (23)	2 Macaques 3 Macaques
ANTIBOTABE	Chahboun *et al.* (19)	1 Macaque
BRAINAGE	Antonow-Schlorke *et al.* (24)	Between 14 and 16 female pregnant baboons (and fetuses), one vasectomised male baboon
COGSYSTEMS	Bonini *et al.* (18) Borra *et al.* (32)	2 Macaques 4 Macaques
EYESHOTS	Bosco *et al.* (17)	3 Macaques
IM-CLEVER	Truppa *et al.* (20)	5 Tufted capuchin monkeys (non-invasive behavioural experiment)
NGIN	Buonaguro *et al.* (35)	24 Macaques
TWOPAN	Herrmann *et al.* (25) Prüfer *et al.* (29)	34 Bonobos, 106 Chimpanzees (non-invasive behavioural experiment) 1 Bonobo (single blood sampling)

the IACUC of the Israeli Weizmann Institute; Porras *et al.* (21) to that of the Chinese Academy of Science; and Antonow-Schlorke *et al.* (24) to the IACUC of the University of Texas, USA. Herrmann *et al.* (25) refer to approval by an internal ethics committee at the German Max Planck Institute for Evolutionary Anthropology, and compliance with the policies of the Chimpanzee Sanctuary & Wildlife Conservation Trust, Uganda, as well as those of two sanctuaries in the Republic of Congo. Reference to animal care committees of institutions located in Italy can be found in the publications of Bosco *et al.* (17), Bonini *et al.* (18), and Truppa *et al.* (20).

AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) accreditation of the laboratories in which the primate experiments were performed is reported by Antonow-Schlorke *et al.* (24), Klavir *et al.* (22), Livneh and Paz (23), and Porras *et al.* (21).

Reference to housing conditions

Primates have a high level of consciousness and complex physical, social and other behavioural needs that are difficult to provide for in a laboratory environment. Inadequate housing and care, where primates are kept in small cages, deprived of contact with conspecifics, with little environmental enrichment or control over their environment, is acknowledged to cause significant distress over and above the pain and distress caused by the scientific procedures performed. This is recognised in Annex VIII of the Directive, in that "*prevention from expressing natural behaviour including restrictions on the housing, husbandry and care standards*" has to be taken into account when assessing severity. The provision of information on housing and care allows for a more comprehensive assessment of the level of harms for animals, and shows whether current standards of good practice are being applied.

Reference to the animals' housing conditions was made in the following publications:

— Porras *et al.* (21) report single housing of macaques with induced Parkinson-like symptoms throughout the entire duration of the study;

— Truppa *et al.* (20) state that: "*To increase three-dimensional space available to the animals, indoor enclosures were furnished with perches and ropes and outdoor enclosures were furnished with logs, branches, and ropes. Moreover, the presence of natural substrates, including woodchips on the ground, served to promote monkeys' exploratory behaviours.*"; and

— Herrmann *et al.* (25) describe the apes' living conditions in the African sanctuaries: "*The vast majority of chimpanzees and bonobos had access to large tracts of tropical forest (5–40 hectares) during the day. In the evening all apes came back from the forest and stayed the night in indoor enclosures (12–160m²). Apes voluntarily participated in the study and were never food deprived for any reason and they were fed, in addition to the food the apes could eat in the forest, a variety of fruits, vegetables, and other species-appropriate food two to four times daily. Water was either available* ad libitum *or was given to the subjects several times a day (since most of the apes at the sanctuary spent the day in the forest).*"

A specific justification for the single housing reported by Porras and co-authors is not provided. Therefore, it is unclear whether these housing conditions are in line with the revised guidelines for the accommodation and care of research animals implemented in Annex III of *Directive 2010/63/EU* in combination with Commission Recommendation *2007/526/EC* (26). Section 4.1 of the primate-specific section of this Recommendation prescribes that single housing of primates should only be allowed for "*as short a time as possible, under close supervision, and where there is a justification on veterinary or welfare grounds*". Apparently, the procedures described by Porras and co-authors were performed in China (see above). It cannot be determined whether the same procedures, performed in the EU, would have resulted in different housing conditions for the animals. Even though Annex III of *Directive 2010/63/EU* will only come into effect as of 1 January 2017, it should nevertheless already be considered a standard requirement for EU-funded projects.

Reference to Three Rs measures

Provision of information on Three Rs measures applied during a project serves a number of functions. It demonstrates that such measures have been applied in accordance with legislation and other guidelines. It facilitates dissemination of good practice, and contributes to an assessment of the level of harms that the animals experienced. Publication of such information is now encouraged by some journals and in guidelines, such as the ARRIVE guidelines (27).

There was very little information relating to Three Rs measures in the publications. The only statements were:

— Klavir *et al.* (22), and similarly Livneh and Paz, (23): "*food, water, and enrichments (e.g., fruits and play instruments) were available* ad libitum *during the whole period, except before medical procedures*";

— Porras *et al.* (21): "*Veterinarians skilled in the healthcare and maintenance of nonhuman primates supervised animal care. All reasonable efforts were made to minimize animal suffering. The use of primates was minimized by using an experimental design that permits statistically significant changes to be demonstrated with the smallest number of animals per group and the smallest number of groups, consistent with scientific rigor*"; and

— Bosco *et al.* (17): "*During training and recording sessions, particular care was taken to prevent behavioural and clinical signs of pain or distress.*"

Reference to the origin of the primates

The source of the primates used is a further factor contributing to the overall animal welfare costs of a procedure. Thus, Article 10 of *Directive 2010/63/EU* foresees a phasing out of the use of wild-caught primates for scientific purposes, because of the additional stress this causes (Recital 19 of the Directive confirms this concern, stating: "*the capture of non-human primates from the wild is highly stressful for the animals concerned and carries an elevated risk of injury and suffering during capture and transport*"). There are also serious stresses associated with the use of captive bred animals, where these are imported from overseas. Primates may have to endure lengthy, multistage journeys to Europe from breeding colonies in Asia.

In the project-related publications, indications of the origin of the primates are scarce. Porras *et al.* (21) mention the use of "*F2-bred macaques*", further referring to "*Xierxin*" (China), which is possibly the supplier of the animals. Beignon *et al.* (28) indicate that "*twelve outbred males and adult cynomolgus macaques […] from the Indian Ocean Island of Mauritius*" were used.

The five tufted capuchin monkeys (20) and the one bonobo (29) used were "*born in captivity*". Finally, Herrmann *et al.* (25) report: "*All apes came to the sanctuaries as orphans as a result of the illegal bushmeat trade, were raised by humans together with peers...*"

Examples of Specific Procedures Involving Primates in FP7-funded Projects and their Severity Classification

Neither the procedures that primates are subjected to, nor their severity, are described in the CORDIS objectives. Therefore, publications relating to the projects were searched for more-detailed information that might allow the level of harm inflicted upon the animals to be determined. The severity of the procedures was then assessed in accordance with the 'severity classification of procedures' described in Annex VIII of *Directive 2010/63/EU*. This states that: "*the assignment of the severity category shall take into account any intervention or manipulation of an animal within a defined procedure. It shall be based on the most severe effects likely to be experienced by an individual animal after applying all appropriate refinement techniques*". Most importantly, the severity should be classified on a case-by-case basis, taking into account all individual factors involved in the given procedure. Such factors include "*cumulative suffering within a procedure*" and all "*methods used to reduce or eliminate pain, suffering and distress, including refinement of housing, husbandry and care conditions*".

The following examples are intended to provide an illustration of the spectrum of procedures carried out on primates in FP7 projects, and of the level of detail that is publicly available. In general, there was insufficient information available in any of the sources searched to make anything other than a tentative assessment and categorisation of the severity of harms experienced by the animals.

Example 1: Macaques with induced Parkinson-like symptoms

The use of macaques with chemically-induced Parkinson-like symptoms is reported for the project AGELYSPARK (Role of lysosomal dysfunction during aging, and implication for Parkinson's disease; see Table A3). According to the CORDIS objective, the *in vivo* research performed in the course of this project involves "…*injecting filtrated fractions coming from cerebrospinal fluid from PD patients into the brains of non-human primates, and we will follow-up on these animals getting older for years…*"

In publications related to AGELYSPARK, Porras *et al.* (30) provide an overview of different primate 'models' of Parkinson's disease (PD). Porras *et al.* (21), describe the use of 37 F2-bred female macaques housed individually. These animals were either treated with L-DOPA (which is used as dopamine replacement therapy for PD, but also induces dyskinesia) twice daily for three months, or daily with MPTP hydrochloride, to induce a Parkinson-like syndrome: "*Following stabilisation of the MPTP-induced syndrome*", the animals either received saline, or L-DOPA for three months. The paper reports that: "*13 animals developed severe and reproducible dyskinesia, presenting choreic-athetoid (characterized by constant writhing and jerking motions), dystonic, and sometimes ballistic movements (large-amplitude flinging, flailing movements), whereas 6 others did not.*"

Seven dyskinetic chronically L-DOPA-treated MPTP-intoxicated animals were kept alive for further behavioural investigations after intracerebral injection of L-DOPA/carbidopa (an anti-Parkinsonian drug combination) to reverse PD symptoms. These investigations began four weeks after a surgical intervention, the details of which are not reported, although, presumably, it served to implant a device for the intracerebral injections. During the behavioural experiments, the severity of the remaining dyskinesia and the duration of anti-Parkinsonian action were measured.

Other than these animals, there is no indication of the fate of the macaques at the end of the procedures (21). Berthet *et al.* (31) report killing the animals by sodium pentobarbital overdose, 60 minutes after the final substance administration, *"a time at which dyskinesia was maximal in the dyskinetic group"*.

With regard to *severity classification*, in accordance with Annex VIII of *Directive 2010/63/EU*, procedures shall be classified as severe, if "*the animals are likely to experience severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress*", or if they "*are likely to cause severe impairment of the well-being or general condition*". Taking into account the spectrum of symptoms developed by a number of animals, the duration of the experiments, the number of individual procedures, and the individual housing, the authors of the present survey believe that the severity classification of these procedures should be 'severe'.

Example 2: Intracranial microelectrode and fMRI recordings of the brains of awake macaques

Intracranial microelectrode and functional magnetic resonance imaging (fMRI) recordings of the brains of awake-behaving macaques are reported for a number of projects (see Table A3). Further information was sought on two of these: AMY-MPFC-EXTINCTION (Functional connectivity between the primate amygdala and the medial prefrontal cortex: Role in extinction of emotional memories), and COGSYSTEMS (Understanding actions and intentions of others).

According to the CORDIS objective of AMY-MPFC-EXTINCTION, the procedures involve first recording "*…simultaneously from the amygdala and medial prefrontal cortex of awake-behaving monkeys during rest, electrical stimulation, and temporary inactivation of one of the structures. Then, we will record during acquisition and recall of extinction of fear-associations…*" The CORDIS periodic project summary report mentions "*recordings of over 1000 neurons in the amygdala and prefrontal cortex of three behaving monkeys*".

Further details of the experiments performed during this project are described in the *Methods* sections of Livneh and Paz (23) and Klavir *et al.* (22). Three and two macaques, respectively, had a recording chamber implanted above the respective area of the brain under investigation. The surgery was performed under deep anaesthesia and aseptic conditions. Anatomical MRI scans were undertaken, to guide the positioning of the chamber on the skull during surgery, and also to guide the intracranial positioning of the electrodes.

In the study presented by Livneh and Paz (23), intracranial recordings were performed with 3–4 microelectrodes inserted into the brain, while the animals were exposed to different pleasant or aversive odours via a nasal mask held on the macaque's nose, or while they were exposed to different tones delivered through a speaker. Modulations in inhalation patterns upon experimental stimulation were measured.

In the study conducted by Klavir *et al.* (22), the macaques were seated in a dark room and submitted to a "*classical conditioning task*" (pairing an unconditioned aversive stimulus of an air puff located proximally 5cm from the left eye with a visual or auditory cue). Neural activity was recorded by using intracranially-placed microelectrodes and eye blinking, with the help of a computerised digital video camera adapted for night conditions. Klavir and co-authors report performing "*92 sessions overall*". In the study by Livneh and Paz (23), an indication of the number of sessions performed could not be found. Neither article referred to the fate of the macaques at the end of the procedures.

In the CORDIS objective to COGSYSTEMS, the primate experiments are described as follows: "*In the first part we investigate the neural organization of monkey area F5, an area deeply involved in motor act understanding. By using a new set of electrodes we will describe the columnar organization of the area F5, establish the temporal relationships between the activity of F5 mirror and motor neurons, and correlate the activity of mirror neurons coding the observed motor acts in peri-personal and extra-personal space with the activity of motor neurons in the same cortical column. In the second part we will assess the neural mechanism underlying the understanding of the intention of complex actions, i.e. actions formed by a sequence of two (or more) individual actions.*"

Borra *et al.* (32) and Bonini *et al.* (18) provide further details on the procedures undertaken for this project. Bonini and co-authors report the use of two female macaques: "*Before recordings, monkeys were habituated to sit in a primate chair and to interact with the experimenters.*" Then they were trained to perform specific motor tasks of different degrees of complexity. Upon completion of the training period, "*a head fixation system and a titanium recording chamber were implanted under general anaesthe-*

sia… followed by postsurgical pain medications". Food rewards were provided when the animals successfully completed the required tasks. Neuronal recordings were performed with the help of single glass-coated microelectrodes inserted through the intact dura. Animals were euthanised at the end of the procedures, for histopathological investigations of the brain.

With regard to *severity classification*, there is insufficient information available in the CORDIS summaries and the publications associated with these projects to determine what procedures the animals were subjected to, and what the overall severity would be. Nevertheless, a number of factors that are relevant for a severity classification can be discerned. These are: habituation to sitting in a primate chair, surgical intervention, head-fixation during the procedures, and the exposure to aversive stimuli. In accordance with Annex VIII of *Directive 2010/63/EU*, "*procedures on animals as a result of which the animals are likely to experience short-term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress as well as procedures that are likely to cause moderate impairment of the well-being or general condition of the animals shall be classified as 'moderate*"'. In the Annex, examples for procedures assigned to the category 'moderate' include *"surgery under general anaesthesia and appropriate analgesia, associated with post surgical pain, suffering or impairment of general condition".* Examples include craniotomy and surgical implantation of catheters or biomedical devices. Taking into account the spectrum of the interventions that the macaques are submitted to, intracranial microelectrode recordings on awake macaques have to be assigned at least to the category 'moderate'. Specifically, the use of macaques, in a total of 92 sessions, involving repeated air puffs to the eye is assigned to the category 'severe'.

The information retrieved on the procedures performed in the course of the projects AMY-MPFC-EXTINCTION or COGSYSTEMS provides no indication that the animals used were deprived of water in the course of the experiments. However, depriving macaques from *ad libitum* water intake is a technique commonly applied during intracranial electrophysiological recordings, to ensure that the animals will work for a fluid reward. The delivery of fluid rewards is described by Savaki *et al.* (33), related to the working group of project VISATT (Interactions between prefrontal cortex and area V4 in attention): "*Training lasted for 1 hour per day during 3–6 months until the monkeys perfected their performance (approx. 95% success rate). Successful completion of trials was rewarded with water delivered through a tube attached close to their mouth. Monkeys had their arms restrained on a primate chair for the duration of the [45-minute] [^{14}C]-deoxyglucose experiment*" (i.e. a method for obtaining images of the distribution of metabolic activity in the brain; see Table A3). Accordingly, water deprivation is retained over the entire period of the experiment, which has to be taken into consideration on the determination of the severity of such procedures.

Example 3: Maternal food deprivation during pregnancy

In the CORDIS objective to BRAINAGE (Impact of prenatal stress on brain ageing), it is stated that "*human subjects, non-human primates and rodents (including transgenic models) exposed to maternal stress, glucocorticoids or under-nutrition are examined in order to determine structural (MRI-based volumetry) and functional (metabolomics, brain function, cerebrovascular tone) indicators of brain age [and to] relate them to susceptibility to stroke and cognitive decline*" (Table A3).

In a study published in the context of BRAINAGE, the maternal food deprivation consists of feeding six pregnant baboons with 70% of the previously recorded *ad libitum* food intake, starting from the thirtieth day of gestation (24, and similarly, 34). On the ninetieth day, the fetuses were obtained for immunohistochemistry of their brain tissues.

With regard to *severity classification*, according to Annex VIII of *Directive 2010/63/EU*, food deprivation is classified as mild when feeding "*modified diets that do not meet all of the animals' nutritional needs and are expected to cause mild clinical abnormality within the time-scale of the study*". The level of clinical abnormality caused by feeding pregnant baboons 70% of their normal daily intake over a time period of two months, while maintaining group housing, would have to be determined on a case-by-case basis. It seems likely that this will be assigned at least to the category 'mild'. Additionally, however, some kind of procedure will have been used to obtain the fetuses at day 90 of gestation. Unfortunately, there is no indication of the type of procedure, or of what happened to the females afterwards. If a hysterectomy (or Caesarean) was performed and the animals survived, then in accordance with the Directive's definition of 'moderate' severity (see example No. 2), the performance of a hysterectomy has to be assigned to the 'moderate' severity class.

Example 4: Immunisation procedures

Immunogenicity of HIV-1 immunogens on macaques

The CORDIS objective for NGIN (Next generation HIV-1 immunogens inducing broadly reactive neutralising antibodies; see Table A4) describes the

development of immunogen/adjuvant combinations, and the evaluation of those proving most effective in eliciting broadly neutralising antibodies, both systemically and at the mucosal level, for their immunogenicity and efficacy upon challenge with a live heterologous virus.

In a publication related to this project, Buonaguoro *et al.* (35) divided a total of 24 female rhesus macaques into four different treatment groups, and immunised the animals with HIV virus-like particles (HIV-VLPs) or HIV DNA by the intranasal route. One group received two further boosting doses of VLPs by the intramuscular route, 22 weeks after the last intranasal administration. Sera were collected from 10ml of whole blood, one week before and one week after each antigen administration, for the determination of antibody titres. Vaginal washes were collected on the same days as the serum, to determine mucosal antibody levels. There is no indication that the animals were challenged with virus in the course of the procedures. However, according to the CORDIS objective, this is likely to be part of further procedures. The fate of the animals at the end of the experiments is not reported.

Immunisation with antibodies against toxin

The CORDIS objective of ANTIBOTABE (Neutralizing antibodies against *Botulinum* toxins A, B, E) states: "*Six corresponding immunogens will be produced in recombinant form, and utilized to immunize macaques*" (see Table A6).

In the ANTIBOTABE-related study presented by Chahboun *et al.* (19), one macaque is immunised with four subcutaneous injections of *Botulinum* neurotoxin light chain A1. Three of these injections were administered at one-month intervals, and the fourth injection was given with an eight-month interval. After the immunisation, RNA was isolated from the bone-marrow. There is no indication as to the time-point of this isolation, or whether the samples were taken from the live animal or after euthanasia. Likewise, there is no indication of the fate of the animals at the end of the experiments. No further information was available from the ANTIBOTABE summary (available at: www.antibotabe.com) or from the preliminary project results presented by Sesardic *et al.* (36).

Immune system-related therapy

As presented in the CORDIS objective, the project TRIAD (Tolerance restoration in autoimmune diseases by selective manipulation of the CD28 costimulatory pathway; see Table A6) will begin by studying the efficacy of a new selective antagonist of CD28 (i.e. FR104) in primates (CD28, is a costimulatory molecule on the surface of T-cells, the activation of which is necessary for HIV transcription and regulation; anti-CD28 substances are under consideration as drug candidates for HIV treatments). Afterwards, the potential immunological toxicity of the antagonist will be studied in primates, to exclude agonist activity *in vivo*. Parallel studies with rodents address further issues.

According to the TRIAD project website, Work Package (WP) 2 of the project "*will study the preclinical in vivo efficacy of FR104 in non-human primate models of Multiple Sclerosis, Rheumatoid Arthritis, psoriasis... The immunological toxicity will be examined by WP3… in non-human primate models... Additionally, WP3 will evaluate immunogenicity, viral status and potential for progression to malignancy in primates*". Details of the procedures are not available.

With regard to *severity classification*, the information retrieved for these projects is insufficient to enable the severity of procedures to be determined. According to Annex VIII of *Directive 2010/63/EU*, the administration of substances might be assigned to any of the severity categories — mild, moderate or severe — depending on the level of the adverse effects elicited. The category 'mild' is assigned to the "*administration of substances by subcutaneous, intramuscular, intraperitoneal routes, gavage and intravenously via superficial blood vessels, where the substance has no more than mild impact on the animal, and the volumes are within appropriate limits for the size and species of the animal*".

Moderate severity is to be expected upon "*frequent application of test substances which produce moderate clinical effects*", and severe procedures include "*vaccine potency testing characterised by persistent impairment of the animal's condition, progressive disease leading to death, associated with long-lasting moderate pain, distress or suffering*". Generally, challenge tests are to be classified as severe: animals are infected with the respective pathogenic, and potentially lethal, organisms, and, at least in the non-immunised or non-treated group, are expected to develop the resulting symptoms.

The information obtained for the NGIN, ANTIBOTABE and TRIAD projects does not provide any proof-of-evidence that challenge tests were performed. Nevertheless, the collection of sera (examples: *Immunogenicity of HIV-1 immunogens on macaques,* and *Immune system-related therapy*) or of bone-marrow samples (example: *Immunisation with antibodies against toxin*) is likely to involve at least 'mild' or 'moderate' suffering, since all these procedures will involve restraint or anaesthesia.

Furthermore, WP2 of the project TRIAD refers to primate models of multiple sclerosis, rheumatoid arthritis and psoriasis. These are serious con-

ditions that cause a great deal of suffering in humans. There is no information about how the models are created or the adverse effects on the animals, which could be severe, or for how long the animals are kept.

Example No. 5: Behavioural experiments

The CORDIS objective of IM-CLEVER (Intrinsically motivated cumulative learning versatile robots) aims at "*reproducing with bio-mimetic models the results of empirical experiments run with monkeys, children, and human adults*" (see Table A3).

In this project, Truppa *et al.* (20; supplemented by [37] and the IM-CLEVER project summary [38]) report the use of five adult tufted capuchin monkeys, 2–27 years old and born in captivity, living in three groups, each housed in an indoor–outdoor enclosure. Just before the daily testing session, the animals were separated from their group by accessing an adjacent experimental cage through a sliding door. In the experimental cage, water was freely available at all times; fresh fruit, vegetables, and monkey chow were provided in the afternoons, after testing. Trials consisted of 'matching-to-sample' tasks where the monkeys had to respond to stimuli presented on a computer screen to obtain food rewards in return for the correct responses. The monkeys performed these trials whilst roaming freely, with sessions taking place between 10:30 and 16:00, depending, among practical issues, on the individual animal's motivation. There was no indication as to the fate of the animals at the end of the procedures; however, they had previously been used in similar experiments.

The CORDIS objective of TWOPAN (Genomic and phenotypic evolution of bonobos, chimpanzees and humans) is to "*generate a genome sequence for the bonobo and to collect extensive data from chimpanzees and bonobos on cDNA sequences, variation in coding and non-coding parts of the genomes, expression of mRNAs, microRNAs and proteins in five tissues, and phenotypic parameters in terms of clinical chemistry, and behavioural and cognitive traits*" (see Table A5).

In the course of this project, Herrmann *et al.* (25) tested 34 bonobos (5–22 years of age) and 106 chimpanzees (3–21 years of age), living in sanctuaries in the Congo and Uganda, where they had been brought as orphans and raised together with peers. At the time of testing, the majority of the animals lived in social groups. The bonobos and chimpanzees were challenged to solve cognitive tasks, to imitate the solutions of other animals to problems, to communicate non-verbally with each other, and to understand the goals and perceptions of other animals.

Also related to the TWOPAN project, Prüfer *et al.* (29) sequenced the genome of a female bonobo at the Leipzig zoo, born in captivity, making use of a blood sample that was drawn during a routine examination by the veterinarian.

With regard to *severity classification*, in determining the lower threshold level of distress of scientific procedures, Article 2 of *Directive 2010/63/EU* defines procedures as "*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*". In accordance with Annex VIII of the Directive, "*studies involving short-term deprivation of social partners*" are to be classified as 'mild'. The experiments described in these two projects are likely to be classed as 'below threshold' or 'mild'.

Inquiry with Grant Holders and the Responsible Commission Officer Regarding the Ethics Review Process

Response to inquiry

The grant holders — i.e. the project coordinators, contact persons, or scientists responsible for the project work packages — of 43 projects involving primates were addressed via the CORDIS project contact form and by post. In addition, several project coordinators were contacted by telephone. The responsible Commission official was also asked about his experience with the FP7 ethics review process.

Responses were received for 15 (35%) of the projects, namely, eight 'neuroscience' projects, four 'infectious disease research' projects, one 'evolutionary biology' project, and two projects assigned to the 'other topics' category. In addition, one project coordinator responded that he was unable to provide the information requested, and the secretary of a further project coordinator replied that the person in charge would not have the time to respond. One respondent stated that the ethics review process was performed by the Commission, and referred the authors of the present report back to Commission officials for further questions.

The comments received are summarised in the following sections.

Benefit *versus* complexity of the FP7 ethics review process

The overall view of the respondents was that the FP7 ethics review process was "*necessary*", "*mean-*

ingful" and "*beneficial*", and provided "*a means of ensuring that the project complies with EU directives and national legislation*", and of ensuring that "*ethics is embedded in the research*". Several respondents said that the ethics review process forced their consortium to discuss ethical issues systematically and in detail, which was seen as a helpful quality control process:

— "*The ethical review process was the opportunity to write down a protocol including all aspects of animal handling and therefore clarifying aspects such as cumulative pain. It also allowed our team to be more comfortable, i.e. under the open recognition of representatives of the society.*"

— "*Apart from providing the EU with all the information they requested and sometimes with more details than we initially did, the entire process has been very friendly and easy going.*"

At the same time, there was general agreement among the grant holders that the ethics review process was complex and labour-intensive. It was repeatedly reported that replying to the comments addressed in the Commission's Ethics Review Report resulted in responses of ten pages, or more. A number of project coordinators, however, only had vague recollections of the contents, or outcome, of the ethics review process, referring to the principal investigators of the primate experiments for such issues.

In addressing the complexity of the procedure of applying for EU funding as such, one grant holder pointed out the outstanding role of commercial administration companies in meeting the EU requirements and in submitting proposals. Apparently, such a commercial administration company supported the scientists in writing the ethics sections, "*making sure that every word was in the right place*".

Ethics review panels' Ethics Review Reports

According to the responses of the grant holders, comments provided by the ethics review panels in the Ethics Review Reports dealt with all aspects of the respective projects. This included: justification for the numbers of animals used; specifications of distress and suffering of the animals; very detailed information regarding anaesthesia and analgesia; and indications of the accommodation of the animals, with the latter covering aspects such as social housing and cage dimensions. In addition, the implications of the outcome of the primate research for further clinical research on humans, or the coupling of primate research with research involving other animal species, were addressed. The grant holders repeatedly reported that the ethics review required specific refinement or reduction measures to be implemented. Overall, it was acknowledged that the comments made were to the point and were objective, and that the resulting modifications to the procedures improved the experiments: "*Questions were all fair and valid ones. We therefore improved incrementally from one project to another.*"

One respondent, however, questioned whether the reviewers had ever been actively involved in primate experiments. This respondent referred to a reviewer who proposed the use of mice instead of primates. In the end, the applicant convinced the review panel that primates were necessary for the purpose of the study.

Another respondent commented on the level of scrutiny applied to non-invasive procedures as compared to invasive procedures: "*We had the feeling that the EU sometimes does not know the research teams and what they do with the monkeys and therefore are 'obliged' to be as inquisitive with the ethologists […] that study spontaneous behaviour as they should be with scientists that carry out more invasive research. But this is what they should do.*"

Efficiency of the ethics review process

The implication of the ethics review process for the time-frame of project evaluation was a controversial topic. Some respondents questioned its efficiency: "*The ethical review is slowing down time to grant acceptance, some issues are looked at in much detail*".

In this context, the lack of transparency with respect to the different steps of the evaluation procedure was deplored: "*The applicants have to adhere to very strict deadlines in the course of the evaluation of their applications, but there are no deadlines from the side of the Commission.*"

In addition, in the applications, the ethically-relevant information is often too general to begin with, so the ethics review panel requests further information.

Delays in the grant acceptance process relating to the ethics review also depend on the expertise of the applicants, as was revealed by a number of responses: "*We initially feared about the timelines. However our ethical committee has been very professional and revised our protocols on time*"; and "*since the Principal Investigator was experienced, he knew the required answers, and all issues were dealt with very quickly.*"

An efficient ethics review process was seen to depend on a good balance between experienced scientists in charge of the performance of the primate experiments, the ethics review panel and the Commission working together: "*The review was conducted in a timely manner, and dialogue was possible to ensure that requirements were incorporated into the contract.*"

With regard to communication between the Commission and the applicants, several grant holders regretted that they never received feedback, either on their replies to the comments in the Ethics Review Reports, or to their comments in the interim reports on how ethics requirements were being taken into account during the projects: "*We never heard from them again. Therefore I assume that they were satisfied.*"

Outcome of the ethics review process

The grant holders addressed in the course of the survey had their research proposals evaluated with a favourable outcome. Refusal or replacement of proposed procedures involving primates did not seem to have been an issue. It is not possible to say how this compares with other projects submitted for funding under EU framework programmes.

According to the provisions of FP7, the justification for an application is determined during its scientific evaluation. The subsequent ethics review does not revisit the scientific evaluation, but addresses the ethical issues, including the methodologies proposed by the applicants. As reported by the Commission officer, one project proposal submitted under the previous FP6 was turned down because of ethical issues involving the use of primates. Apart from this one particular instance, however, the ethical review process mostly seems to address *reduction* and *refinement* measures, which also seems to be the case in the course of other ethics review processes, such as the national project authorisation procedures in Germany (39).

Interplay between Commission and national authorities during project evaluation

The interplay between the FP7 ethics review process and project authorisation at the national level was also highlighted. Two respondents considered that obtaining the national licence was the main hurdle to pass when planning a project involving primates: "*I have nothing to complain about the ethical review process during the evaluation. It went smoothly and the points raised were straightforward to address. In contrast, getting the national licenses seems to be much more difficult.*"

One respondent deplored the fact that the ethics review process was unnecessarily cumbersome, stating that the national and EU authorities addressed identical questions, but in a slightly different format, so applicants were forced to address the same issues twice. This respondent wished for the Commission to delegate more responsibility to the national authorities, especially since they were responsible for supervising adherence to the EU provisions.

Procedures involving primates performed outside the EU

A number of experiments of FP7-funded projects were performed outside the EU. As a rule, the FP7 provisions include 'equivalence requirements' as reported by the Commission official, requesting that animal welfare standards in collaborating countries outside the EU are equivalent to EU standards. However, the Commission official further acknowledged that enforcement of this requirement was problematic. In addition, the responsible non-EU scientists' awareness of EU legislation seemed to differ between different projects, as was revealed by responses from the grant holders: "*We had to describe that the [non-EU] authorities and ethics review procedures were equivalent to the EU authorities"; and "if the research is made in the [non-EU country], do the [non-EU country] regulations only have to be followed, or also the European regulations?*" (Question posed by Principal Investigator located in a non-EU country.)

Follow-up of projects involving primates

During the FP7 period, the Commission implemented provisions allowing for a follow-up of the ethical requirements laid down in the project agreements. The aim was to visit the institutions in the course of the projects, to supervise adherence of the grant holders to the ethical measures imposed, both legally and in terms of quality. So far, an ethics follow-up has only been conducted for one project, without any complaints with regard to the procedures involving primates. The responsible Commission official was expecting follow-ups to become an important instrument in the upcoming framework programme, Horizon 2020, to ensure that ethical requirements and recommendations imposed as an outcome of the ethics review process are fully addressed and serve to minimise animal numbers and animal suffering.

Grant holders' opinions on the implications of *Directive 2010/63/EU* for the EU FP ethics review process

A broad spectrum of responses was received with regard to the implications of *Directive 2010/63/EU* for the future ethics review process. Several grant holders emphasised that they had been working in accordance with the Directive's provisions before 1 January 2013. Asked whether they foresaw any changes in the ethics review procedure as a result of the new animal welfare provisions, a number of grant holders argued against any change: "*The ethical review of projects involv-*

ing non-human primates is already very tough. I don't see any reason to render it even tougher"; "*no change, it's pretty intense already*"; and "*the process is robust and appears to be working well, so I see no need for changes*."

Unsurprisingly, the expected implications of the transposition of *Directive 2010/63/EU* were different in institutions located in Member States that already had animal welfare provisions in place which exceeded those of the previous *Directive 86/609/EEC*, and those in Member States that merely complied with its provisions. Previously, in some Member States, the FP7 ethics review was performed in addition to the evaluation necessary to comply with specific national legislation, whereas in others, the FP7 ethics review process was the only ethical evaluation a project had to undergo.

Scientists from Member States that had previously implemented minimal requirements were expecting profound systematic changes under the new Directive, which would increase their workload when preparing for the ethics review and project licensing processes. The requirement for a retrospective assessment of projects and the appointment of animal welfare bodies were seen to present the biggest changes when putting the new provisions into effect. Some respondents deplored the fact that, toward the end of 2012, they had not been informed of their new national animal welfare provisions, even though national legislation was required to come into force at the beginning of 2013.

Summary: Outcome of the inquiry with regard to the functioning of the FP7 ethics review process

In general, grant holders affirmed that they considered the ethics review process to be meaningful and necessary, because it forced them to reflect on the ethical issues in detail, and because important *reduction* and *refinement* measures were added to the work plan in the course of the negotiations. Nevertheless, there was also some reticence in a number of answers. This was evidenced by a strong reaction to possible changes under the new animal welfare legislation, or by criticism of the delay in project acceptance due to the ethics review process, or the workload involved in compiling the required ethics documents.

Individual differences in dealing with the ethics review are unavoidable, and some scientists are more inclined to address such matters positively, while others are more reluctant (39). In a compendium on "*Ethics for Researchers*" aiming at facilitating research excellence in FP7, it is deplored that "*ethics is often misunderstood by researchers as hindering scientific progress*" (40; commissioned by the Commission).

Some project coordinators did not seem as involved in the ethics review, nor were they as knowledgeable about the ethical implications of their project as the scientists directly involved in the procedures with primates. Seemingly, the ethical weighing had not been performed in the entire research consortium. From the point of view of animal welfare, however, the ethical debate on potentially contentious parts of a project should be conducted within the entire research consortium, and should necessarily include the project coordinator.

Conflicting information was obtained on whether or not the ethics review process unnecessarily delays project acceptance. A sound ethics review process clearly requires sufficient time for the ethics experts to perform a robust review. However, the steps in the ethics review process at the level of the Commission seem to lack transparency for grant holders, and feedback on the measures they had taken as a result of contractual ethical requirements had often been insufficient.

In the survey at hand, it was not possible to obtain concrete information on specific ethical requirements or recommendations for a given project, let alone to access the information provided by the applicants, since such information is considered confidential. Therefore, the comprehensiveness of the harm–benefit analyses underlying the final ethical evaluation of the projects could not be assessed. Kolar (39) reported insufficient levels of details of harm–benefit analyses and missing pieces of relevant information, in a survey on the ethics review process of project proposals under the fifth FP.

The projects in FP7 were initiated and largely conducted under *Directive 86/609/EEC*, which had no specific mention of primates, the Three Rs, project evaluation, or harm–benefit assessment. The revised *Directive 2010/63/EU* addresses all of these issues in some detail, setting out the information required for prospective evaluation and retrospective assessment of research projects, and setting some restrictions on the use of primates (see also below). The Commission is currently compiling detailed guidance documents for grant applicants to describe the ethical information to be provided when applying for EU funding in the next FP. With regard to research involving animals, the respective guidance documents are to follow the provisions of *Directive 2010/63/EU*.

In this context, it should be noted that the FP7 ethics review serves a different purpose than is served by the national authorisation of a procedure. The former evaluates whether a project deserves to receive funding, and the latter determines the legal compliance of a project (39). However, in the case of primates, both require that ethical issues be considered. Since similar information is required for the authorisation process

and for the ethics review, this should enable the two processes to be better aligned.

Conclusions and Recommendations

Public accountability and FP7-funded projects involving the use of primates

The present survey reveals that the information on FP7-funded research involving the use of primates that is available in the public domain is limited and not easily accessible. Therefore, it was not possible to tell whether all of the relevant projects were identified, neither was it possible to be certain of the types and severity of the procedures to which primates were subjected, although in some projects the level of harm was 'severe' in the view of the authors of the present report. Information was also extremely scarce with regard to the numbers of animals used, the sourcing of animals, their housing and care, application of the Three Rs within the projects, the adverse effects, and the eventual fate of the animals. It would therefore be impossible for the public to gain a proper understanding of the harms suffered by primates in these EU-funded projects, or for that matter, of the benefits expected from the research, factors that would be a prerequisite for an independent evaluation of the harm–benefit analysis underlying any ethical review. Detailed information on all of these issues would presumably be included in the application that is submitted to ethical review panels, so as to facilitate an in-depth estimation of the ethical implications of the work, but it was not possible to confirm this.

The need to publish more-comprehensive information on animal studies has been argued for many years. Recently, the scientific, ethical, and economic implications for the entire research process, of failure to describe research methods and to report results appropriately, have been recognised (27; 41). There are now guidelines (the ARRIVE guidelines, 'Animal Research: Reporting *In Vivo* Experiments') that list the issues to be covered when presenting *in vivo* studies in scientific publications (27). These have been accepted by many scientific journals. By following these guidelines when publishing Commission-funded work, a framework would be provided to permit an independent assessment of the harm inflicted upon the animals and the benefit resulting from the procedures.

The difficulty in accessing information on research involving primates enabled, or supported, by Commission funding, contradicts the Commission's commitment to ensuring transparency on policy issues. Considerable improvement in the accessibility of information is required, if the Commission is to fulfil its aims in this respect.

Stakeholders should be able to obtain a comprehensive overview of all EU-funded research involving animals in general, and, specifically, primates. They should be able to independently assess the harms inflicted upon the animals and the expected outcome of the respective research projects, allowing them to verify the ethical review undertaken in the course of evaluating project applications for EU-funding. This should be especially true in an area of such high public concern as scientific research involving the use of non-human primates. Consequently the information provided, e.g. on the CORDIS websites, needs to be sufficiently detailed to enable a comprehensive overview of the harms inflicted upon the animals and the benefits of the research to be obtained.

Recommendations

Far more information on EU-funded projects involving the use of primates should be made available in the public domain, in an attempt to aid transparency and accountability with respect to the concerns of EU citizens and the use of public money.

The Commission is therefore invited to amend the structure of the CORDIS project information pages:

— to include key words with regard to the animal species used and the methodologies applied, as well as a description of these methodologies (so that a comprehensive overview of the harms inflicted upon the animals used can be obtained); and

— to indicate the specific objectives of the respective projects, as well as their concrete outcomes.

The Commission is also invited to request that grant holders:

— adhere to the ARRIVE guidelines when designing and publishing the results of EU-funded projects;

— provide a summary of all of the procedures applied, including housing conditions and any Three Rs measures, up to the end of the experiments (including the fate of the animals). This information could also be used for the additional CORDIS project information as requested above;

— publish key results of the projects in open access journals, and include such publications in the OpenAIRE inventory, linking the latter to the respective project-related CORDIS websites consistently.

Ethics review of EU-funded projects involving the use of primates in the light of the provisions of *Directive 2010/63/EU*

It was the Commission's intention to incorporate strong incentives in the revised animal experimentation Directive to move toward the ultimate goal of phasing out the use of primates in experiments (16). However, very few restrictions were eventually included in the text of the Directive. Article 8 sets limits on translational, or applied, research which can only be undertaken for "*debilitating or potentially life threatening clinical conditions in human beings*", but basic research without any such qualification is still allowed. Nevertheless, there are strong statements in the recitals about the need for primate use to be restricted to "*essential*" biomedical research, where "*no alternative replacement methods are yet available*". From the point of view of animal welfare, for these newly-introduced provisions to be more than empty phrases (42), certain purposes of primate use that previously were considered acceptable should no longer be permissible.

The Directive now also requires prior authorisation of projects through a project evaluation process that includes a harm–benefit analysis of the project, "*to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment*" (Article 38[2]d). The ethical review of proposals for EU funding should carry out a similar harm–benefit analysis, albeit at the European rather than the national level, and sufficient information will need to be available to facilitate this. It should take into account the broader scope of the EU project, which covers a number of interlinked work packages. Projects authorised at the national level are normally only one part of the overall EU project.

It was not possible to evaluate whether, or how, this issue was addressed in the reviews carried out during the period covered by this survey, but the information requirements in Article 38 and Annex VI for the evaluation of projects, provide a useful framework for the future. It would be a sensible approach for all future applications, conducted either under FP7 in the year 2013 or under Horizon 2020, to be required to include similar information to that required for project evaluation. This would provide an additional check on whether there was sufficient justification for primate use, which would give the Commission a better insight into the ongoing use of these animals in its research programmes.

The retrospective assessment of projects, compulsory for procedures involving primates (Article 39 of *Directive 2010/63/EU*), will be an important tool for verifying whether the objectives of a project were achieved, how much harm was inflicted on the animals, including the numbers and species of animals used, and the severity of the procedures. It should also act as a driver for implementing the Three Rs as projects progress and in future work. The results will be used to update the non-technical project summaries and will be published (Article 43). It would be valuable for these also to be linked to the project summaries in CORDIS.

Recommendations

The ethics review process for applications for EU funding under the Framework Programmes needs to ensure that, for projects involving primates, the special requirements of *Directive 2010/63/EU* relating to the use of these animals have been properly addressed, with the aim of limiting and ultimately replacing the numbers of primates used, and of limiting the harms inflicted on the animals that are used.

The Commission is therefore invited to:

— ensure that the information requested during the ethics review process includes an analysis of the level of pain, suffering or distress inflicted upon the animals, and that procedures classified as 'severe' are only considered acceptable, if they can be shown to be of outstanding, essential and applied medical benefit, that the results are directly translatable to the clinic, and that the expected outcome is highly likely to be achieved;

— only fund research with primates (both in and outside the EU), if their housing and care is in accordance with the minimum standards laid down in Annex III of *Directive 2010/63/EU* in combination with Commission Recommendation *2007/526/EC*, and if the research is conducted according to the standards laid down in the Directive;

— encompass the principles of retrospective assessment of animal procedures in its own ethics follow-up, to assess the actual and not only expected severity of the procedures, to establish whether the predicted benefits were achieved, and to recognise and implement Three Rs measures in future research projects, as well as in future funding policies; such assessment decisions should also be made available on the CORDIS project information websites; and

— in future framework programmes, to actively promote the development of replacement methods in scientific areas involving distressful procedures with primates, by publishing calls that specifically address this research goal.

At the Member State level, the authorities in charge of authorising procedures are invited to:

— initiate discussions on what constitutes a "*potentially life-threatening condition*", and cases of "*a reduction in a person's normal physical or psychological ability to function*" (Article 8 of *Directive 2010/63/EU*), and, if necessary, to put contentious views with regard to these legal provisions before the European Court of Justice. From the point of view of animal welfare, it should be ensured that the meaning of these provisions is clearly explained in the guidance for those submitting and assessing applications for EU funding.

Strengthening of the inherent value of the EU-based ethics review process

The provisions of *Directive 2010/63/EU* apply as of 1 January 2013. Therefore, the Commission should ensure that all future projects involving the use of primates (either in the final FP7 calls in 2013, or in the next Framework Project, Horizon 2020) are submitted to an independent EU ethics review process, including an in-depth harm–benefit analysis compliant with Article 38 of the new Directive. In this context, the Commission's intention to compile and publish detailed ethical guidance documents to support applicants in writing their grant applications is welcomed.

Although *Directive 2010/63/EU* now provides for an authorisation procedure at the national level for projects involving animal experiments, which includes an evaluation of the harms and benefits of the research, the FP ethics review process continues to have an inherent value over and above that of the national review. This is because the FP review encompasses the wider issues around what research the EU as a whole considers it is ethically acceptable to fund. Furthermore, the research is carried out within the framework of an international consortium, often with partners outside the EU, and it is essential to ensure that such experiments are performed under animal welfare standards that fully comply with EU legal provisions.

In the context of EU-funded projects involving primates, the ethics follow-up and audits are recognised as valuable tools in ensuring that all ethical requirements and recommendations spelled out during project acceptance are fully implemented. The follow-up and audits also ensure that possible further ethical issues that were not recognised during the application procedure are revealed and addressed without delay.

The authors believe it is important to develop a universal understanding and acceptance of the ethical issues relating to animal use in scientific procedures. Educating young scientists in dealing with ethical issues and in recognising and assessing the different ethical aspects of the research they intend to perform, is seen as an important factor in promoting widespread acceptance of the ethics review process, and in recognising it as an integral part of the design of high-quality research projects. Ethical review should not be seen as an obstacle standing in the way of a favourable project evaluation and grant award. Instead, in-depth discussion of ethical questions should be seen as an integral part of the design of any project, and all partners should be encouraged to actively engage in such discussions.

Recommendations

The ethics review process for Commission funding applications needs to be maintained and strengthened to ensure a robust ethical review of the individual projects, and to develop a wider understanding and acceptance of the importance and relevance of ethical discussions to animal welfare, science and public accountability.

— Clear guidance is needed for applicants for EU Framework Programme funding, which explains the issues that need to be addressed and why these are important. The guidance should cover relevant details of *Directive 2010/63/EU*, to ensure that the harms and benefits are adequately described and that the Three Rs principle is firmly applied in the course of project application, evaluation and award.

— Similar guidance is also needed for members of the ethics review panels that evaluate applications. In this context, it is imperative that ethics review panels should include appropriate animal welfare and Three Rs experts with knowledge and experience relevant to the welfare and Three Rs issues in the projects under evaluation, and to ensure adequate reimbursement for the experts.

— EU project applicants should be required to involve all partners of the consortium in discussion of the welfare and ethical issues within their funding applications, as well as in discussions on science and practical aspects.

— From the point of view of animal welfare, not only research involving primates, but also all other animal species covered by *Directive 2010/63/EU*, should be included in the mandatory EU ethics review process.

— Ethics follow-ups and ethics audits of EU-funded projects involving primate use should be conducted on a regular basis. Such follow-ups should also serve to improve the communication between grant holders and the Commission.

— The Commission (and Laboratory Animal Science and other relevant organisations) are

encouraged to organise seminars addressing research-related ethical topics and to encourage the creation of platforms facilitating constructive ethical debate within the scientific community.

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Appendix

Table A1: Numbers of FP7 projects retrieved via CORDIS search, and assignment to general scientific topic, as well as to type of procedure performed on primates

	Invasive procedures	Non-invasive procedures	Unclear[a]	Total
Neuroscience	16	3	2	21
Infectious diseases research	11	0	1	12
Evolutionary biology	0	6	0	6
Other topics	4	1	3	8
Total projects involving primate use	**31**	**10**	**6**	**47**
Project judged not to include research involving primates	—	—	—	23
Total projects retrieved via CORDIS search				**70**

[a]*Based upon the information collected, the type and extent of the procedures involving primates is unclear.*

Table A2: Projects referring to primates, but judged not to involve experiments with primates

Project acronym	Acronym description	Comment
A LIGHT ON VISION	Controlling conscious visual perception with light.	Mention of previous non-human primate work, but the project uses mice.
ABACUS	Advancing behavioral and cognitive understanding of speech.	Passing mention of apes.
ATTENTIONLOOP	Investigating the neural mechanisms of feature-based and spatial attention in a network model of two coupled brain areas.	Computational analysis of attention; no indication of new non-human primate studies.
EUPRIM-NET II	European Primate Network: Advancing Three Rs and international standards in biological and biomedical research.	Facilities, training, equipment; best practice; advancing the Three Rs.
GRASP	Emergence of cognitive grasping through emulation, introspection and surprise.	Robotics; mentions primate hand control, no indication of non-human primate use.
HAR1MC	Structure determination of human and chimpanzee HAR1F RNA by NMR.	No suggestion of non-human primate experiments.
INYVAX	Optimisation of the development of poverty-related-diseases (PRD) vaccines by a transversal approach, addressing common gaps and challenges.	Project seems rather directed at networking, in accordance with final project summary, very unlikely that there would have been direct research involving non-human primates.
IVOR	Neuronal substrates of invariant visual object recognition in rats.	Visualisation; mentions non-human primate work, but uses rats.
KRAB-ZNF	KRAB zinc finger gene biology in evolution and disease.	Evolutionary genetics; mentions primates, but no indication of non-human primate use.
MULTIMODAL-ATTENTION	Multimodal imaging of spatial attention networks in the human brain.	Bridging human–monkey brain research on attention; no suggestion that non-human primate research is involved.
NBATTENTION	The role of the basal forebrain in attention and learning.	Basal forebrain in attention and learning; primate mentioned as gold standard, but uses mice.

Table A2: continued

Project acronym	Acronym description	Comment
NEF-PATHO-GENESIS	The importance of Nef effects on HIV-1 infectivity for viral pathogenesis.	Primates mentioned, but uses "humanised" mouse model.
NEURONAGE	Molecular basis of neuronal ageing.	Uses *C. elegans*; passing reference to primates.
OBJECTPOP-CODESIMMM	Visual object population codes relating human brains to non-human and computational models with representational similarity analysis.	Computational analysis of brain research; no indication of new non-human primate studies.
OPTONEURO	Optogenetic neural stimulation platform.	Optical technology; refers to past primate research.
PERCEPT	Cortical circuits of visual perception.	Uses mice instead of non-human primates.
PHARVAT	Platform for the harmonisation of vaccine adjuvant testing.	Involves primate centre, but most likely only for information input.
ROCK'N...	Researchers on the Rock.	Public outreach; passing reference to non-human primates.
RODATTN	Mechanisms of attentional modulation of neural responses in visual cortex of mice.	Uses mice; passing reference to non-human primates.
SPATIAL MEMORY	Cerebral representation of object-location memory.	Human studies, apes mentioned.
TMVP	From theory of mind to vicarious perception.	Mention of primates, but no indication of experimental work at all.
TOAFOLNR	Exploring the dark matter of the human brain transcriptome: The origin and function of long non-coding RNAs.	*In silico* and *in vitro* experiments to identify and functionally characterise long ncRNAs in the human genome.
VTHAND-CENTRED SPACE	Visuo-tactile cortical mechanisms for a hand-centred spatial representation in humans.	Human studies; reference to previous work on non-human primates.

Table A3: FP7-funded projects involving experiments on primates assigned to the general category 'neuroscience'

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
Projects with procedures judged to be invasive					
1. AGELYSPARK	Role of lysosomal dysfunction during aging, and implication for Parkinson's disease.	45,000	PUBL	03.12.2010 to 02.12.2013	"hypothesis will be tested [...] *in vivo*, by injecting filtrated fractions coming from cerebrospinal fluid from PD patients in non-human primates brains and we will let those animals get older for years" .
2. AMY-MPFC-EXTINCTION	Functional connectivity between the primate amygdala and the medial prefrontal cortex: Role in extinction of emotional memories.	100,000	PUBL	01.10.2009 to 30.09.2013	"…record simultaneously from the amygdala and mPFC of awake-behaving monkeys during rest, electrical stimulation, and temporary inactivation of one of the structures; then… record during acquisition and recall of extinction of fear-associations".
3. BIOMOTIV	Why do we do what we do? Biological, psychological and computational bases of motivation.	1,346,000			three approaches described, one of which: "primate neurophysiology, which is essential to describe information processing at the single-unit level and to derive causality by observing behavioural consequences of brain manipulations".
4. BRAINAGE	Impact of prenatal stress on brain ageing — fetal programming, undernutrition and stress.	2,998,420	www.brain-age.eu PUBL	01.03.2012 to 28.02.2017	"...access to well-defined human and non-human primate cohorts (age range 25-115 y equivalents) that have been exposed to different types of prenatal stress... apply innovative techniques to characterise brain ageing, namely MRI based volumetry, non-linear analysis of EEG and ANS, advanced molecular techniques including epigenetics and metabolomics and neuropsychological and behavioural tests... Human subjects, non-human primates and rodents (including transgenic models) exposed to maternal stress, glucocorticoids or under-nutrition".
5. BRAINSHAPE	Objects in sight: the neural basis of visuomotor transformations for actions towards objects.	1,499,200	PUBL	01.11.2010 to 31.10.2015	"...integrated approach to study the transformation of visual information into motor commands in the macaque brain, combining functional imaging, single-cell recording, micro-stimulation and reversible inactivation" [topic-related information: 43].
6. COGSYSTEMS	Understanding actions and intentions of others.	1,992,000	PUBL	01.05.2010 to 30.04.2015	"...investigate the neural organisation of monkey area F5, an area deeply involved in motor act understanding. By using a new set of electrodes we will describe the columnar organisation of the area F5, establish the temporal relationships between the activity of F5 mirror and motor neurons, and correlate the activity of mirror neurons coding the observed motor acts in peri-personal and extra-personal space with the activity of motor neurons in the same cortical column".
7. DEFCON1	A new definition of consciousness.	2,344,800		01.03.2009 to 28.02.2014	"Experiments in man and monkey will test essential predictions of the new definition of consciousness, using techniques such as intracortical recording, EEG, fMRI and pharmacological intervention, combined with psychophysics, learning paradigms or manipulations of consciousness".

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A3: continued

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
8. DEVELAGE	Pathways common to brain development and ageing: Defining strategies for preventive therapy and diagnostics.	2,994,137	www. develage.eu	01.01.2012 to 31.12.2014	"Pathways examined in humans will be validated in animal models, including a non-human primate, and *vice versa*".
9. EYESHOTS	Heterogeneous 3-D perception across visual fragments.	2,400,000	www. eyeshots.it PUBL	01.03.2008 to 28.02.2011	Project website: "macaques trained to execute reaching movements in the dark or in full light; sitting in primate chair, single cell recordings using glass-coated microelectrodes" [see also: 17].
10. GRASP CONTROL & BMI	Grasp-related neuronal activity in monkey and human and its applicability in BMI (brain-machine interface).	209,092	PUBL	01.06.2012 to 31.05.2014	"…investigate grasp-related neuronal activity in monkeys and human volunteers based on recordings of intracortical single-unit activity and local field potentials through multiple electrodes in monkey primary motor cortex (M1), ventral pre-motor cortex (PMv) and boundary areas between M1 and PMv" [topic-related information: 44].
11. NEURAL-CODES_EMO	Deciphering neural codes of valence-based emotional memories.	1,671,620		01.01.2012 to 31.12.2016	"...develop a comprehensive battery of behavioural paradigms that targets emotional learning and memory in non-human primates; ...combine large-scale inter- and intra-regional simultaneous electrophysiological recordings in the primate amygdala and prefrontal-cortices, with a set of focused paradigms that use behavioural generalisation as a tool to probe the underlying neural building blocks".
12. NEURO-CONSC	Converging criteria for consciousness: Using neuroimaging methods to characterise subliminal and conscious processing.	2,486,640		01.07.2010 to 30.06.2015	"...measure fMRI activation in monkeys during the same tests, thus allowing for a direct comparison of monkey and human signatures of conscious processing".
13. NEUWALK	Neuroprosthetic interface systems for restoring motor functions.	8,800,000	www. neuwalk.eu PUBL	01.06.2010 to 31.05.2014	"Elaboration and validation of the NEUWalk concept will be carried out in rats with spinal cord injury and non-human primates with Parkinson disease symptoms" [see also: 45].
14. PRIMLID	Priming for L-dopa-induced dyskinesia and neurotransmitter receptor trafficking dysregulation in parkinsonism.	165,145		01.06.2010 to 31.08.2011	"…investigate the role of neurotransmitter receptor homologous desensitisation and its consequences upon main intracellular signalling cascades, i.e. the canonical pathway and the mitogen-activated protein kinase cascade through activation of different scaffolds, in various experimental models: namely an *in vitro* nigrostriatal slice model, the rat model of abnormal involuntary movements and the non-human primate model of L-dopa-induced dyskinesia" [Project linked to AGELYSPARK, see above, most likely only available tissues from non-human primates with induced parkinsonism used in this project].

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A3: continued

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
15. REVERSIBLE COGNITION	Prefrontal and cingulate interactions in cognitive control: Reversible inactivation and electrocorticograms.	185,748	PUBL	01.03.2012 to 28.02.2014	"In macaque monkeys performing a well-established test of multiple elements of cognitive control, we will reversibly inactivate targeted regions of ACC and PFC whilst simultaneously recording continuous neurophysiological data using chronically implanted electroencephalography… record the same data during reversible localised blockade of targeted neurotransmitter systems, beginning with dopamine, and then to functionally disconnect ACC and PFC" [see also: 46].
16. VISATT	Interactions between prefrontal cortex and area V4 in attention.	not available	PUBL	01.03.2010 to 28.02.2014	"…conduct neurophysiological experiments in non-human primates engaged in a behavioural task in which attention is guided on the basis of object features. We will carry out extracellular recordings in the prefrontal cortex and area V4 simultaneously in order to study how neurons across the two areas interact and how their interaction is modulated during attention" [related information: 47].
Projects with procedures judged to be non-invasive					
17. IM-CLEVER	Intrinsically motivated cumulative learning versatile robots.	5,899,884	www.im-clever.eu PUBL	01.01.2009 to 30.04.2013	"The study of these issues will also be fuelled by a reverse-engineering effort aiming at reproducing with bio-mimetic models the results of empirical experiments run with monkeys, children, and human adults".
18. PRIMARCH	Primate archaeology: an evolutionary context for the emergence of technology.	1,454,310		01.01.2012 to 31.12.2016	"…analysis of non-human tool use behaviour, including standardised documentation of the technological signatures of multiple wild non-human primate species; recording the spatial (from site to landscape) and chronological patterns of primate tool use".
19. SOMACCA	The syntax of the mind: A comparative computational approach.	1,957,598		01.09.2009 to 31.08.2014	"The types of patterns recognisable by different species will be tested using innovative empirical testing methods… the animal species tested include non-human primates and birds".
Projects where, based upon the CORDIS information, primate use is unclear					
20. CONEURON	Drawing neuronal circuits without seeing them.	100,000		01.04.2011 to 31.03.2015	"…analyze and model data from multielectrode recordings in monkey primary visual cortex using state of the art and our own developments of analytical, computational and simulation techniques".

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A3: continued

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
21. NEUROMAN	Identifying the genes responsible for the expansion of the human cerebral cortex.	2,496,000		01.10.2010 to 30.09.2015	"…characterise the differences between mouse and human cerebral cortex with regard to the molecular and cell biological features of neural stem and progenitor cells, their mode of division, and the generation of neurons from these cells. Among the observed differences, human-specific features of cortical progenitor cells will then be identified by comparison with various non-human primates".
Total sum EU funding of projects (€)		**41,145,594**			

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A4: FP7-funded projects involving experiments on primates assigned to the general category 'infectious disease research'

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
1. EVIMALAR	Towards the establishment of a permanent European virtual institute dedicated to malaria research.	12,000,000	www.evimalar.org	01.10.2009 to 30.09.2014	Project website: "New *in vivo* models of adhesion-based pathology using imaging technology will include *Plasmodium cynomolgi* in marmosets… one objective will be to determine common and unique host responses in the spleens of mice, monkeys and humans".
2. FLUPLAN	Novel strategies to combat future influenza pandemics.	2,187,758		01.06.2010 to 31.05.2015	"The added value of including a relevant […nucleoprotein] in the immunisation schedule to obtain broader and longer protection will be determined in a macaque infection model".
3. HIVNONILV	A novel non-integrating replication limited lentiviral- (NONI-LV) based vector for HIV vaccination.	75,000	PUBL	01.07.2011 to 30.06.2014	"...evaluate the immunogenicity and the safety of our novel NONI-LV vectors and the protection against pathogenic viruses in the non-human primate model of HIV ...explore the immune responses induced in monkeys ...explore the efficacy of induced immune responses to protect immunised monkeys against heterologous pathogenic viruses".
4. ICRES	Integration of Chikungunya research.	2,999,938	www.icres.eu	01.12.2010 to 30.11.2014	"characterise rodent and non-human primate models of acute and chronic infection to further study the pathogenesis and provide models for antiviral and vaccine screens".
5. MALSIG	Signalling in life cycle stages of malaria parasites.	3,000,000	www.malsig.lille.inserm.fr	01.02.2009 to 31.07.2012	"approaches will include proteomics, reverse genetics, structural biology, and the use of animal models of malaria".
6. MD-THIV	Migration and differentiation of Th17 cells in HIV/SIV infection.	180,801	www.irb.ch PUBL	01.06.2009 to 31.01.2012	"...a progressive impairment of the immune system... characterises the infection with HIV 1 in humans and with simian immunodeficiency virus (SIV) in macaques... investigate the mechanisms that mediate Th17 cells trafficking and activities at mucosal sites together with their decrease in frequency during HIV/SIV infection" [review by: 48].
7. NANOTRYP	Development of new tools to control infections due to parasites of the *Trypanosomatidae* family.	2,714,608	www.nanotryp.org	01.02.2009 to 31.12.2012	Project website: "Nanobody-tools for diagnosis and treatment of *Trypanosoma brucei rhodesiense* and *T. brucei gambiense* infections… adapt selective nanobody sequences to monkey antibody sequences... analysis of an experimental model for *T. brucei gambiense* infections in vervet monkeys".
8. NEWTBVAC	Discovery and preclinical testing of new vaccine candidates for tuberculosis.	11,996,730	www.tbvi.eu	01.02.2010	CORDIS periodic summary report: "A selection of vaccine candidates for the for 48 months non-human primate model of vaccine evaluation has been postponed to the third year to ensure accommodation of the best possible candidates selected from lower vertebrates in this model".
9. NGIN	Next generation HIV-1 immunogens inducing broadly reactive neutralising antibodies.	7,534,742	www.ngin.eu PUBL	01.02.2008 to 31.07.2012	"Immunogen/adjuvant combinations that prove most effective in eliciting broadly Nabs both systemically and at the mucosal level will be evaluated in non-human primates for their immunogenicity and efficacy upon challenge with live heterologous virus".

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A4: continued

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
10. OPTIMALVAC	Initiative on optimising malaria vaccine lab assays evaluation.	1,000,000	www.optimalvac.eu	01.04.2009 to 31.03.2012	Project website: "The major research activity of the [primate centre] is the application of molecular, biochemical and immunological approaches to provide a rationale for new vaccine and therapeutic strategies for malaria and tuberculosis. …houses a large colony of rhesus macaques, and has extensive knowledge on primate immunology" [and physiology and experience with the specific requirements for housing and handling of primates].
11. WINGS	West Nile integrated shield project: epidemiology, diagnosis and prevention of West Nile virus in Europe.	2,938,497	www.west-nile-shield-project.eu PUBL	01.02.2011 to 31.01.2014	"…develop a vaccine for humans and last but not least to establish a scientific network to collect, investigate and standardise biological data associated with West Nile virus records using standardised methods [project partner primate center" [see also: 49].
Projects where, based upon the CORDIS information, primate use is unclear					
12. TRANSVAC	European network of vaccine development and research.	9,899,999	www.transvac.org	started in 2009 and runs until 2013	"…accelerate the pharmaceutical and clinical development of promising vaccine candidates by bringing the gap between academic research and clinical trials through carefully managing the advancement of promising vaccine candidates from preclinical animal models to early proof-of-principle studies in humans" [TRANSVAC website offers free workshops on animal models].
Total sum EU funding of projects (€)		**56,528,073**			

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A5: FP7-funded projects involving experiments on primates assigned to the general category 'evolutionary biology'

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement in CORDIS taken as indication for primate use
1. DA	No two halves are identical: Quantitative study of cranial asymmetry in human and non-human primates.	30,000	http://www.geo.uni-tuebingen.de/arbeitsgruppen/urgeschichte-und-naturwissenschaftliche-archaeologie/palaeoanthropologie/forschung/evolutionary-processes.html PUBL	01.02.2011 to 31.01.2013	"...examine the evolutionary origin of directional asymmetry in hominoids... examine the development of such asymmetric features in a large ontogenetic sample... use quantitative methods such as landmark-based 3D geometric morphometrics to collect and analyse cranial measurements obtained from living human and non-human apes such as gibbons, orangutans, gorillas and chimpanzees" [information on methodologies: 50; 51].
Projects with procedures judged to be non-invasive					
2. EMREP	A comparative genomic study of the contribution of epigenetic mechanisms to regulatory evolution in primates.	235,535	http://www.unil.ch/dee/page22707_en.html	01.09.2012 to 31.08.2015	"high-resolution gene expression data, methylation state, and histone modification profiles from a set of five tissues from multiple human, chimpanzee, and rhesus macaque individuals".
3. IDCH PRIMATESDS	Identification and characterisation of primate-specific duplications and an assessment of intra-specific patterns of selection and copy-number variation.	233,921	PUBL	01.06.2008 to 30.11.2010	"segmental duplications detection and analysis of non-human primate genomes" [see also: 52].
4. PRIMATE HETEROTACHY	The speed of molecular evolution: Rate shifts, gene function and natural selection in primate history.	162,568		01.11.2009 to 31.10.2011	"...investigate changes in the speed of primate gene evolution, using complete genome sequences from at least six species of primates augmented by data from other species in the Order, including Neanderthals; to identify functional classes of genes... whose rates of evolution diverge from general trends in primate gene evolution... to build a picture of the gene functions that characterise human evolution integrated over the 20,000 to 25,000 human genes, and — to relate these functional classes to selective processes at the level of primate ecology".
5. PRIMATESVS	Identification and characterisation of primate structural variation and an assessment of intra-specific patterns of selection and copy-number variation.	1,599,999		01.12.2010 to 30.11.2014	"...discover the extent of genome structural polymorphism within the great ape species by generating next-generation sequencing datasets at high coverage from multiple individuals of diverse species and subspecies, characterising structural variants and validating them experimentally".

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A5: continued

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement in CORDIS taken as indication for primate use
6. TWOPAN	Genomic and phenotypic evolution of bonobos, chimpanzees and humans.	2,199,996	http://www.eva.mpg.de/primat/research-groups.html PUBL	06.01.2009 to 31.05.2014	"generate a genome sequence for the bonobo and to collect extensive data from chimpanzees and bonobos on: cDNA sequences, variation in coding and non-coding parts of the genomes, expression of mRNAs, microRNAs and proteins in five tissues, and phenotypic parameters in terms of clinical chemistry, and behavioural and cognitive traits. We will combine these data with the extensive data already collected on humans and perform integrated analyses of between- and within-species variation of genomic and phenotypic traits in humans, bonobos and chimpanzees" [further information: 53].
Total sum EU funding of projects (€)		**4,228,098**			

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).

Table A6: FP7-funded projects involving experiments on primates assigned to the general category 'other topics'

Project acronym	Acronym description	EC funding €	Project website	Duration	Statement taken as indication for primate use (source: CORDIS project information unless otherwise stated)
Projects with procedures judged to be invasive					
1. ANTIBOTABE	Neutralising antibodies against botulinum toxins A,B,E.	2,966,386	www.antibotabe.com PUBL	01.09.2010 to 31.08.2014	"antibodies against Botulinum neurotoxins: The six corresponding immunogens will be produced in recombinant form, and utilised to immunise macaques (*Macaca fascicularis*), from which phage-displayed immune libraries will be built. ... The six most neutralizing scFvs will then be super-humanised (germline-humanised) and expressed as IgGs, which will be tested *in vivo*, in a standardised model of protection and against toxins obtained from collections of clostridia strains".
2. CHAARM	Combined highly active anti-retroviral microbicides.	11,999,998	www.chaarm.eu PUBL	01.01.2010 to 31.12.2014	"...test efficacy of selected microbicide combinations in macaque models of vaginal and rectal challenge" [see also: 54].
3. RDCVF	Rod-derived cone viability factor.	2,623,333	www.rdcvf.eu	01.03.2010 to 28.02.2013	"...toxicology studies will be performed in normal and mutant mice and rats, and in monkeys".
4. TRIAD	Tolerance restoration in autoimmune diseases by selective manipulation of the CD28 co-stimulatory pathway.	2,959,590	www.triad-cd28.eu	01.01.2012 to 31.12.2014	"...study of the efficacy of a new selective antagonist of CD28 in non-human primate models and the exploration of the potential efficacy of surrogate CD28 antagonist in rodent models... evaluation of potential immunological toxicity of the antagonist in humanised SCID mice and non-human primate, to exclude agonist activity *in vivo*. Previously identified mechanisms of action (i.e. costimulation blockade and induction of regulatory T cells in the context of AID will be confirmed in experimental models. Formulation and preclinical toxicological studies will be run before initiating PhaseI/II trial in patients".
Projects with procedures judged to be non-invasive					
5. HYBRIDBAB	Genetic, behavioural, and demographic consequences of long-term hybridisation in savanna baboons.	75,000		01.10.2009 to 30.09.2012	"...gaining a detailed understanding of the genetic, behavioural, and demographic consequences of hybridisation in the well-studied wild Amboseli baboon population in particular and across the boundary of the southern Kenyan baboon hybrid zone as a whole".
Projects where, based upon the CORDIS information, primate use is unclear					
6. CD14	Innate and adaptive immune responses to nanocell-based tumor-targeted cancer therapeutics.	330,100		01.03.2010 to 28.02.2012	"...research and evaluation of applicability to patients in Europe will be continued at the return host institution... provides expertise by ... Primate Centre".
7. IRLVGTMND	Improved retrograde lentiviral vectors for gene therapy in motor neuron diseases.	2,000,000		01.04.2009 to 31.03.2014	"...experiments with rabies-G pseudotyped vectors in non-human primates have failed to give good efficiency of transduction of MNs so as to translate this approach to the clinic".
8. MACACA	Determinants of mandibular form during intra-oral food processing.	30,000		01.12.2010 to 30.11.2012	"The models will then be validated against experimental *in vivo* bone strain data. A series of statistical analyses will be also employed to study strain magnitudes and orientations in the primate mandible in relation to loading and unloading times, chewing rates, chewing frequencies and gapes".
Total sum EU funding of projects (€)			**22,984,407**		

'PUBL' indicates that project-related publications were used in the present survey to supplement CORDIS information (and, possibly, information from project websites).