The use of non-human primates in research: The RSPCA's response to the Weatherall Report

1 General comments on the report

The first and third of the four terms of reference for the Weatherall Committee were:

(i) "*to examine the scientific basis for recent, current and future use of non-human primates within biological and medical research*" and

(iii) "*to review the use of alternatives to non-human primates in different fields of biological and medical research*."

Given these aims, the Society had expected the Weatherall Committee to critically examine the scientific validity and necessity for primate use in an open-minded and innovative way, and to facilitate the development of a strategy for the replacement of primates in all types of scientific experiment other than regulatory toxicology (since this was outside the Committee's remit).

The report falls far short of these expectations, offering little that is challenging, new or progressive. As a result, the report largely describes and supports the *status quo*. It explains why people *believe* non-human primates are needed, rather than constructing a scientifically supported analysis of whether they *really are.*

The report sets out the basis for the Committee's investigation into primate use in section 4 ("*The investigation into the scientific basis for current non-human primate research*"). However, the 4 pages that are allocated to this do not say much, other than arguing that there is little difference between fundamental and applied research, something that must surely be widely known, and which does not in any case address the subject of the title. The decision to focus the investigation on some key fields of research in which primates are currently used was sound. However, overarching considerations such as the validity of using primates as surrogates (models) for humans are not even mentioned. In fact, the reason why the scientific case for using primates should be questioned at all is not explained. Only moral objections are discussed.

The RSPCA finds it especially surprising that the Committee did not undertake a review of the outcome of non-human primate research as an integral part of its investigation, but instead shifted the responsibility to funding organisations (see Recommendation 4).

The chapters on specific research fields do not, in our opinion, explore the scientific basis for non-human primate use in sufficient detail. The Committee has cited a great many 'assertions' and 'arguments' relating to the necessity for primate use, and statements to the contrary, but these assertions are rarely tested or assessed in depth. On the other hand, a great deal of space is devoted to the importance of the medical problems addressed, which should be obvious to most readers, and which has little bearing on the question of scientific validity. A few highly specific case studies would have had much greater value in bringing out the basic scientific considerations i.e. when and why using primates is considered to be the only possible approach, what the limitations and uncertainties of primate experiments are, and when these are considered to be outweighed by the urgency of a research problem.

The process by which the Committee weighed the evidence and reached its conclusions is not explained. The lack of comprehensive scientific argument throughout the report means that its position does not come across as scientifically robust. This means that the Committee seems too ready to accept that non-human primate experiments can sometimes yield useful information and are therefore necessary.

The conclusions reached by the Committee are somewhat vague and uninformative. For example, Section 6, *Neuroscience*, concludes that '*non-human primate work has been essential at some stages of research on a particular disease, and not others*.' A partial explanation for this is offered, but it is difficult to identify any basic principles that might help to guide future research. Similarly, the final overarching conclusion (Recommendation 2), is that there is a strong scientific case for maintaining the use of non-human primates in some aspects of work in the fields addressed. Although it is possible to identify those aspects of current research that the Committee regarded as scientifically justified (by reading the report in detail), the lack of any guiding principles for assessing the scientific case is very unsatisfactory. The report seems simply to invite scientists to continue to use non-human primates whenever they see fit.

The report also takes a somewhat narrow view on some issues. The use of primates is repeatedly justified on the grounds that the equivalent rodent model is not satisfactory. This approach – the question can only be addressed by using either a primate or a rodent model – is neither constructive nor forward thinking. We would have hoped that the Committee would have encouraged respondents to think about genuinely alternative approaches, i.e. to examine the scientific problem and all possible solutions to it.

The fourth term of reference for the study was: "*In undertaking these assessments, to take account of associated ethical, welfare and regulatory issues, particularly with regard to the 3Rs principle of refinement, reduction and replacement.*" With respect to primate welfare, we recognise that it was not the intention to undertake a detailed analysis of the animal welfare issues. The RSPCA welcomes the recommendations made within chapter 9 with regard to improving animal welfare by raising standards of husbandry and care, training (of staff and animals), transport, supply issues, and dissemination of information on animal welfare and the 3Rs, although none of them is new. We particularly welcome the Committee's support of the recommendations in the APC's report on primate supply[1], and those in the Society's own report on primate transport (Prescott and Jennings[2]).

The report, however, makes little attempt to set out in any detail the harms that animals experience as a consequence of their use in research, yet the accumulated harms for primates from procedures and their effects, housing, transport, restraint and eventual death can be substantial. This is a serious omission in a report that asks whether the continuing use of non-human primates is justified (Chapter 13), since justification is about more than scientific validity and necessity (see Jennings

[1] Animal Procedures Committee (2006) Acceptance of overseas centres supplying non-human primates to UK laboratories. A report by the primates sub-committee of the APC. Home Office.

[2] Prescott M.J. and Jennings, M. (2004) Ethical and welfare implications of the acquisition and transport of non-human primates for use in research and testing. *Alternatives To Lab Animals* **32**, 323-327.

and Silcock, 1995[3]). It requires the weighing of harms and benefits, yet the lack of information on harms presented in the report does not allow this to be done.

2. Comments on recommendations

The RSPCA's comments on specific recommendations are outlined below. They are listed as they appear under the sub-headings in chapter 13 of the report, to put them into context.

- ***Is the continuing use of non-human primates in fundamental biological and medical research justified?***

Recommendation 1: *There is a strong scientific case for the carefully regulated use of non-human primates where there are no other means to address clearly defined questions of particular biological or medical importance.*

- ***The role of non-human primates in communicable disease, neuroscience, reproductive biology and ageing research***

Recommendation 2*: In the fields of research considered in this study, namely communicable disease, neuroscience and reproductive biology, there is a strong scientific case for maintaining the use of non-human primates in some aspects of this work, at least for the immediate future.*

These recommendations are discussed here together because they address similar questions. Both are conclusions, not recommendations - neither gives any guidance or direction and it is entirely inappropriate to present them as recommendations. Even as conclusions, these statements fail to adequately define the limits of the scope of the investigation, or to indicate where conclusions differed between fields of research. They are therefore rather meaningless. In addition, both simply endorse the *status quo*; neither emphasises the need for case-by-case scientific and ethical evaluation of experiments on non-human primates (which is mentioned many times in the report text). The RSPCA is therefore extremely concerned that these conclusions may be quoted as support for any primate experiments in the defined research fields.

With specific reference to recommendation 1, this appears to be offered as an answer to the question in the subheading *"Is the use of non-human primates in fundamental biological and medical research justified?"* However, it does so solely on the basis of the scientific case for using them. Justification, however, does not rest solely on the scientific case, but also on ethical judgements as we stated earlier. It is an unfortunate feature of the whole report that the concept of a scientific case is not clearly defined, and distinguished from other aspects of the case 'justifying' primate use.

In fact, a scientific case could only be established by demonstrating that the results of experiments on primates yield information of value in achieving the objectives of the research. The justification for primate use would then depend on the importance of the scientific objectives, the likelihood of achieving those objectives, the lack of any alternative strategy or method, and an ethical analysis based on a harm-benefit

[3] Jennings, M. and Silcock, S. (1995) Benefits, necessity and justification in animal research. *Alternatives To Lab Animals* **23**, 828-836.

assessment, taking into account a full evaluation of the lifetime experience of the animals.

However, the conclusion in recommendation 1 seems to have been arrived at simply by surveying a number of research fields in which primates are used. In the RSPCA's view, the conclusions in recommendations 1 and 2 both seem to have been unduly influenced by the importance of the medical problems in question, rather than the scientific case for using primates to address them, or by the actual benefits of the research. The implication is that the strength of the scientific case for using non-human primates is directly proportional to the seriousness of the medical problem. In our opinion, the scientific case is completely independent of this issue.

Given that the general case for continuing non-human primate research was considered strong in some instances but not others, we would have expected to see comprehensive and clear recommendations which, at the very least, underlined and reinforced the need for a rigorous assessment of the scientific and ethical arguments in each case, together with the need to ensure maximum application of reduction and refinement.

- ***Assessing the case for the use of non-human primates in biological and medical research***

Recommendation 3: *The major specialist organisations involved in research fields that utilise non-human primates, particularly neuroscience, communicable disease, and reproductive and developmental biology, should regularly collate information about evolving research technology in their fields, with particular respect to the need for non-human primates. This information should be disseminated to funding bodies, ethics committees and regulatory agencies.*

The RSPCA agrees with the principle underlying this recommendation. However, it is not clear what information is actually being sought, which 'specialist organisations' are involved or which regulatory agencies it is referring to, particularly since the report specifically did not deal with regulatory testing in any depth. Neither is it clear how information will be collected and by whom.

The most valuable information to collate, from the animal welfare viewpoint, would be ideas that enable primate use to be reduced or avoided, and possibly the phrase "*with particular respect to the need for non-human primates*" is meant to convey this point. However, information relating to the successful refinement of procedures would also be very important. Who will be in a position to identify and describe the right sort of information and what sort of process is there for doing this? Further explanation of this recommendation is essential if it is to be successfully implemented.

Recommendation 4*: As part of their ongoing programmes to assess the outcomes of their research, the major funding organisations should undertake a systematic review of the outcome of all their research using non-human primates supported over the last decade.*

The RSPCA welcomes this recommendation[4] and believes that it is an essential exercise, although it is extraordinary if funders do not already critically review the

[4] Note that the term 'systematic review' has taken on a rather specific meaning (as in the Cochrane reviews) which is not necessarily appropriate here (and probably not intended), but it would certainly be useful to review outcomes and assess the value of research with primates in a systematic way.

outcomes of the research they fund, especially as much of the research is likely to be closely focussed on solving medical problems. In addition to retrospective review of outcomes, the RSPCA believes an ongoing assessment of current research projects and directions is also extremely important.

Given the terms of reference of the Weatherall Committee, the RSPCA also finds it astonishing that the Committee did not carry out such a review as part of its own study. We thought that this would comprise a major part of the Committee's work, and in our view it is not possible to conclude that there is a strong scientific case for using primates (as in 'recommendations' 1 and 2) without doing this.

- ***Working towards non-human primate alternatives***

Recommendation 5: *UK research funding organisations, both governmental and charitable, should continue to take every opportunity to encourage and fund research into developing alternatives to the use of non-human primates for both research and toxicology. Funders should expand their support for research into refining non-human primate research practices, particularly in the behavioural neurosciences.*

The RSPCA supports this recommendation but believes that it should call for *more* investment in identifying and deploying alternative strategies that will allow the use of non-human primates to be replaced or avoided. As written, it suggests that research-funding organisations already take <u>every</u> opportunity to develop alternatives to the use of primates, but we can see no evidence in the report that this is the case. Some of the techniques that might be useful are briefly surveyed in chapter 9, but it is very disappointing that potential alternatives are not explored in much more detail. Furthermore, the chapter is somewhat conservative and cautious in its approach - on page 107, for example, it states:"*the picture that is emerging is of a <u>potential</u> to <u>move towards</u> the <u>gradual reduction</u> in the requirement of animals for biological research and toxicological studies*" – hardly a bold and motivating position. The most important paragraph in this chapter, written in more compelling language[5] is not reflected in the recommendation.

Identifying the true scientific barriers to replacing primates in research is fundamental to designing research on alternatives. It is only by thorough and creative consideration of the specific problems involved in replacing primates that meaningful research approaches will be identified. The RSPCA has repeatedly called for a co-ordinated strategy to achieve this and it is disappointing that the Committee did not formulate a more specific and targeted recommendation in this respect.

The RSPCA also supports the latter part of the recommendation, assuming *that "research practices*" refers to the refinement of housing and care as well as procedures. Note that the RSPCA does not believe that invasive procedures should be carried out on animals solely to evaluate refinements. It is often possible to gain information that can inform and facilitate refinement during procedures that have already been licensed for other purposes. For example, physiological data such as

[5] "*The considerable promise of this field should compel bodies that fund biological or medical research to take every opportunity of supporting research directed at developing alternative approaches. At the same time, regulatory authorities need to be vigilant to innovations and new developments, such that they can fully appreciate the potential and complexities of the science involved. Achieving the undoubted potential of this rapidly moving field in as short a time as possible requires clear and sustained channels of communication between the regulators, researchers of alternative techniques and the wider scientific community*."

heart rate can be obtained form animals who have already been implanted with telemetry devices and this can be used to compare their responses to different husbandry regimes or dosing techniques. This approach avoids causing additional pain, suffering or distress. Funders should also increase their efforts to make it clear to applicants that they are prepared to fund refinement measures such as environmental enrichment, as in our experience some researchers are not aware of this.

- ***Improving non-human primate welfare***

The Committee states "*that this is an area of active investigation on the part of several organisations and specifically mentions APC and NC3Rs"*. The work of both bodies is important but responsibility does not just lie with them. We recognise that some individuals and establishments within the research community are working to reduce suffering and improve welfare, but far greater commitment and resources are required from the research community as a whole.

The Committee also states that "*there are still a number of areas that need examination and improvement"* with respect to primate welfare. This is an understatement. Nevertheless, we are pleased that in the body of the text the Committee mentions the need for education, access to information and increased funding with respect to implementing primate husbandry refinements. All of these are essential.

Note that ALL of the welfare recommendations have been made before by different authoritative bodies and individuals, including the RSPCA, and the report should have developed the issues further, not just restated them. The outstanding question for all of these is: when will something actually be done?

Recommendation 6: *Retrospective reporting on the severity of procedures for non-human primates, as recommended by the LASA/APC pilot study, should be introduced as soon as possible.*

The RSPCA agrees. The Society believes that better reporting of animal suffering will not only lead to greater openness relating to animal use, but also help to reduce suffering by helping and encouraging researchers to become more effective in recognising, alleviating and preventing pain and distress and in improving welfare.

The RSPCA supports the LASA/APC group's initial proposal for a 'double code' system and understands that a more widely scoped pilot study to trial the new system, and explore how such a scheme could be implemented in practice, has been jointly commissioned by the APC and LASA. This is expected to report to the APC in 2007 and it is to be hoped that the results will facilitate a practicable means of reporting severity retrospectively.

However, retrospective review, as opposed to retrospective reporting, is also very important. Considerable progress in implementing the 3Rs would also be made if the local ethical review process (ERP) at every establishment using primates carried out a retrospective review of its primate use as required by the core functions of the ERP set out by the Home Office[6], and described in Jennings and Howard (2004)[7].

[6] Home Office (2006) Appendix J: The ethical review process pp 99-100, in: Guidance on the operation of the Animals (Scientific Procedures) Act 1986 HC321 TSO, London.

Recommendation 7*: Improvements in the supervised continuous training of research workers in non-human primate research should be instituted.*

The RSPCA agrees that training could and should be greatly improved and has said this many times. Modular training for personal and project licence holders is recognised as only providing an introduction to the many legal, ethical, scientific and animal welfare issues involved when carrying out scientific procedures on animals (see APC review of modular training, 2006[8]). The training does not cover animal welfare and the 3Rs in detail, and this would not be possible in the short time available, even on the species-specific courses for personal licensees. Continuous Professional Development is vitally important and this applies to the whole research team, including scientists, animal technicians and Named Persons.

Recommendation 8*: Scientific journals should include details of animal welfare and steps taken to ameliorate suffering in all published papers that involve non-human primate research.*

The RSPCA agrees. The Society has been working on this issue for some time, both in-house and through its membership of the Boyd Group and the Nuffield Council of Bioethics Working Party on the Ethics of Research Involving Animals. Both of these groups have made recommendations on journal policy and the content of published papers [9,10].

The RSPCA believes that all journals publishing research involving the use of animals have a significant role to play in ensuring that ethical and animal welfare issues are given full consideration. Journals should publish a clear statement outlining the limits of the type of research they are prepared to publish, and be more proactive in encouraging the submission and publication of 3Rs information within manuscripts. This will improve the dissemination of information and further promote the implementation of these principles, both in the UK and internationally. Inclusion of information on adverse effects is also important for scientific as well as ethical reasons since it is increasingly recognised that good science is dependent on good animal welfare.

Recommendation 9: *Work should be accelerated towards improving and applying current best-practice regarding housing of non-human primates, including minimum cage size, an emphasis on the avoidance of single housing, how cage fittings and conditions can be accommodated to the purpose of individual experiments, and a better assessment of the advantages of outside access and visual stimulation.*

The RSPCA agrees. It is absolutely essential that the Home Office Codes of Practice are recognised as establishing minimum standards and that primate users continually investigate and apply what is believed to be current best practice. However, it is not

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7 Jennings, M and Howard, B. Eds. (2004). Guidance notes on retrospective review: A discussion document prepared by the LASA Ethics and Training Group. Available at: http://www.lasa.co.uk/position_papers/publications.asp

8 Animals Procedures Committee (2006) APC Education and Training Subcommittee: Review of Modular Training. Available at: http://www.apc.gov.uk/reference/reports.htm

9 Nuffield Council of Bioethics report on the ethics of research involving animals (2005). ISBN 1 904384 102 London.

10 Boyd Group (1998): Working Group Report: Advancing Refinement of Laboratory Animal Use. *Laboratory Animals* **32**, 137-142.

clear what is meant by the statement "*how cage[11] fittings and conditions can be accommodated to the purpose of individual experiments*". If this means that some form of environmental stimulation can always be provided, but it may need to be adapted for some studies, then we support this approach. It is extremely important to recognise that perceived practical or scientific constraints to providing better housing can usually be overcome.

- ***The role of non-human primates in regulatory toxicology***

Recommendation 10: *Further efforts should be made to improve interactions between regulatory bodies at national and international levels and between regulatory bodies and the scientific community. Given the current speed of research in the biological sciences, new approaches to improve these interactions are urgently required.*

The RSPCA agrees, but the recommendation gives no indication of how this can be facilitated and who should be responsible. This type of statement has been made repeatedly over the last 10 years in a variety of fora. It is time some more specific and targeted actions were proposed and somebody took responsibility for taking them forward.

Recommendation 11: *Steps should be taken to make the results of toxicological studies involving non-human primates publicly available, in the same way as initiatives to register and publish the results of all human clinical trials.*

This recommendation is presumably aimed at pharmaceutical companies and trade associations. The RSPCA agrees that this would be very useful, particularly in the case of drugs that do not progress to clinical trials, so that the adverse effects observed would inform companies thinking of developing similar drugs, prevent duplication and provide valuable data for developing alternative approaches.

Recommendation 12: *It would be premature to make firm recommendations on how a reduction in the number of non-human primates used in regulatory toxicology might be achieved before the completion of the NC3Rs/ABPI study. However, we urge government and other stakeholders to act on the recommendations of this study, and in the light of its findings, to re-examine responses to the 2002 APC report.*

The RSPCA disagrees with the first point. The NC3Rs/ABPI study is important, but is not the only initiative in this area and is not addressing regulatory toxicology in its entirety. It is perfectly possible for others who are expert in this area to consider options for reduction, and the Committee should have recommended that this be considered as a matter of high priority. Furthermore, there are issues in the APC report that are not being taken forward in the NC3Rs/ABPI study.

It is now 5 years since the APC report was published and its recommendations should be re-examined now to see whether any progress has been made on each one.

[11] Note that the RSPCA would have preferred the use of the term "enclosure", as we believe that cages should not be the default housing for primates.

- ***Promoting a strategic and integrated approach to UK non-human primate research***

The RSPCA had hoped to see this study recognise that ending non-human primate use is a desirable goal. This would surely have been perfectly acceptable to most stakeholders, given that the Nuffield Council of Bioethics report on the ethics of research involving animals (2005)[9] was prepared to conclude that "*A world in which the important benefits of research could be achieved without causing pain, suffering, distress or lasting harm or death to animals involved in research must be the ultimate goal*."

We believe that any strategic approach must include the replacement of primates as a high level priority (see attached Resolution on primate use introduced at the World Congress on Alternatives in 2005). However, the main elements that appear to be suggested in the Weatherall Committee report relate to financial costs, reducing harassment of researchers and creating centres of excellence. Giving priority to these factors rather than animal welfare is unacceptable in the RSPCA's view, notwithstanding that such centres could facilitate refinement.

We note that in a press release responding to the report, Sir David King states that the Government "*will bring stakeholders together to develop a national strategy for the use of non-human primates in science*". The RSPCA has considerable expertise in science, animal welfare and ethics, and represents a very large sector of the public that is concerned about the use of primates. It thus holds a major stake in this area, as do other animal welfare organisations and humane research trusts. These bodies should thus have full and fair representation in any stakeholder group.

Recommendation 13: *Concerns that costs and harassment by activists are forcing scientists and research companies to pursue non-human primate work overseas require urgent examination by the relevant UK research funding and regulatory bodies*

We have yet to see conclusive evidence, in the report or elsewhere, that companies are relocating overseas primarily due to the financial costs specifically associated with animal research. The reasons that pharmaceutical companies set up overseas are many and various and they include: cost of land and building development, ease of obtaining planning position, availability and cost of labour, ease of recruitment, and position in world markets.

It would be completely unacceptable to reduce the financial costs of scientific procedures by lowering standards, either by reducing standards in the UK or by exporting research to countries where standards are lower. If this were done it would belie the often-made assertion that 'animal welfare is a high priority for industry'.

Harassment by activists is no longer exclusive to the UK and, in any case, according to the Government this is now under control.

Recommendation 14: *The major funding bodies, together with government, other stakeholders, scientists, primatologists, vets and welfare specialists, should give careful consideration to the creation of UK centres of excellence for non-human primate research.*

There is insufficient detail on what is envisaged by this recommendation to enable the RSPCA to evaluate it properly. In the report, the case for such centres is based on them being well equipped in terms of facilities and expertise, and led by expert

primatologists who are motivated to optimise welfare. This could have advantages for the animals in terms of reduction and refinement.

However, given the highly significant welfare and ethical concerns regarding the use of non-human primates, the other "R", replacement, is of primary importance. The Committee identified the potential of centralisation to result in the loss of the multidisciplinary approach that is conducive to developing replacement. This is a significant concern. In addition, in the view of the RSPCA there is a risk that long term investment into primate housing and research facilities will contribute towards sustaining or even increasing primate use.

Another option briefly mentioned in the report is a "virtual centre of excellence", whereby the current facilities would improve their alliances and networks, which would permit the sharing of expertise and ensure good practice. This may help facilitate implementation of the 3Rs, but it does not address the fact that further improvements in primate husbandry and care are required - the Committee itself recognised that improvements could be made in the speed with which innovations are translated into practice. The RSPCA believes that sufficient commitment and resources must be made available to do something about this immediately.

There are clearly pros and cons associated with both real and virtual centres of excellence from a welfare and scientific viewpoint. The RSPCA believes that welfare specialists and organisations have an essential role to play in ensuring that the relevant decision making process gives due priority to avoiding and replacing primate use and to ensuring that all three Rs will be optimally implemented.

- ***Promoting constructive debate***

Recommendation 15: *All bodies involved in engaging the public around issues of science and medicine, including the UK government, should ensure that the whole field of research utilising animals, including non-human primates, has a major place in their future programmes. Given the extremely rapid pace of development in the biological sciences, mechanisms for regular meetings between scientists and the media should be further explored.*

The RSPCA encourages wider public debate on this issue and would therefore welcome greater public engagement. However, an informed debate should be informed on <u>all</u> the issues, including meaningful exposition of the harms to animals and a realistic and honest appraisal of the likely benefits of the research. Overplaying the potential benefits and glossing over the harms, as is commonly done (for example in many of the abstracts of research on the Home Office website or in some literature from professional scientific bodies), is unacceptable.

- ***Next steps***

Recommendation 16: *The bodies that sponsored this study should establish a mechanism for monitoring progress in achieving the aims of these recommendations over the next few years.*

This is an extraordinarily weak recommendation with which to conclude. The sponsors of the study should surely have a duty to <u>respond actively</u> to the report's recommendations and not simply to "monitor progress". Furthermore, as we stated at the beginning of our response, the aims of the study have not in our view been achieved. By the Committee's own admission, much of the evidence was anecdotal and a far more in-depth study of each research field is necessary. An active

response to the proposal in recommendation 4 for a systematic review of primate research by the funders would be a start.

Furthermore, the recommendations say little that has not been said before in a number of reports and authoritative fora - the RSPCA has repeatedly called for all of these issues to be addressed. In our view the report does not take the issue any further forward, other than to demonstrate again (if that is really necessary) that yet another group of people seem to agree on the issues of concern. Most of these recommendations require additional resources and an innovative and challenging approach in order to take them forward. Something concrete now needs to be done.

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